

Peer Review File

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First Round of Review Comments

Reviewer A, Comment 1: “The introduction should be more crisp and explain why this study is important rather than delve into the the controversy of oligometastatic disease and its management. That can be edited better.”

- Reply 1: Thank you for this suggestion. We agree the introduction needed to be clearer and have made a number of edits to the introduction. Multiple changes were made to all 4 paragraphs of the introduction.

Reviewer A, Comment 2: “The manuscript has several grammatical errors and some that are plain oversight. This appear randomly at several places in the manuscript. The authors are requested to run the manuscript by a language editor or an expert.”

- Reply 2: Thank you for pointing this out. We have closely reviewed the manuscript text and ensured correction of typographical errors. These changes are highlighted throughout the tracked changes version of the manuscript.

Reviewer A, Comment 3: “It is important to know if there were more deaths within 30 days of receipt of any treatment and therefore we would recommend including those patients in the study. Alternatively justify why this cohort was eliminated and at least add a statement that mentions that addition of these patients in the study impacted the results in any way.”

- Reply 3: Thank you for this comment. We would like to emphasize that we excluded patients within 30 days of diagnosis, and not treatment. We reviewed the excluded cases and found that none of these patients received cancer-directed treatment, so they would not have been eligible for the study even if they survived longer. Hence, their exclusion had no impact on the results. We have edited page 5, lines 16 to clarify this.

Reviewer A, Comment 4: “Page 5 line 17 is incomplete and also please define what is HMO?”

- Reply 4: Thank you for pointing this out. This sentence has been revised (page 7, lines 22-23). HMO (health maintenance organization) is now defined where it first appears, on page 5, line 18.
- Changes in text: “We then used linear models with matched group as a random effect to compare hospitalizations and their associated costs.” “Patients were also excluded if they were enrolled in a health maintenance organization (HMO) during the 12 months before and after diagnosis in order to ensure complete Medicare claims record.”

Reviewer A, Comment 5: “Among the several limitation of this study an important limitation is that you were not able to retrieve data on the reasons for admission. The median older age of the SBRT cohort may also suggest that they may have more comorbidities and therefore, may get admitted more often for the intercurrent illnesses impacting the results. If possible, the rate and duration of hospitalization of the age matched cohort without cancer would be best suited for this comparison. It would especially be better if such indices are available for smokers without cancer who truly match this cohort. The absolute increase in the hospitalization rates are the true attributable costs of hospitalization due to treatments.”

- Reply 5: We would like to thank the reviewer for these thoughtful comments. First, regarding reasons for admissions, we would like to kindly point that admissions diagnoses were collected, and included in the appendix. We modified the text on page 7, lines 4-5 and page 10, lines 10-11, to make this more clear. To control for the possible confounding effect of age and comorbidity, we used a subsample of SBRT and chemotherapy patients matched on age, Charlson comorbidity score, disability status, in addition to other covariates listed on page 7, lines 20-21 and in Table 4. Although we did not have age-matched controls without a cancer diagnosis in our database and hence could not determine the increased hospitalization cost due to treatment for NSCLC, our objective was to compare differences between SBRT and chemotherapy.
- Changes in text: “The length of stay, total cost and admission diagnosis were determined... ” and “Admission diagnoses are listed in the appendix, with the most common diagnoses being shortness of breath and pneumonia (appendix).” “To compare hospitalizations and their associated costs a subsample of chemotherapy patients who were similar to SBRT patients in terms of age, T, N, disability status and comorbidity status was selected using propensity score matching based on a logistic regression model, with 1:4 nearest neighbor matching without replacement.”

Reviewer B, Comment 1: Why did the authors look at hospitalization rates between SBRT and chemotherapy – why would one expect more hospitalization rates/costs in patients undergoing SBRT?

- Reply 1: Thank you for this comment. We agree our hypothesis was not clear and have added it to the introduction for clarity. This can be found on page 4, lines 10-17.
- Changes in text: “There is growing recognition that hospitalizations represent a substantial proportion of cancer expenditures, primarily related to complications from systemic therapy, such as neutropenia. Therefore, ongoing evaluation of utilization and hospitalizations of cancer treatments is warranted. Currently, the patterns of care utilizing SBRT in elderly metastatic NSCLC patients and the impact on survival are unclear. The impact potential of SBRT use on hospitalizations is also not known, and we hypothesize that improvements in disease control from SBRT may result in more time off chemotherapy, thereby decreasing hospitalizations.”

Reviewer B, Comment 2: “Second, the time period of 2004-2014 is a bit unfortunately when looking at the role of SBRT in oligoprogressive disease as it was really after this period that randomized data really

began supporting the role with guidelines changing also in support. So that small percent change is very minimal and not surprising as this period was mostly before the recent data in support of SBRT”

- Reply 2: We agree with the reviewer that this is a limitation. We expanded on this in the discussion on page 13, lines 13-14.
- Changes in text: “In addition, prospective data supporting the use of SBRT has accrued since this time (10-12)”

Reviewer B, Comment 3: “In the introduction, I would also site the phase II Iyengar trial as well.”

- Reply 3: Thank you for identifying this omission, we have added this reference, and can be found on page 3, lines 18-20.
- Changes in text: “Similarly, the use of consolidative SBRT prior to maintenance chemotherapy nearly tripled progression-free survival in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone.”

Reviewer B, Comment 4: “Why was SBRT alone compared to chemotherapy? Why not compare SBRT+chemotherapy to chemotherapy alone? That would seem like a better comparison analysis. What was done with patients who received SBRT AND chemotherapy – were they excluded? Or how were they coded? If the SBRT group also received chemotherapy, that should be made more clear.”

- Reply 4: We regret that the original manuscript did not make this clear. We compared patients who received SBRT as **initial treatment** to those initially treated with chemotherapy. However, after initial treatment, we did not exclude patients based on subsequent treatment. Overall, fewer than 1% of the overall sample crossed over from SBRT to chemotherapy or visa vicera. Not surprisingly, these are mostly SBRT patients who then received chemotherapy (24.5%). Whereas, among chemotherapy patients, only 0.5% subsequently received SBRT. We clarified this in the methods section, page 5, lines 20-25 and page 6, lines 1-2.
Changes in text: “Some patients (108 or less than 1% of the overall sample) subsequently received the other treatment and were retained in the study to ensure that the results were representative of treatment provided in real-world clinical settings. These were mostly SBRT patients. Among patients who received SBRT as initial treatment, 24.5% subsequently received chemotherapy (24.5%). Among patients who received initial chemotherapy, only 0.5% subsequently received SBRT.”

Reviewer B, Comment 5: “Is number of metastatic sites known using SEER-Medicare? I don’t believe it is and unfortunately that is a huge limitation of a trial where the only role of SBRT would be in the oligometastatic site. In the discussion, I would emphasize that the selection bias may be due to # of metastatic sites as those patients undergoing SBRT were likely to have a few sites of disease whereas those with multiple sites underwent systemic therapy and this would contribute dramatically to your survival outcomes.”

- Reply 5: We agree this a limitation of studies based on observational rather than clinical trial data and acknowledge the potential for selection bias at the beginning of the discussion, page 11, lines 6-11. We added that the number of metastatic in particular is not available to emphasize this point.

- Changes in the text: “This is because detailed information regarding the extent of metastatic disease, or number of metastatic sites, cannot be determined with certainty from the SEER-Medicare data.”

Reviewer B, Comment 6: “I don’t understand the statement on higher cost and days while hospitalized for SBRT due to longer survival. That doesn’t really make a lot of sense unless you are just saying SBRT makes patients live longer and so inherently they are likely to be hospitalized more times than someone who dies sooner? It is an odd connection to make and not sure if SBRT directly impacts this.”

- Reply 6: The SBRT patients in our study did live longer, which is why we analyzed the hospitalization and cost data both as total amount and amount per month of survival. As Table 4 indicates, the costs associated with the two treatments do not differ significantly when expressed per month of survival. We have added text to the discussion on page 11, lines 21-24 and page 12, line 1, to clarify this and to point out that the findings are observational and may not be causal.
- Changes in text: “When normalized by months of survival, the number of hospitalizations was lower in the SBRT patients and costs did not differ significantly from the chemotherapy patients. It should be emphasized that this is an observational and not causal relationship, meaning that the observed differences in healthcare utilization may reflect fundamental differences in these population, such as the extent of disease.”

Reviewer C, Comment 1: “Page 5, Lines 17-18: Could the patients who received chemotherapy have also received SBRT at some point (or vice versa)?”

- Reply 1: We agree with the reviewer that this was not clear. This point was also raised by Reviewer B (Comment 4). Please see our reply and changes: crossover was allowed however this occurred in fewer than 1% of our sample, and as expected, most involved patients who underwent initial SBRT followed by subsequent chemotherapy.

Reviewer C, Comment 2: “Page 10, Lines 7-9: I agree that the extent of metastatic involvement is an important but unknown variable, and the authors are to be credited for pointing this out in Discussion.”

- Reply 2: We certainly agree with this limitation and further emphasized the number of metastatic sites is not known in response to Reviewer B, Comment 5, above.

Reviewer C, Comment 3: “Page 11, Lines 5-6: The finding of higher SBRT use among patients who are more elderly and have poor disability is not necessarily counterintuitive: These patients are likely to be the ones that cannot tolerate systemic therapy, so they’re left with radiation as the only viable treatment option. Perhaps the treating oncologist felt that SBRT (as opposed to other radiation strategies) was the optimal way to treat the NSCLC aggressively given the circumstances.”

- Reply 3: This is an excellent point, and we agree it could potentially explain our findings. This could represent differences in SBRT use in clinical trials and what is being observed with “real world data.” We expanded our discussion on page 12, lines 10-17.

- Changes in text: “Our finding that SBRT use is higher among patients with increased age and poor disability warrants discussion. In the three aforementioned randomized phase II trials of SBRT in oligometastatic cancer, the median age of SBRT patients was 64-67, with Eastern Cooperative Oncology Group performance status of 0-2 (10-12). Our study is limited to Medicare-eligible patients and hence an older population. Older, more frail patients receiving SBRT in our population could suggest that outside of clinical trials, SBRT is being used in patients who cannot tolerate systemic therapy. Regardless, it is plausible that survival advantage SBRT may be underestimated in our study, given the differences in baseline characteristics we observed compared to the phase II studies.”

Reviewer C, comment 4: “Page 12, Line 3: I agree that not having information on immunotherapy is a big limitation of this study. Since the bar to receive immunotherapy is much lower than chemotherapy, patients presenting similarly today may receive immunotherapy first (rather than SBRT, even if considered ineligible for chemotherapy).

- We agree, and intend to study these trends using more contemporary data.

Reviewer C, minor comments 1-3: 1. It would be helpful for the costs to be clearly labeled (e.g., “\$33,063” instead of “33063”). Similar issues also arise at Lines 8 and 10. 2. “9=.94” should read “p=0.94” 3. “higher significantly higher” should read “significantly higher”

- Reply: Thank you for suggesting these edits, they have been made on page 10, lines 7-10.
- Changes in text: “Similarly, the total cost of hospitalization was higher for SBRT patients (\$33,063 vs. \$23,865, $p < .001$) but the cost per month of survival was nearly the same as for chemotherapy patients (\$3,883 vs. \$3,924, $p = .94$). However, the average cost per hospitalization was significantly higher for SBRT patients (\$13,647 vs. \$10,432, $p < .001$).”

Second Round of Review Comments

Reviewer A, Comment 1. Line 59-66 - Please quote the studies by their author's last name like xyz et al. rather than repeat a randomized phase II study for all 3 of them.

- Reply 1: we have made these changes on p.3, lines 16 – 21.

Reviewer A, Comment 2. Line 80 : Therefore, ongoing evaluation of utilization and hospitalizations of cancer treatments is warranted--- is unclear and would have to be rephrased for better understanding.

- Reply 2: We agree, and changed this to, “Therefore, characterizing admitting diagnoses and costs from hospitalizations during cancer therapy is warranted” on P.4, lines 12-13

Reviewer A, Comment 3. Line 113 shows repeated 24.5% and should be deleted

Reviewer A, Comment 4. Line 161 -- delete the repeated word 'use'

- Replies 3-4: Thank you, these edits have been made (p. 6, line 1; p. 9, line 2)

Reviewer A, Comment 5. I would strongly urge the authors to report median age rather than mean with SD as most studies report median with inter-quartile range and it is so much easier to compare. Especially as authors themselves make a comparison of the 3 phase -II study population with this cohort and find that the median ages are not comparable with the current study's mean age.

- Reply 5: We agree with the reviewer and are now reporting median ages and IQRs throughout the manuscript, including: p.9 lines 3-4 and Table 1.

Reviewer A, Comment 6. Line 164: please add the word 'with' --> treated with chemotherapy

- Reply 6: Thank you, this has been corrected on P. 9, line 5.

Reviewer A, Comment 7. Line 193: The differences in the admission diagnoses were largely in septicemia and infections in chemo and shortness of breath in SBRT cohort. It would benefit the readers if this distinction was made here as this also helps you bring the cost of treatment in perspective in discussion.

- Reply 7: We added the following on P. 10, lines 10-13: "Admission diagnoses are listed in the appendix, with the most common diagnoses being shortness of breath (27%) and pneumonia (20%), with shortness of breath being more common among SBRT patients, and infections being more common among chemotherapy patients (appendix)."

Reviewer A, Comment 8. A general point that I would make is that --> It is important for the authors to acknowledge that the world is moving towards local consolidation and OMDT No one is replacing chemotherapy/ targeted/ immunotherapy with SBRT alone for patient with extensive metastases who may be able to tolerate systemic therapy well. The authors make an impression that SBRT is on its way to replace systemic therapy for metastatic NSCLC which is not the case at all. The readers would benefit from having this point brought into perspective.

- Reply 8: This is an excellent point and we did not intend to convey this message. We edited the following which we hope emphasizes the point that this work identifies favorable outcomes when SBRT was added to standard-of-care systemic therapy: P. 2, lines 19-21: "Despite these patients having worse prognostic factors, the addition of SBRT to chemotherapy was associated with improved OS." P. 13, lines 20-P.14, line 1: "In conclusion, we observed increased use of SBRT from 2004-2013 and its addition to standard systemic therapy was associated with longer survival. Although fewer SBRT patients were hospitalized, there was an increased cost associated with hospitalizations that was primarily due to their longer survival. Our findings support the ongoing evaluations of SBRT in combination with systemic therapy in elderly patients with metastatic NSCLC."

Reviewer A, Comment 9. Line 220: Kindly add that this was being compared mostly against chemo induced febrile neutropenia and intercurrent infections which may be easier to manage than radiation pneumonitis or SBRT related severe toxicities. The grade 4 febrile neutropenia can't be directly compared even with the grade 3 radiation induced pneumonitis.

- Reply 9: Thank you for this suggestion. We added the following on P. 12, lines 4-7: "As more chemotherapy patients were admitted with intercurrent infections and SBRT patients were

admitted with shortness of breath (possibly pneumonitis), it is plausible that SBRT-related complications may be more difficult to manage.”

10. Line 229: It is best to compare the median age with median age rather than mean. Please incorporate it for a fair comparison.

- Reply 10: we agree and have changed our reporting to median age throughout (please see Reply 5 above).

11. Line 256: may 'improve' rather than persistent

- Reply 11: This edit has been made on P.13, line 18

Third Round of Review Comments

Reviewer A, Comment 1. “I understand that the authors have changed their text to address a prior comment (Reviewer A, Comment 8). However, I would reword the authors’ new conclusion statements as they are somewhat misleading. Only 24.5% of patients received SBRT followed by chemotherapy (the others presumably received SBRT alone). Thus, we can say that SBRT may play a role in management of select metastatic NSCLC patients in addition to standard-of-care chemotherapy, but on the SEER analysis, we cannot use broad statements such as “addition of SBRT to chemotherapy was associated with improved OS” or “its [SBRT’s] addition to standard systemic therapy was associated with longer survival”.

- Reply 1: we agree and have reworded the concluding statements in both the abstract and body of manuscript as follows:
 - Page 2, lines 19-21: “SBRT is increasing among Medicare patients with metastatic NSCLC. Our findings suggest that SBRT may play a role in management of select metastatic NSCLC patients in addition to standard-of-care chemotherapy.”
 - Page 13, lines 20-24: “In conclusion, we observed increased use of SBRT from 2004-2013 and its use was associated with longer survival. Although fewer SBRT patients were hospitalized, there was an increased cost associated with hospitalizations that was primarily due to their longer survival. Our findings support the ongoing evaluations of SBRT in combination with systemic therapy in elderly patients with metastatic NSCLC.”

Reviewer A, Comment 2. “OK as it stands, as it directly addresses Reviewer A’s comment. However, I think the wording can be refined somewhat: The SBRT-related complications are different, but not necessarily more difficult to manage. In the wording of Reviewer A, the toxicities of SBRT vs. chemotherapy cannot be directly compared.”

- Reply 2: Thank you for the suggestion. We reworded the following sentence on Page 12, lines 4-7: “As more chemotherapy patients were admitted with intercurrent infections and SBRT patients were admitted with shortness of breath (possibly pneumonitis), it is plausible that

SBRT-related complications different from chemotherapy, leading to different care needs for hospitalizations.”