Peer review file

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Reviewer A

Comment 1: The authors have excluded patients if follow-up details were not available for them. While the study is trying to evaluate toxicity and the efficacy of a 'novel' schedule of SBRT, analysis of data from consecutive patients treated with this technique and fractionation is important. For eg. It can happen that the treatment you used could be ineffective and many patients died before coming for their 1st follow-up. This can especially be true for elderly and frail patients receiving mediastinal radiation. If such patients are systematically excluded then this technique can erroneously appear to produce better results (selection bias).

Reply 1: We agree that selectively excluding patients could lead to selection bias. We have added that "Patients were also not excluded from the study if they had a documented death but a lack of clinical or imaging follow-up. In such a case, the patient would be included in the survival analysis but not in the assessment of local control." In this way, we sought to maintain an accurate assessment of the survival of patients included in the study; however, without clinical or imaging follow-up, they could not have accurate assessment of toxicity or local failure. For this reason, such patients would be excluded from those analyses.

Changes in the text: "Patients were also not excluded from the study if they had a documented death but a lack of clinical or imaging follow-up. In such a case, the patient would be included in the survival analysis but not in the assessment of local control" (page 3 lines 67-69).

Comment 2. Since this study is literally a mix bag of nearly all types/ stages of NSCLC patients there can be, it becomes very difficult to follow the type of cohort being studied. A detailed CONSORT diagram would be critical for this manuscript to become lucid.

Reply 2: We agree that this was unclear in the manuscript, and we have clarified the patients that were included: "The initial patient set was developed to include all patients treated from 2007 through 2014 who met the above criteria. This resulted in an initial set of 105 lesions treated in 85 patients. A separate review of all treated SBRT cases

from 2007 through 2018 was performed to additionally include all patients with treatments targeting the hilar or mediastinal regions. This resulted in the addition of 30 patients with 43 treated lesions to the dataset." The treatments targeting the hilar and mediastinal regions were recorded separately and, therefore, required a different set of search criteria to identify the cases. However, the authors felt that their inclusion in this cohort would be useful in assisting in an analysis of the stage 3 and node-positive patients treated with SBRT. We felt that their inclusion more completely described the outcomes of our institutional clinical practice.

Changes in the text: "The initial patient set was developed to include all patients treated from 2007 through 2014 who met the above criteria. This resulted in an initial set of 105 lesions treated in 85 patients. A separate review of all treated SBRT cases from 2007 through 2018 was performed to additionally include all patients with treatments targeting the hilar or mediastinal regions. This resulted in the addition of 30 patients with 43 treated lesions to the dataset" (page 3 lines 71-75).

Comment 3. Most of the ethics committees recommend to obtain IRB clearance even for retrospective studies when accessing/studying patient data for clinical outcomes. I would like to know the reason for exemption provided for this study.

Reply 3: In this case, the authors obtained an exemption by the institutional review board to complete this analysis, due to the retrospective nature of the study. A full presentation of the methodology for completing such a retrospective nature was previously provided to the institutional review board, allowing for this exemption to be provided to follow this previously established protocol. The authors followed all recommended institutional protocols to conduct the research in an ethical manner while maintaining patient confidentiality. All methodology was conducted in accordance with the tenets of the institutional review board. We added to the text that the exemption was "due to the retrospective nature of the study and the establishment of a previous protocol for conducting retrospective studies."

Changes in the text: "…due to the retrospective nature of the study and the establishment of a previous protocol for conducting retrospective studies" (page 3 lines 70-71).

Comment 4. In the patient outcomes we would like the authors to clarify if local control

was evaluated even after detection of distant metastases or was the patient censored at that event. Similarly, was regional control evaluated even after distant metastases.

Reply 4: Local and regional control were still assessed even after distant failure. We have added this to the text: “Local control was still evaluated even after the detection of regional of distant metastases. Similarly, regional control was still assessed even after the detection of distant metastases, as opposed to censoring at the time of distant failure.”

Changes in the text: “Local control was still evaluated even after the detection of regional of distant metastases. Similarly, regional control was still assessed even after the detection of distant metastases, as opposed to censoring at the time of distant failure” (page 5 lines 130-132).

Comment 5. The hilar dose fractionation used was considerable low and may also be one of the main reasons for early and higher regional failures. However, it is unclear whether the regional failures were chiefly contributed by those who had regional nodal involvement prior to treatment or node negative patients. This is another important piece of information that will help to guide the hypothesis.

In the discussion the authors have stated that use of lower doses of radiation has led to equally good survival outcome and that low dose RT regimen should be studied prospectively. I find this inference misplaced. Lower doses of RT were typically used for regional radiation which probably led to early recurrences and thus dose-escalation may be more appropriate in that setting.

Reply 5: The doses used in this setting are generally lower than those used in other historical series. This was generally done in an effort to minimize toxicity. We agree that this is valuable information to the add to the manuscript. We have added that “Of these, 11 occurred in patients with stage 3 disease, as opposed to only 3 and 6 cases for stage 2 and stage 1 patients, respectively.”

In the discussion, we recommended a consideration for further study of increased inter-fraction time in an effort to reduce toxicity, and we meant to mention that the lower treatment doses may have been a contributing factor to this reduced toxicity, as well. We did not intend to claim that we were recommending for the study of lower treatment doses with a suggestion of comparable survival, and we apologize for this confusion. We have clarified this section by adding that further study is recommended to assess

the role of "increased inter-fraction time in this setting as a potential tool to reduce toxicity in high-risk patients."

Changes in the text: "Of these, 11 occurred in patients with stage 3 disease, as opposed to only 3 and 6 cases for stage 2 and stage 1 patients, respectively" (page 7 lines 173-174).

"It is likely that the increased inter-fraction time (and potentially the lower treatment doses) used in this analysis contributed to the 0% rate of grade ≥3 toxicity. These outcomes for locally-advanced NSCLC indicate that SBRT may prove beneficial for carefully selected patients (particularly with N2 or N3 disease, rather than large tumor size). Further study is recommended to assess for the role of inter-fraction time in this setting as a potential tool to reduce toxicity in high-risk patients" (page 10 lines 250-255).

Comment 6. Another surprising finding was that prior surgery predicted for increased chances of disease progression. The authors have mentioned in their discussion that this is intuitive and pointed towards advanced disease. While this may be true for chemotherapy, it is certainly not so for surgery as surgery is usually considered for early disease rather than advance disease. Authors need to provide some explanation for the same.

Reply 6: We have changed this sentence to read "advanced or recurrent disease," instead. The authors had meant to indicate that prior thoracic surgery was an indicator of prior treatment, and, therefore, an increased likelihood of advanced or recurrent disease. In the case of prior thoracic surgery, patients presenting for SBRT would most likely have had disease recurrence, and salvage SBRT may represent a different clinical scenario than SBRT in the setting of primary disease. We have also added another reference to better describe this point.

Changes in the text: "…advanced or recurrent disease (21). In the case of prior thoracic surgery, patients presenting with recurrent disease may represent a different clinical scenario for SBRT than patients presenting with primary disease (29)" (pages 10-11 lines 275-277).

Comment 7. Another surprising finding that the authors fail to justify is the improved outcomes with previous course of radiation. It is also unclear if this means radiation to

the same site or a completely unrelated site. This is also important as the median dose in the previous RT regimen was 57Gy in median 5 fractions (indicating SBRT). So it is unclear if this series is reporting re-SBRT of centrally located tumors.

Reply 7: We agree that this result is complex and requires further discussion. The prior radiation therapy group in this study considers a heterogenous groups of patients with prior thoracic radiation therapy including SBRT or concurrent chemoradiation with 60 Gy in 30 fractions. For this reason, we have recommended that these results be interpreted with caution, and we encourage further study into thoracic reirradiation.

Changes in the text: "While it is possible that incorporating increased inter-fraction time could serve to improve toxicity outcomes in cases of reirradiation, further study is needed. The prior courses of radiotherapy included in this cohort were heterogenous, including other courses of SBRT as well as concurrent chemoradiation to 60 Gy in 30 fractions. These significant differences indicate that these findings concerning reirradiation should be considered with caution" (page 11 lines 285-289).

Comment 8. The purpose of dividing the tumors into synchronous lesions, hilar target and central non hilar target was unclear and can be clarified in the methods section

Reply 8: The purpose of this distinction was to include these variables in the multivariate analysis to assess for their potential predictive power for local control. In this case, the term "hilar" was changed to "nodal," as per the recommendation of Reviewer B.

Changes in the text: "The presence of synchronous lesions, as well as the target (nodal vs. non-nodal), were considered as potential predictive factors for local control in the multivariate analysis" (page 5 lines 118-119).

Comment 9. Please clarify the term synchronous lesions whether in the same lobe, different lobes or different lungs in the methods section.

Reply 9: This definition was added to the methods: "Synchronous lesions were defined as two or more lesions present in a patient's lungs. This included two lesions within the same lobe, different lobes, or different lungs."

Changes in the text: "Synchronous lesions were defined as two or more lesions present in a patient's lungs. This included two lesions within the same lobe, different lobes, or different lungs" (page 5 lines 116-118).

Comment 10. SBRT is not a standard treatment for advanced or recurrent disease and therefore great emphasis should be given on the reasons for using it outside of a clinical trial. The reasons provided for using SBRT in these patients are 1. primary cancer 2. recurrence, and 3. not surgical candidate. Out of these only the reason number 3 is self-explanatory. Authors should clarify this

Reply 10: We have added a brief paragraph to the methods concerning this point: "SBRT is not considered the standard of care for advanced or recurrent disease. Patients treated with such disease with SBRT in this study generally were considered to be high-risk candidates for whom concurrent chemoradiation was considered to be a suboptimal choice. Many of these individuals had received prior treatment or declined these more standard treatment approaches, due to concerns regarding toxicity."

Changes in the text: "SBRT is not considered the standard of care for advanced or recurrent disease. Patients treated with such disease with SBRT in this study generally were considered to be high-risk candidates for whom concurrent chemoradiation was considered to be a suboptimal choice. Many of these individuals had received prior treatment or declined these more standard treatment approaches, due to concerns regarding toxicity" (page 4 lines 105-108).

Minor issues:

Comment 1. A surprising finding was that patients that underwent a biopsy confirmation had better outcomes. This may just be a spurious finding but merits discussion if included in the results section.

Reply 1: We had initially not included this result in the discussion because it did not meet statistical significance on multivariate analysis. Even so, we have added the following to the discussion: "Patients who obtained a biopsy trended towards improved overall survival. This may merely be the result of patients with fewer medical comorbidities having an increasing likelihood of obtaining a biopsy, and these patients have improved overall survival, irrespective of their lung cancer."

Changes in the text: "Patients who obtained a biopsy trended towards improved overall survival. This may merely be the result of patients with fewer medical comorbidities having an increasing likelihood of obtaining a biopsy, and these patients have improved overall survival, irrespective of their lung cancer" (page 10 lines 271-274).

Comment 2. The table shows that 111 patients underwent Pre-SBRT evaluation with PET and certainly 111/115 is not 75%. Please rectify.

Reply 2: The number 111 indicates that 111/148 lesions (75%) were assessed with PET prior to treatment. We have changed the word “treatments” to “lesions” to improve readability.

Changes in the text: “Lesions” with pre-treatment PET (page 19 line 415).

Comment 3. Median longest dimension in the table needs to be qualified whether it includes nodes and primary or only primary.

Reply 3: This included nodes and primary disease. This has been added with an asterisk to the table.

Changes in the text: “*This includes nodes and primary disease” (page 19 line 415).

Reviewer B

Suggestions:

Comment 1: The most novel aspect of this work is using SBRT for stage 3 disease (as SBRT for central early-stage node-negative lung cancer has been well-established, and the decreased toxicity found by doing it 1-2 times per week isn't too convincing given relatively short follow-up). I would consider specifically focusing this work on the stage 3 patients (or at least node-positive patients) rather than splitting attention across all stages. Did these stage 3 receive RT alone (i.e. no concurrent chemo or immunotherapy, or also no systemic therapy sequentially either)?

Reply 1: We agree that we should more strongly emphasize the discussion concerning stage 3 disease. We have added phrases to the abstract, introduction, and conclusions to this effect.

We have also added additional information to better characterize this group. In the methods, we added that: “Since many of these patients were treated prior to the emergence of data concerning the benefits of immunotherapy, this data was not recorded.” Further, we added the following in the results section: “The stage 3 group consisted of 27 patients and 42 treated lesions. Of these, only 1 treatment involved concurrent chemotherapy, but most treatments involved prior chemotherapy (55%),

thoracic surgery (31%), or radiation (76%). 43% of treatments involved patients with COPD."

Changes in the text: "…including many stage 3 patients" (page 1 line 18).

"Since many of these patients were treated prior to the emergence of data concerning the benefits of immunotherapy, this data was not recorded" (page 5 lines 119-120).

"The stage 3 group consisted of 27 patients and 42 treated lesions. Of these, only 1 treatment involved concurrent chemotherapy, but most treatments involved prior chemotherapy (55%), thoracic surgery (31%), or radiation (76%). 43% of treatments involved patients with COPD" (page 8 lines 204-206).

Comment 2: The authors shorten "hilar and mediastinal" nodes as "hilar." I think this is a bit misleading since it seems like all the patients had N1 disease rather than N2-3 disease as the authors later stated they had a high proportion of. Perhaps could be called "node-positive," "regional node-positive," or something like that rather than "hilar"?

Reply 2: We agree that the use of the word "hilar" is misleading. We had initially selected the word, due to its use in prior literature concerning hilar SBRT. We have replaced it with "nodal," where appropriate (e.g. "nodal" targets, as opposed to "hilar" targets).

Changes in the text: Generally, "hilar" was replaced with "nodal," where appropriate throughout the manuscript, tables, and figures.

Comment 3: Could the authors describe further the distribution of nodal stage, as well as the full range of doses used for node-positive patients? It would also be interesting to see how much dose mattered in control of the node-positive disease itself (i.e. 20 Gy in 5 fractions seems low to sustain durable control). Especially since SBRT this is so non-standard for non-positive disease, it would be helpful for the authors to show what dose constraints they used for planning purposes, as well as the actual doses achieved to structures like esophagus and proximal tracheobronchial tree.

Reply 3: We have added a more complete description of the doses prescribed to the nodal targets in the methods section: "Other dose-fractionation schemes for nodal targets included 36 Gy in 4 fractions or 45 Gy in 3 fractions. In 11 cases, prescription doses of at least 50 Gy were delivered. This was generally done in the setting of

minimal prior treatment and treatments for the hilar lymph nodes (as opposed to other mediastinal targets). Lower dose regimens, such as 15-21 Gy in 3 fractions (n=6), were sometimes utilized, especially in the setting of reirradiation." Unfortunately, more detailed information regarding the distribution of the nodal staging was not collected in the analysis. We have added this point to the limitations paragraph of the study, as we agree that it would enhance the manuscript.

We have added the following information to describe the dose constraints utilized: "Generally, however, a maximum point dose of 105% of the prescription dose was allowed to the esophagus and proximal tracheobronchial tree. Whenever possible, these maximal doses were kept to less than 30 Gy." Further details were difficult assess due to the heterogenous nature of these patients and the impacts of prior treatment to these lesions.

Changes in the text: "Other dose-fractionation schemes for nodal targets included 36 Gy in 4 fractions or 45 Gy in 3 fractions. In 11 cases, prescription doses of at least 50 Gy were delivered. This was generally done in the setting of minimal prior treatment and treatments for the hilar lymph nodes (as opposed to other mediastinal targets). Lower dose regimens, such as 15-21 Gy in 3 fractions (n=6), were sometimes utilized, especially in the setting of reirradiation" (page 4 lines 95-99).

"Additional information to more completely describe the nodal distribution of the nodal targets in this study would have also proven beneficial" (page 1 lines 294-295).

"Generally, however, a maximum point dose of 105% of the prescription dose was allowed to the esophagus and proximal tracheobronchial tree. Whenever possible, these maximal doses were kept to less than 30 Gy" (page 5 lines 110-112).

Comment 4: Why is the SBRT range as low as 5 Gy total? That doesn't strike me as SBRT dosing, so I think it would be important to state upfront what doses the authors would define as SBRT and only include patients who qualify for this definition. Also I think there is a typo in the text of the manuscript (range 5-6, rather than 5-60 listed in abstract and table).

Reply 4: We have added a paragraph to the methods section to more clearly delineate the reasoning for the use of SBRT in advanced and recurrent disease. This paragraph also seeks to address comment 10 from Reviewer A.

We thank you for catching this typo. It has been corrected.

Changes in the text: “SBRT is not considered the standard of care for advanced or recurrent disease. Patients treated with such disease with SBRT in this study generally were considered to be high-risk candidates for whom concurrent chemoradiation was considered to be a suboptimal choice. Many of these individuals had received prior treatment or declined these more standard treatment approaches, due to concerns regarding toxicity. Due to these constraints, relatively lower treatment doses were often used, as well” (pages 4-5 lines 105-109).
“…5-60” (page 6 line 161).

Comment 5: Figure 1 forest plot would be even more clear if there were arrows to the left and right showing how to interpret values >0 or <0 (since most readers may not be as familiar with the log(HR) scale).
Reply 5: We appreciate this suggestion and have added arrows to improve readability of the figure.
Changes in the text: Arrows were added to Figure 1.