Author's response to reviews

Title: Outcomes after stereotactic body radiotherapy for lung tumors, with emphasis on comparison of primary lung cancer and metastatic lung tumors

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Author's response to reviews: see over
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Professor Dirk Rades
Editor of BioMed Central Cancer
University Hospital Schleswig-Holstein, Germany

Dear Dr Rades

We are grateful for the opportunity to revise our paper 2912851141074262 entitled “Outcomes after stereotactic body radiotherapy for lung tumors, with emphasis on comparison of primary lung cancer and metastatic lung tumors”.

We have updated of ethical approval description in the Methods section.
I hope everything will be all right.

Yours sincerely,

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Responses to the comments of Referee 1 (Dr. Blanck):

1. 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 10 Gy per fraction is meaningless without total dose) and as local control is clearly dependent of BED (> 105 BED see Guggenberger et al. 2013).

Response:
We think what you pointed out is quite right. We re-calculated prescription of 95% coverage with AAA and added information on isocenter doses in the manuscript. However, unfortunately, to comparison of mean GTV doses could not be done because old data (calculated by the former radiation planning system, CADPLAN) were unavailable. BED$_{10}$ was also added to the analysis, and dose per fraction (greater than 10 Gy per fraction or not) was eliminated from the analysis.

2. 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.
Response:

We added information on BED and showed that metastases were prescribed sufficient doses (Table 2). Only 2 tumors of the 57 metastatic lung tumors were prescribed less than 100 Gy (BED\(_1\))\(_{10}\)). Thus, poor LC of metastatic lung tumors could not be explained only by dose, and further discussion was therefore needed.

3. 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.

Response:

As you pointed out, our local control rate was relatively low, and Guggenberger et al. reported very good local control rate and moderate overall survival. However, a difference was seen: their median follow-up period was only 1.3 years, despite the fact that our results showed the median time to local failure was 1.24 years. When we selected cases treated by 48 Gy (or 40 Gy) in 4 fractions, 3-year local control was 89.9%, which was comparable to a Japan phase II trial that had the same dose schedules (Nagata Y et al. J Rad Oncol Biol Phys 2010;78:s27-s28.). Furthermore, the fact that local control itself was associated with overall survival in univariate analysis is very meaningful in this study. Higher BED will result in higher local control but will not always result in high overall survival (Timmerman R et al. J Clin Oncol. 2006 20; 24(30):4833-9.). In RTOG 0236, 3-year local control was 97.6%, but 3-year overall survival rate was 55.8%. Our 3-year overall survival rate (60.9%) was comparable to this result. So, we added discussion about BED, but we did not compare with other series of studies.

4. 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.

Response:
Yes, as you pointed out, these are limitations. We commented about limitations in the manuscript.

5. 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.

Response:
Because our institute is in Japan, Japanese data are more appropriate for our discussion. But we never disregard many of the US and European data. It is true that nine out of the 31 references are Japanese reports, and we reconsidered about this.

6. 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.

Response:
Based on the revision of contents, the abstract was revised. The title was changed, but another referee also mentioned about title change from another aspect. So, the title was revised according to the advice of two referees.
Responses to the comments of Referee 2 (Dr. Onishi):

1. Local recurrence was defined as local progression to $\geq 1.5$ times…..In some cases, post irradiated inflammatory change might show a large mass-like consolidation. How did the author differentiate it from local recurrence?

Response:
To distinguish a mass-like consolidation from local recurrence, further work-up or close follow-up was performed. The work-up included CT, FDG-PET (usually we use SUVmax 5 as a cut-off point), biomarkers (KL-6, CEA, SLX and so on) or biopsy, and then total evaluation was performed. When local recurrence could not be decided, close follow-up was done because abnormal opacities occurred more often than did local recurrence (Takeda A et al. J Rad Oncol Biol Phys 2007;70:1057-65.). We regarded the day that local recurrence was diagnosed by physicians and radiation oncologists as the day of local recurrence.

As our study had relatively long follow-up periods, 37 of the 47 patients (54 local recurrent tumors) died of primary disease. Among the other patients, one patient received surgical resection (confirmed recurrence) and 4 patients developed other metastases (probably recurrence). Although a few of them could not be confirmed (2 patients received re-irradiation, 3 patients were alive or missing), we think this strategy was probably valid.

2. What was the actual difference of the SBRT method between before and after 2005?

Response:
Actually, this difference would be derived from participation in an SBRT phase II study of the Japan clinical oncology group (This was known as JCOG0403.). The protocol of JCOG0403 minimized our interobserver difference in SBRT. After that, spiculation of the tumor included GTV (more precisely, GITV because all tumors were contoured slow-rotation CT scanning images), and homogeneity index (the ratio of maximum dose for PTV and minimum dose for PTV) needed 160% or less. Furthermore, high-resolution CT images at diagnosis were also spread, and that provide us to contour more precisely.

3. The follow-up periods of the cases before 2005 must be longer than that after 2005. So the local control rate of the cases before 2005 naturally got lower than that after 2005. Add a comment about the issue.
Response:
As pointed out, LC rates naturally became lower as the follow-up period became longer. However, the median follow-up periods of 2001-2005 and 2006-2011 were 50.2 months and 41.6 months, respectively, and this was stated in the discussion.

4. How about the actual difference between the cases with or without using EGFR-TKI?

Response:
Because only eight patients (six females, two males) took EGFR-TKI, no significant difference was revealed. However, in females with NCSLC, patients who took EGFR-TKI tended to live longer after disease progression. Median survival times after disease progression in patients who took EGFR-TKI and those who did not were 35.0 months and 6.5 months, respectively (p=0.1938, log-rank test). Two of the six female patients had stable disease for four years or more by continuing to take EGFR-TKI. In contrast, one of the two male patients taking EGFR-TKI developed grade 5 Gefitinib-related fatal lung injury. This case is different from grade 5 radiation pneumonitis in our manuscript. Male gender is now known to be one of risk factors for Gefitinib-related lung injury.

5. Should the factor of severe radiation pneumonitis be included in the prognostic factors in concerning overall survival?

Response: Yes, we added the factor of grade 2 or more radiation pneumonitis in the analysis.

6. What was the difference among “local failure”, “tumor progression”, and “local recurrence”?

Response:
We used these terms as the same meaning. However, the expression “tumor progression” was not appropriate because of confusion of tumor progression with disease progression, so we corrected it.

7. Add the marks of the censored cases and patients number of each subgroups
in the figure 1-3.

Response:
We added the censored cases and patients number (as “No. at risk”) in the Figures 1-3.
Responses to the comments of Referee 3 (Dr. Niibe):

1. The title of this paper is not appropriate. The title does not reflect this study's conclusions. This should be revised according to the following comments.

Response: We corrected the title according to both your advice and another referee’s advice.

2. The authors analyzed both primary lung cancer and metastatic lung cancer. The latter one is included in oligometastases. Recently, the best prognostic factor of oligometastases is considered to maintaining the state of oligo-recurrence. Thus, if the researchers investigate oligometastases, they almost always investigate the data of oligo-recurrence besides oligometastases or sync-oligometastases. However, the authors did not analyze the treatment result of oligo-recurrence and did not mention the status of primary site (controlling or active). This point is very important. The authors should re-analyze and comment and discuss the oligo-recurrence of the lung tumors.

Response: Yes, we also think that what you mentioned is a very important point for survival but not always important for local control. We added the status of the primary site (All sites were controlled. Of the 37 cases, 35 cases underwent surgical resection, another case was controlled by chemoradiation for esophageal cancer and the other case was controlled by transarterial chemoembolization for hepatocellular carcinoma.), and we added this issue to the manuscript. Although analysis for survival with emphasis on the maximizing benefit/toxicity ratio was limited by this issue, the analysis for local control was important. In view of local therapy, we did not restrict a metastatic lesion to be a state of oligo-recurrence. Because SBRT has great advantages represented by minimally invasiveness and minimally interruption of other treatments, SBRT could be potentially applied to many metastatic lesions. For example, we sometimes experienced a situation in which the cancer showed heterogeneous sensitiveness to chemotherapy, and the metastatic lesion that was resistant to chemotherapy could be a target of local therapy. As systemic therapy improves, such situations will increase until systemic therapy alone is effective enough to cure cancer. So, we think that the possibility of radioresistance of metastatic tumors in our results, whether the tumor is an oligo-recurrence, oligometastasis or not, is very important.

3. Oligometastases and oligo-recurrence is well-written in the papers as follow. The authors had
better cite these papers and explain.


Oligometastases or oligo-recurrence of lung tumors have been studied by other groups. The authors cite and discuss this study and previous studies.


Response: Yes, we corrected the manuscript and we cited some of the recommended reports. However, the problem was that all of the recommended reports were from Japan, and our discussion (before revision) was indicated by another referee that our discussion did most reflect on Japanese data and disregard others. Although there are few reports on oligo-recurrence from the USA and Europe in comparison with reports from Japan, we could not cite all of the recommended reports.