Peer Review File

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Reviewer A

Comment 1: Well written report however information on radiotherapy details is missing. There is no description whether this was stereotactic or just conformal hypofractionated palliative radiotherapy.

Reply 1: Considering this comment and your second comment, we agree that "hypofractionated" would be a more standard definition in the USA as several patients were treated with 6-10 fractions. We, however, must state that patients were treated with SBRT protocols in terms of image guidance and motion management.

Changes in the text: We have now added the following information regarding radiation technique (see Page 6, line 136):

Patients were immobilized with upper body vac-lok cushions in an arms-up position. 4D CT scans were acquired using the real-time positioning management (RPM) system (Varian Medical Systems, Palo Alto, CA) to record the breathing trace. Depending on the amplitude of motion and regularity of breathing, a decision to gate treatment was made for each patient. Specifically, if tumor motion was larger than 5 mm, gated treatment centered around exhalation was typically recommended. The ITV (internal target volume) was delineated by a treating physician on the MIP (maximum intensity projection) and on scans of the respiration phases to ensure the ITV encompassed the full range of motion of the tumor within the selected gating window. Dose calculation was performed on a CT scan that averaged the corresponding respiration phases selected for treatment. Patients were treated with either 2-4 arc VMAT or 5-8 field IMRT. Plans were commonly normalized to deliver 100% prescribed dose to 95% of the PTV, or to at least 98% of GTV or ITV. An on-board imaging system was used for image guidance according to clinically used SBRT protocols. Orthogonal kV (kilovoltage) images were used to straighten and align patients, followed by a KV cone-beam computed tomography scan to align the tumor. For gated treatments, real-time fluoroscopy images were used to confirm the tumor motion during the selected gating window was encompassed by the ITV. Gated treatment using the real-time positioning management system was used in 74 of 92 treatments.

Homogeneity index, defined as the ratio of the maximum point dose to the prescribed dose, was (mean, standard deviation) 1.19±0.09. Conformity index, defined as the ratio of the volume receiving prescribed dose to the PTV volume was 1.02±0.08.

Comment 2: Please provide information on the prescription isodose line (and conformity and homogeneity index) and if the dose was prescribed at more than 90% isodose line, then consider changing the title to hypofractionated rather than stereotactic. Otherwise nicely written manuscript which should get published and it would add value to the existing literature.
Reply 2: Thank you for this comment. We have now included additional information regarding radiation technique including information regarding prescription isodose lines as detailed in the response above. Additionally, we have changed the title and included a statement regarding our use of the term SBRT interchangeably with hypofractionated. (see Page 7, line 123)
Changes in the text: All patients underwent standard SBRT protocols as described below, though given that we allowed patients with up to 10 fractions this could also be defined as hypofractionated radiotherapy given the standard USA definition of SBRT representing 5 fractions or less.

Reviewer B
This retrospective review titled "Stereotactic Body Radiation Therapy as Palliative Management for Symptomatic and Local Control of Advanced Thoracic Malignancies" is an important topic to publish to help guide clinicians' optimal radiation dose regimens for effective palliation of advanced thoracic malignancies. I would recommend the following:

Comment 1. Consider renaming title to "conformal hypofractionated radiation" rather than SBRT bc 5 Gy per fraction with 10 fractions is not typical SBRT dose. This may also deter reviewers from associating high cost for palliation. This dose regimen can likely be safely delivered with conformal 3D plan as long as dose constraints met. Since only 26% cohort received 40 Gy/5 fxn, others treated more like hypofractionated regimen.
Reply 1: Thank you for this comment. We have renamed the manuscript (see Page 1, line 1) Hypofractionated Radiation Therapy as Palliative Management for Symptomatic and Local Control of Advanced Thoracic Malignancies. Though we have now clarified as per response above to Reviewer A that this was not conformal radiotherapy based on the technique utilized for treatment. Though we agree that 3D conformal techniques could still likely meet dose constraints for several patients included on this study and would be reasonable to mitigate costs of treatment.
Changes in the text: Hypofractionated Radiation Therapy as Palliative Management for Symptomatic and Local Control of Advanced Thoracic Malignancies (Page 1,

Line 1).
All patients underwent standard SBRT protocols as described below, though given that we allowed patients with up to 10 fractions this could also be defined as hypofractionated radiotherapy given the standard USA definition of SBRT representing 5 fractions or less. (Page 7, line 127)

Comment 2. If you have the dose constraints to bronchial tree, central structures, heart, lung, total lung, esophagus, other normal critical structures, please include as this would be very helpful for clinicians.
Reply 2: Thank you for this comment. We have now included dose constraints which were used in table 3 (see Page 22).
Changes in the text: Dose constraints used in plan optimization for selected organs at risk (OAR) are described in Table 3.

Comment 3. Please provide more toxicity data (if you have it): pulmonary toxicity/fibrosis, pneumonitis, esophagitis, strictures, or pain.
Reply 3: Thank you for this comment. Unfortunately, due to the retrospective nature of this review with very heterogenous follow up we did not feel that the data that we were able to obtain through review meaningfully adds to existing literature. Given the known safety associated with much higher biologic doses of SBRT in the curative setting, we did not expect to find significant toxicities that would meaningfully add to existing prospective literature documenting toxicities. We have now included the toxicity data that we have available, though also included a comment regarding the limitations when evaluating this data.

Changes in the text:
Toxicity
Among our entire cohort of 76 patients, we found 9 patients who had reported toxicities at follow up. This included 4 patients with dysphagia (5%), 2 with dermatitis (3%), 2 with pneumonitis (3%), and 1 with chest wall pain related to prior RT. (Page 12, line 256)
We believe that our study is limited in terms of toxicity reporting based on poor follow up and likely underreporting of acute symptoms which may have self-resolved by the time of first follow up post treatment. We would encourage future studies to evaluate toxicity data associated with SBRT in advanced lung malignancies such as pulmonary fibrosis, pneumonitis, esophagitis, and strictures which would be far more likely to be helpful when evaluated in the prospective setting. (Page 13, line 294)

Reviewer C

Thought-provoking, small, institutional cohort study assessing palliative "SBRT" for non-curative NSCLC and/or pulmonary/mediastinal metastases, demonstrating reasonable local control and symptom stability/palliation. The cohort is somewhat heterogeneous in terms of primary histologies and dose/fractionation regimens utilized, which is to be expected in a study of this type. While some of the regimens utilized are not heavily ablative (BED's well under 100) and would not meet the USA definition of SBRT (10-fraction regimens utilized), this is still valuable in that it provides evidence for shorter-course, higher-dose regimens for palliation in this patient population, which can be convenient and relatively effective options for these patients. See below for specific comments/questions:

Intro

Comment 1. Would also cite Pielkenrood BJ et al. (IJROBP 2021) and Hoskin P (IJROBP 2021) when discussing controversy of pain response after SBRT vs. conventional RT for bone mets

Reply 1: Thank you for suggesting these relevant articles on pain response in spinal metastases. Pielkenrood's IJROBP paper has now been included when discussing the controversy of pain response after SBRT vs conventional RT for spinal and bone metastases as well as Dr. Hoskin's editorial.

Changes in the text:

In the realm of spinal and bone metastases, recent studies have assessed the role of SBRT in the palliative setting with overall mixed results in pain relief response (13-17). (Page 4, line 95)

The differences among these trials have resulted in an ongoing debate without clarity on the role for SBRT in palliation (19). (Page 13, line 281)

Comment 2. Would clarify the "advantage" of the shorter treatment courses and give citation if possible beyond the obvious—patient convenience? Patient satisfaction? Departmental resources/staffing? Any clinical endpoints?

Reply 2: Thank you for this suggestion. Shorter treatment courses have obvious benefits to patients in terms of convenience and likely patient satisfaction due to limited visits. Additionally, since most patients in our study had metastatic disease (When concurrent chemoradiation is not recommended for palliation – Moeller PRO 2018) the shorter course also holds the advantage of limiting delay to subsequent systemic therapies following a more protracted course of palliative radiation. Because the goal is overall symptom palliation rather than elongated survival outcomes, shorter courses allow for prioritization of patient's time away from the hospital and

overall convenience. This was originally delineated in our discussion (originally on Page 11, line 248), but we will further describe the advantage of higher biologic doses in shorter courses in the introduction.
Changes in the text: Hypofractionated radiotherapy has the advantage of providing dose escalated radiotherapy as well as higher overall biologic dose without a protracted treatment course which is much more convenient for patients and limits delay to subsequent systemic therapies. (Page 6, line 101).

Comment 3. In the sentence "…highly conformal treatment which spares…", please correct "spares" to "spare," "has the potential" to "have," and "patient's" to "patients."
Reply 3: Thank you for this grammatical correction. These changes have been incorporated into their respective sections
Changes in the text: Additionally, SBRT allows for highly conformal treatments which spare adjacent normal tissues and have the potential to increase the therapeutic ratio in patients receiving treatment. (Page 6, line 104)

Comment 4. In the last paragraph, the first two sentences are very redundant. Please condense into one sentence.
Reply 4: Thank you for this careful review. The first two sentences have been condensed to effectively demonstrate the purpose of our study
Changes in the text: The aim of our study is to evaluate the efficacy of SBRT in the palliative management of advanced thoracic malignancies ineligible for curative-intent therapy for both symptom management and durable control of intrathoracic tumors. (see Page 6, line 107)

Materials and Methods
Comment 5. Please elaborate on "intra-thoracic disease." I know you lay this out in the Results section, but I would just add that intra-thoracic disease included parenchymal, perihilar, and mediastinal lesions.
Reply 5: Thank you for this suggestion. The intra-thoracic tumors ineligible for curative intent radiation were described further in the Methods section in addition to the Results section.
Changes in the text: All patients had thoracic tumors involving parenchymal, perihilar, and mediastinal lesions that were not candidates for curative intent radiation due to comorbidity, metastatic disease at presentation, inoperable advanced stage with poor performance status, and/or prior radiation treatment. (see Page 6, line 122).

Comment 6. Please describe the simulation, setup, and IGRT techniques that were utilized to deliver SBRT.
Reply 6: Thank you for this comment. The simulation, setup, and IGRT techniques have been incorporated into the Methods section (see Page 7, line 137).
Changes in the text:
Patients were immobilized with upper body vac-lok cushions in an arms-up position. 4D CT scans were acquired using the real-time positioning management (RPM) system (Varian Medical Systems, Palo Alto, CA) to record the breathing trace. Depending on the amplitude of motion and regularity of breathing, a decision to gate treatment was made for each patient. Specifically, if tumor motion was larger than 5 mm, gated treatment centered around exhalation was typically recommended. The ITV (internal target volume) was delineated by a treating physician on the MIP (maximum intensity projection) and on scans of the respiration phases to ensure the ITV encompassed the full range of motion of the tumor within the selected gating window. Dose calculation was performed on a CT scan that averaged the corresponding respiration phases selected for treatment. Patients were treated with either 2-4 arc VMAT or 5-8 field IMRT. Plans were commonly normalized to deliver 100% prescribed dose to 95% of the PTV, or to at least 98% of GTV or ITV. An on-board imaging system was used for image guidance according to clinically used SBRT protocols. Orthogonal kV (kilovoltage) images were used to straighten and align patients, followed by a KV cone-beam computed tomography scan to align the tumor. For gated treatments, real-time fluoroscopy images were used to confirm the tumor motion during the selected gating window was encompassed by the ITV. Gated treatment using the real-time positioning management system was used in 74 of 92 treatments.

Comment 7. Was any RT delivered concurrently with systemic therapy?
Reply 7: None of the patients in this study received concurrent chemotherapy. We have now included a statement in the methods to this effect (see Page 11, line 219).
Changes in the text: None of the patients in this study received concurrent chemotherapy.

Results
Comment 8. Regarding the breakdown of the distribution of the lesions, please add how many lesions qualified as “central” or “ultra-central” lesions, and provide the dose/fractionation regimens used for these lesions.
Reply 8: Thank you for this comment. We have re-reviewed our data and assessed the dose and fractionation specifically for lesions which would have met standard definitions of either central or ultracentral and have now included this in the results.

(Page 10, line 209)
Changes in the text: There were 37 patients with lesions which would be defined as "central" or "ultracentral." Among this cohort there was an even distribution of fractionations utilized which included 30 Gy in 5 fractions (32%), 40 Gy in 5 fractions (24%), 50 Gy in 10 fractions (24%), and 25 Gy in 5 fractions (19%).

Discussion

Comment 9. Many of the regimens used were not to ablative doses, and/or would not meet the USA definition of SBRT (e.g. 10-fraction regimens used), so this should be noted.

Reply 9: Thank you for this comment. We have changed our title to "hypofractionated" to accurately describe all the doses included in our analysis (see Page 1, line 1). Additionally, we noted previously that our analysis only included patients who were not treated with a curative intent to lesions being irradiated (see Page 7, line 122).

Changes in the text: Hypofractionated Radiation Therapy as Palliative Management for Symptomatic and Local Control of Advanced Thoracic Malignancies

Comment 10. 9-10% progression at 1-6 months after SBRT is relatively high (compared to curative-intent lung SBRT regimens). Again, would note the difference here in that the doses used were often lower BED than curative-intent regimens, at least partially explaining the relatively higher rates of early progression.

Reply 10: Thank you for this emphasis on the not insignificant progression rate. The difference in the doses used being often lower BED than curative intent RT regimens have been incorporated into our discussion (see Page 14, line 284).

Changes in the text: The small rate of progression at 1-6 months is partially expected due to the non-ablative doses in the non-curative setting.

Figures/Tables

Comment 11. Table 3: Would explicitly state "Lung" dose-volume metrics. Mean lung is mentioned at the end of the sentence, but it would be more clear If it was in the beginning. Also you refer to the table in the caption as Table 2, but it is Table 3. Please correct.

Reply 11: Thank you for this suggestion. Table 3 caption has been modified to explicitly state "lung dose-volume metrics" rather than solely describing it in the last sentence. Due to separate feedback regarding table 2, this table is now table 2. (see Page 22, line 425).

Changes in the text: Lung dose-volume metrics for plan assessment for both physical dose and equivalent dose in 2 Gy fractions (EQD2).

Reviewer D

General comments

The authors performed a single-institutional retrospectively cohort study without control arm. They concluded SBRT has the advantage of higher biologic dose without protracted course for patients with limited prognosis. SBRT-treated patients showed significant symptom palliation and long-term control. Palliative SBRT represents a reasonable treatment modality for incurable thoracic malignancies.

Palliative SBRT has been used for vertebral metastasis. Palliative SBRT for other metastasis will be tried in the future, and focusing point of the current study has value; however the current study had flaws.

Comment 1. Originality, and Importance and Research question

Please describe what was already known, and what was not known using relevant references in the Introduction section. The descriptions of the first paragraph and the third paragraph in the discussion section is better to be mentioned in the Introduction section. The comparison to previous reports may reveal the originality of the current study.

Reply 1: Thank you for this thoughtful suggestion. The beginning half of the third paragraph in the discussion has been incorporated and condensed into the first paragraph of the introduction. Previous reports of palliative SBRT have been referenced in both the introduction and discussion to further emphasize the originality of this current study in thoracic malignancies.

Changes in the text: Currently, there is minimal data regarding the role of SBRT versus conformal radiation for the palliation of symptoms due to malignancy. Additionally, a conflicting body of evidence surrounds the role of a higher biologic dose for an ideal palliative radiation dose for symptomatic thoracic malignancies… Most literature assessing the efficacy of SBRT has been in the curative or oligometastatic setting (4-12). In the realm of spinal and bone metastases, recent studies have assessed the role of SBRT in the palliative setting with overall mixed results in pain relief response (13-17). However, no studies have yet explored the role of palliative SBRT in thoracic malignancies. (see Page 5, line 84)

Comment 2. Please describe the problems of hypofractionated conventional

radiotherapy. The problems of conventional radiotherapy may reveal SBRT matter to clinicians, researchers and patients.
Reply 2: Thank you for this suggestion. As we described above (Reviewer C, comment 2), the problems associated with conventional RT is that a significant portion of patients receive protracted treatment courses due to the conflicting literature which demonstrates that there is potentially a group of patients who stand to benefit from a higher biologic dose of RT. In order to obtain that higher biologic dose with conventional radiotherapy, patients often have more protracted radiotherapy courses which stands to delay their time to treatment with systemic therapies and potentially mitigate any survival benefit that may be associated with RT in addition to any palliative benefit. This has been emphasized in the introduction (see Page 6, line 99).
Changes to the text: (See response to reviewer C, comment 2 above)
SBRT has the advantage of providing dose escalated radiotherapy as well as higher overall biologic dose without a protracted treatment course which is much more convenient for patients and limits delay to subsequent systemic therapies. Additionally, SBRT allows for highly conformal treatments which spare adjacent normal tissues and have the potential to increase the therapeutic ratio in patients receiving treatment.

Participants
Comment 3. I think that it is better to exclude the patients with Stage I, II, III. Prognosis and effectiveness of local control is different.
Reply 3: Thank you for this suggestion. We considered this, though because the purpose of our study is to study the efficacy of SBRT in symptom palliation and long-term local control of thoracic malignancies rather than solely lung malignancies that are stage IV, we have chosen to include all stages of thoracic malignancies which were ineligible for curative intent treatment due to either stage (stage IV) or comorbidities (advanced age, prior definitive therapy, etc.). We acknowledge that this limits ability to assess prognosis and survival of the entire cohort which is not a primary endpoint of our study.
Changes to the text: N/A

Methods
Comment 4. Adverse events should be collected.
Reply 4: Thank you for this comment. Unfortunately, due to the retrospective nature of this review with very heterogenous follow up we did not feel that the data that we were able to obtain through retrospective review meaningfully adds to existing

literature. Given the known safety associated with much higher biologic doses of SBRT in the curative setting, we did not expect to find significant toxicities that would meaningfully add to existing prospective literature documenting toxicities. We have now included the toxicity data that we have available, though also included a comment regarding the limitations when evaluating this data.

Changes in the text:
Toxicity
Among our entire cohort of 76 patients, we found 9 patients who had reported toxicities at follow up. This included 4 patients with dysphagia (5%), 2 with dermatitis (3%), 2 with pneumonitis (3%), and 1 with chest wall pain related to prior RT. (Page 12, line 256)

We believe that our study is also limited in terms of toxicity reporting based on poor follow up and likely underreporting of acute symptoms which may have self-resolved by the time of first follow up post treatment. We would encourage future studies to evaluate toxicity data associated with SBRT in advanced lung malignancies such as pulmonary fibrosis, pneumonitis, esophagitis, and strictures which would be far more likely to be helpful when evaluated in the prospective setting. (Page 15, line 312)

Comment 5. Structured descriptions of statistical analysis are needed.
Reply 5: Thank you for this comment. We have included a sequential description (see Page 9, line 176).
Changes to the text:
Summary statistics are reported for patient demographic and clinical variables as detailed in Table 1, where baseline continuous data are compared with student's t-test, single categorical data with 2-proportion Z test, and multi-group categorical data compared with Chi-square test. Patients were divided into primary thoracic (Cohort P) and metastatic other primary (Cohort M). Descriptive statistics, including mean and proportion, for age at consult, type of treatment planning, radiation dose, fractionation scheme, previous chemotherapy, symptom response to SBRT, and radiologic response to SBRT. The Kaplan-Meier method was used for overall local control estimates with censoring performed for patients lost to follow-up. All statistical analyses were performed with statistical software R, version 3.5.1.

Comment 6. Please clearly describe endpoints.
Reply 6: Thank you for your suggestion. Our primary endpoints are symptom response and local failure as seen on CT imaging via RECIST criteria (see Page 8;

line 167)
Changes to the text: Additionally, primary endpoints assessed included symptom response to treatment and local control. Symptom response was determined by a 0-4 score based on 1 point for documented symptoms of hemoptysis, chest pain, shortness of breath, or cough at time of consult and whether these improved at the first follow-up between 1-6 months post-treatment based on the same 0-4 scoring system. Patients who had none of these symptoms at follow-up were considered to have a complete response and those with any improvement in symptoms were considered to have a partial response. Lastly, we reviewed follow-up CT imaging to evaluate for local control using RECIST criteria (18).

Results

Comment 7. Table 1 should be mentioned in the Result section.
Reply 7: Thank you for this comment. Table 1 has been mentioned in the Methods and now the Results section (see Page 10, line 199).
Changes in the text: 57% (n=52) of those thoracic lesions were of primary lung origin (Cohort P) while 43% (n=40) were metastatic from other sites (Cohort M) as described in Table 1.

Comment 8. The details of symptoms should be described in Table 1.
Reply 8: Thank you for pointing out areas areas where our tables could provide further clarity in addition to information available in the text. We have now added detailed symptoms prior to radiation therapy to our table 1 (Page 20, line 407)
Changes to the text: See table 1.

Comment 9. I think that Table 2 and 3 is not necessary.
Reply 9: We have now removed the prior Table 2 based on this feedback since the same information is available in the text. However, we feel that it would be helpful to continue to leave Table 3 (now Table 2) available for reference for dose volume metrics to be able to compare our dose metrics to those of other studies and this information is much easier to review in a table format as opposed to the text.
Changes to Text: Table 2 removed.

Comment 10. I am afraid that the results of the multivariate analysis were not mentioned in the Result section.
Reply 10: After careful consideration, we believe including this analysis does not contribute significantly to the purpose of this manuscript. We describe SBRT as a method of local control and palliation. Including the results of our survival

multivariate analysis may fall outside of the scope of this current study and draw focus away from our primary endpoints.
Changes in the text: Removed the description of multivariate analysis from the methods section. (Page 10, line 191)

Comment 11. The value of Stage (at the time of RT) in the cohort M is blank in Table 1.
Reply 11: Thank you for this observation. Stage was removed from cohort M because, by definition, all lesions included in cohort M are metastatic lesions to the thoracic cavity indicating they are all stage IV by definition. Clarification has been noted (see Page 18, line 387)
Changes in the text: Table 1 now includes n=40 (100%) for cohort M to emphasize their stage (see Page 21, line 410)

Comment 12. I cannot understand the meaning of the p-value of Stage (at the time of RT) in Table 1.
Reply 12: Thank you for this comment. We included this p-value for completeness of the table, comparing whether there was a significant difference between stage distribution of lung and non-lung malignancy. Understandably, non-thoracic malignancies with lung lesions will necessarily be Stage IV, and there will be a significant difference between the two groups for stage distributions. We have now consolidated all patients in Cohort M into one group and omitted this comparison in Table 1 for clarity.
Changes in the text: Condensed stage distribution for Cohort M into one group and replaced ‘p<0.01’ with ‘-‘ in Table 1. (see Page 20, line 410)

Comment 13. Figure 1 is not necessary. Instead, a symptom controlled curve is better to be described.
Reply 13: We appreciate this feedback and considered this when initially developing our manuscript. We ultimately felt that figure 1 is a more reliable indicator of long-term success of the treatment than symptom reporting over time. While ideally, we would be able to provide a curve showing control of symptoms over time, in practice this is difficult to do reliably as part of a retrospective study. Local control of tumors will be more likely to demonstrate whether the treatment itself continues to be effective and is more reliably available through CT imaging (see separate comments regarding toxicity reporting). Additionally, if a patient were to have initial improvement in their pain and then have recurrent pain 6 months later this is not necessarily a true “failure” for purposes of a symptom control curve if the index lesion remains controlled and pain is at a different site. Therefore, we feel that the

current figure 1 is the best surrogate for assessment of “control” over time.
Changes to the text: N/A

Interpretation and conclusions

Comment 14. Table to show the effectiveness and safety in the previous studies of SBRT and conventional radiotherapy for palliation and the current one is useful.
Reply 14: Thank you for outlining an opportunity to provide further clarity to research which has already been performed in this arena. (Page 23, line 440)
Changes to the Text: An additional table 4 has been provided outlining these trials.