Peer Review File

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Reviewer A

This single institution prospective observational study included patients with active hemoptysis treated with radiotherapy and aimed to determine symptom control probability, durability, and influencing factors.
We would like to offer them some observations.

Comment A1:

Introduction
In general, this section is well structured and show in a clear way the epidemiologic data about lung cancer, its associated symptoms, the mechanism of hemoptysis and its treatment choices.
Row 63- Authors argued that "several studies have aimed to establish a standard of care radiotherapy regimen to palliate chest tumor related symptoms. However, bleeding control was not a primary end point in most studies, and durability of hemostasis was not defined".
In my opinion, this is a inaccurate affirmation. There are seminal studies that addressed the hemostatic role of radiotherapy and its duration. I could recommend the successive studies by the MRC:
1- Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomised trial of palliative radiotherapy with two fractions or ten fractions. Report to the Medical Research Council by its Lung Cancer Working Party. Br J Cancer. 1991 Feb;63(2):265-70. doi: 10.1038/bjc.1991.62.
2- A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. Br J Cancer. 1992 Jun;65(6):934-41. doi: 10.1038/bjc.1992.196.
3- Macbeth FR, Bolger JJ, Hopwood P, Bleehen NM, Cartmell J, Girling DJ, Machin D, Stephens RJ, Bailey AJ. Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party. Clin Oncol (R Coll Radiol). 1996;8(3):167-75. doi: 10.1016/s0936-6555(96)80041-0.

Reply A1:

We thank Reviewer A for their valuable comments, observations and feedback

We do agree that the hemostatic role of palliative radiotherapy was addressed in several large trials and that a standard has been established. The wording has been modified to better clarify that identifying hemoptysis severity, and the factors that influence hemostatic control remain a challenge.
Changes in text: We modified the text in the introduction and added the references, page 6, line 92.

Methods

Comment A2:
Row 103: Authors captured and monitored hemoptysis severity via the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, which is an standard and widely known tool. They also applied an in-house developed PROM.
Pre-treatment CTCAE score is provided (all patients had score 3 or greater) but post-treatment CTCAE is not informed. If it decreased, there was a correlation with PROM scores?
We do not know if PROM was pilot-tested on a sample group to establish face-validity, ease of completion, content, and completion time (critical importance in patients with poor performance status). Thereby, is not possible to know if this tool is accurate for measuring the presence, amount and intensity of hemoptysis. If it is a good tool for evaluating response to treatment, is also unknown.
Reply A2:
We agree with avoiding unvalidated tools, however at the time of study design (2015), there were limited available options to consider for specific bleeding evaluation (such as quality of coughed sputum, frequency of bleeds, amount of blood in sputum).
For example, The EORTC 'Quality of life Questionnaire' (QLQ-LC13) validated tool evaluates various chest-related symptoms with only 1 out of 13 questions related to bleeding. Specifically asking "did you cough up blood?" without further details. We did include CTCAE grading throughout the study. However, the PRO-CTCAE tool was not considered at the time of study design. The current PRO CTCAE library only contains nosebleeds, and vaginal bleeding symptoms.
Thus, the authors attempted to develop an in-house tool. This study collected the necessary preliminary data for validation testing (including face validation, content, construct validation, and internal consistency) following the COSMIN guidelines. However, describing this was out of scope for this paper and as such will be published in a separate manuscript.

Comment A3:
Row 112: Findings and conclusion of the current study are based in a tool neither published or well described nor validated. I think there is a severe methodological error when authors say that description of the tool will be published in a separate paper (This should be the first step in a seriously conducted study).
Reply A3:

The current study focuses on hemoptysis control in terms of its presence or absence (CR) post RT (absence is simply CTCAE 0, or PROM score of 0). However, we do agree that perhaps mentioning and reporting the in-house tool scores in this study (in parallel with CTCAE) is premature. We could exclude the PROM scores entirely from this study; our reported clinical outcomes will likely remain unchanged as we used presence/absence of bleeding and hemoptysis related deaths in our survival analysis.

Results

Comment A4:40 patients were included. The majority of patients were treated with multi-fraction schedules. At 2 weeks 32 patients were alive (14-day mortality 20%), a complete response was found in 17(53%). In those alive at 3 and 6 months complete responses were observed in 15 (79%) and 8 (80%), respectively.

It would be interesting that authors could address these results critically regarding palliative objectives of radiotherapy and evidence based dose/fractions. A high proportion of patients in this study die within 2 weeks after treatment. A retrospective study found that more than half of patients treated with thoracic palliative radiotherapy who died within 30 days after treatment were treated with 4 or more fractions.

4- Vargas A. Audit of 30-day mortality following palliative radiotherapy: are we able to improve patient care at the end of life? Rep Pract Oncol Radiother. 2024 Feb 16;28(6):720-727. doi: 10.5603/rpor.97734.

Reply A4:

We agree that the use of protracted palliative regimens was over used in our cohort. As this was an observational study, fractionation and treatment decision was left at the discretion of the primary oncologist. We agree that our results put into question the frequent use of a 5-fraction regimen in this patient population, we will update our key findings, our discussion and our conclusions to reflect this.

Changes to text: Key findings was modified page 5 line 70, abstract conclusion was modified page 3 line 62, discussion was modified page 11 line 247, conclusion modified page 14 line 312

Comment A5:

Row 157: How the satisfaction with their radiotherapy was measured? Yes/No question? By PROM? Other?

Reply A5:

We modified the methodology section as advised, patients were asked a yes/no question if they were satisfied, and why if not satisfied

Changes in the text: Methodology section page 8 line 145

Comment A6:

Row 162: “None of the patients received re-irradiation”.

If 3 patients recurred after a complete response, why re-treatment was not performed?

There were patients treated with palliative chemo after radiotherapy?

Reply A6:

The majority of patients continued with palliative chemotherapy after RT and there were no surgical interventions for any re-bleeding event. This was added in the results section

Changes in the text: Results section page 10 line 213.

Only one of the 3 patients with hemoptysis recurrence passed away, and it was due to disease progression, added in results

Changes in the text: Results section page 10 line 207

Regarding re-irradiation, the study did not mandate re-irradiation for hemoptysis recurrence, thus it was left for the primary oncologist to decide. Their decision on why not to re-irradiate was not captured. We added this text in the discussion section

Changes in the text: Discussion section page 11 line 249

Comment A7:

Row 163: “On univariate analysis, ECOG status (p=0.012) and prior radiation (p=0.006) were strongly associated with freedom from hemoptysis survival, while baseline hemoptysis score was borderline (p=0.072)”.

I think a table showing the results of univariate analysis would be more explicative because is not clear which variables were included in this analysis. Baseline hemoptysis was not “borderline”, an statistically significative relation was not found.

Reply A7:

We agree, text in results section was modified as advised

A new table for univariate analysis was added

Changes in the text: Results section page 10 line 224

Comment A8:

Row 165: “Treatment related response and toxicity rates are outlined in (Table 3)”.

Toxicity is not stablished as an objective (abstract, introduction, methods). The way for assessing it is not explained in methods. Information in Table 3 is not clear and the reader cannot know which toxicities were measured (esophagitis? Dermatitis? Asthenia?).

Reply A8:

We assessed toxicity based on the RTOG adverse event reporting system; we added that in the methodology section.

Changes in the text: Methodology section page 8 line 146, Table 3 modified

Discussion

Comment A9: Row 175: “Radiotherapy was effective in controlling bleeding in over 50% of patients surviving at 2 weeks and over 75% of patients surviving at 6 months”.
Available evidence show that in patients with lung cancer treated with 16 Gy/2 fractions palliation was reached in week 5, while patients treated with 30Gy/10 fractions reached it at week 7. Which could be the cause of the very good result at 2 week after treatment in the current study? Could be this difference the result of the applied tool for do the measure?
I could recommend the randomized study by Kramer et al:
5- Results of the Dutch National study of the palliative effect of irradiation using two different treatment schemes for non-small-cell lung cancer. J Clin Oncol. 2005 May 1;23(13):2962-70. doi: 10.1200/JCO.2005.01.685).
Reply A9:
The Dutch study corroborates our findings of a good hemostatic rate early on compared to other palliated chest symptoms. As indicated from their results section (All symptoms, except hemoptysis, initially intensified as the number of the patients suffering from that particular symptom rose and/or the severity of the symptom increased as a result of acute toxicity)

Comment A10:
Row 177: “Although our study allowed for several fractionation regimens the majority of participating physicians chose moderate dose fractionation schemes such as 20 Gy in 5 fractions and 30 Gy in 10 fractions. One possible explanation is the bulky tumor size and PTV volumes in our cohort”.
I think a finding like this deserves a more in deep discussion. At one hand randomized trials (by the MRC) showed the equivalence between single and multifaction schedules for palliating symptoms in lung cancer patients.
In the other hand, in all of those studies the radiotherapy was delivered with 2D techniques through opposing portals. The allowed area was 200 cm2. In the study by Kramer et al, Irradiation was given using two opposing anterior-posterior fields with 6- to 18-MV photon beams, the treatment portals encompassed the tumor, with a margin of 1 1/2-2 cm and no limitations were set for the target volume.
We do not know if in the current study, treatment were performed with 3DCRT or IMRT, but certainly patients were treated with a dedicated TC. It is possible that factors other than PTV volume could influence the frequency of multi-fraction treatments in poor prognosis patients (55% ECOG 2-3)

Moreover, Radiation Oncologists should be aware that available evidence shows that higher doses and more fractionated regimens increase acute toxicity, do not provide better or more durable palliation and their use in prolonging survival is not supported by strong evidence.

I could recommend:

6- Stevens R, Macbeth F, Toy E, et al. Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. Cochrane Database Syst Rev. 2015; 1(1): CD002143, doi: 10.1002/14651858.CD002143.pub4.

In addition, from a palliative care point of view if 20% of patients die within 2 weeks after treatment, multi-fraction treatments could be not justified because its associated toxicity, the time necessary for complete it and because finally, could be a futile treatment.

Reply A10:

Thank you for your valuable comments and feedback

Regarding radiotherapy technique:

We specified the radiotherapy techniques used

Changes in text: Methodology section page 7 line 134

and image guidance used

Changes in text: Methodology section page 7 line 136

Additionally, we described the techniques used in the study results

Changes in text: Results section page 9 line 196

We agree with your comments regarding caution on dose/fractionation used for palliation and have modified the discussion section as advised

Change in text: Discussion section page 11 line 253

Comment A11:

Row 184: “Many of these studies were conducted to assess toxicity and symptom palliation effectiveness, with limited focus on bleeding dynamics and hemostatic control”.

I could recommend the MRC trials (mentioned above).

Reply A11:

We agree that this comment is not accurate, and was removed

Changes in text: Discussion section page 11 line 248

Conclusion

Comment A12:

In my opinion, the author´s conclusions are not consistent with the findings of the study.

Row 237: Results do not allow to draw that 20 Gy/5 fractions has acceptable durability.

In patients with recurrence after complete response (n=3), the cause for not offering re-treatment is not clear.

Reply A11:

We have modified the conclusions of our study to better reflect the interpreted findings

We have added a diagram that tracks the response of all our evaluable patients

Changes in text: Added a new figure, changes the conclusion section page 14

This study has potential. Authors have identified a very interesting topic but this project needs to mature to blossom in the best way. However, in its current form I do not recommend for publication in Annals of Palliative Medicine, because its finding cannot be supported by a validate or piloted tool and do not add new good quality data.

Reviewer B

EBRT is highly effective for hemoptysis, as demonstrated by previous studies, also cited by the authors.

Similar outcome was demonstrated in this study. However, I have a doubt if other uncertainties related to RT for hemoptysis were resolved (effect duration, fractionation schedule) by this study. Some issues deserve more explanations.

Comment B1. Forty patients were initially included, 32 were included in the hemoptysis specific analysis, but a reason of exclusion of 8 patients was a death during the first two weeks. At least one of them died from massive hemoptysis during the first two weeks, as described in the Discussion section. It is surprising that for a hemoptysis being a main end-point, such patient was excluded. Obviously, for him an evaluated method was ineffective. Additionally, the cause of death for remaining seven was unknown. We cannot exclude hemoptysis for them, can we? This is confusing.

Reply B1:

We thank reviewer B for his valuable comments and recommendations

We concur that the discussion section illudes to the patient passing away within 2 weeks due to massive hemoptysis. However, that was not the case.

We have adjusted the discussion section (then relocated to results) to reflect the following:

We included 3 patients with elevated PROM scores (not necessarily massive hemoptysis) all of the 3 patients passed away from disease progression as per death certificate reports.

Changes in text: Discussion section then relocated to results section (per reviewer recommendations) page 11 line 228

We found it extremely challenging to more specifically determine the cause of death as many have ongoing life-threatening conditions such as aspiration pneumonia, leptomeningeal disease, airway obstruction and poor lung function. However, we did identify 2 deaths in our cohort related to bleeding one of which was before the first assessment, both patients were included in the bleeding related survival. The 8 patients were excluded from the freedom from hemoptysis rate (one had bleeding and the rest due to disease progression). That patient was excluded due to lack of any available follow up hemoptysis scores or assessments and since that patient passed away only 2 days following RT, it was to soon to determine if RT was ineffective.

Comment B2. How "Bleeding related survival" was defined? Death from any cause was censored?

Reply B2:

We revised the manuscript as advised and added the definitions

Changes in text: methodology section page 8 line 166

Comment B3. "Complete response was achieved in 17 (53%) of surviving patients at 26 weeks (z= -4.2, p<0.001), 15 (79%) at 3 months (z= -3.5, p<0.001), and 8 (80%) at 6 months (z= -2.6, p=0.004)." This may be interpreted as a durable response (from the first effect), or durable response + delayed response (some did not respond at first evaluation, but responded at the time of the next interview), or may be there were some who responded at the first evaluation, but failed after, and this demonstarted improvement in numbers is a result of deaths from other reason and decreased number at risk. I think that any diagram evaluating this would be helpful.

Reply B3:

We agree that the data may be interpreted differently, we added a new figure demonstrating patients response throughout the study

Changes in text: Added new figure, added text results section page 10 line 208

Comment B4. Key issue: What about the use of anti-hemorrhagic medicaments, like Tranexamic acid, Etamsylat in the group of included patients? This probably interfered with the outcome, in some patient the effect of drugs would be prevalent over radiation. Did you take into account this factor? It is hardly imaginable that the use of these drugs was prohibited in the trial.

Reply B4:

Although we did collect pertinent medication data and the use of anti-platelets/anti-coagulants (60% of our patients where on those medications), we did not specifically look into anti-hemorrhagic medications, we agree that this is a limitation of the study and was added into the limitation section of the discussion

Changes in text: Discussion section page 13 line 303

Comment B5. For discussion of an issue of fractionation: there are a few meta-analyses and prospective studies indicating that single fractions are as effective as protracted radiation schedules for symptom palliation but less effective for survival (Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. J Clin Oncol 2008;26:4001-11; Stevens R, Macbeth F, Toy E, et al. Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. Cochrane Database Syst Rev 2015;1:CD002143. Bezjak A, Dixon P, Brundage M, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer. Int J Radiat Oncol Biol Phys 2002;54:719-29.
An observational study like the submitted trial cannot demonstrate an opposite. This should be acknowledged.

Reply B5:

We agree and acknowledge this fact, discussion section modified as advised and references added
Changes in text: Discussion section page 11 line 253

Comment B6. A very short survival of included patients is striking. Thus a question arises: should RT be used for this population of patients, especially in case of moderate bleeding as in some proportion of included patients. A high 30-day mortality after palliative RT calls into question the rationale for its use. This also should be discussed.

Reply B6:

We concur with you on this point, discussion section modified as advised
We have also updated our conclusions and key highlights to reflect this important finding
Changes in text: Discussion section, page 12 line 256

Reviewer C

Comment C1: Line 50 Add Malignant Airway Obstruction (MAO) to symptoms because it could be one of the causes of hemoptysis above all in the advanced and metastatic lung cancer that they need a pallative treatments

Reply C1:

We modified the text as advised
Changes in text: Introduction section page 5, line 78

Comment C2: Line 62 Add references, write a median dosage that is used in the literature. From published data it is approximately 30 Gy with a range of approximately 6 - 50 Gy. (references : -Ahn GS, Bruggeman AR, Qiao EM, Moiseenko V, Ray X, Sharabi A, Murphy JD, Sandhu AP.

Hypofractionated radiation therapy as palliative management for symptomatic and local control of advanced thoracic malignancies. Ann Palliat Med. 2021 Oct;10(10):10360-10368. doi: 10.21037/apm-21-1779. Epub 2021 Oct 9. PMID: 34670382. -Facondo G, Reverberi C, Ceschia T, Parisi G, Vullo G, Moretti E, Trovò M. Short-course Radiotherapy for Airway Stenting in Malignant Airway Obstruction: A Case Report and Literature Review. Cancer Diagn Progn. 2024 May 3;4(3):359-362. doi: 10.21873/cdp.10332. PMID: 38707719; PMCID: PMC11062153)

Reply C2:

We modified the text as advised

Changes in text: Introduction section page 6, line 90, references added

Comment C3: line 88 Table 1 Exlusion criteria : Why were patients with RT overlap removed given that a palliative dosage was used as retreatment?

Reply C3:

We will clarify that this is related to excluding definitive radiotherapy doses (≥40 Gy) at the same site of hemostatic radiotherapy within a short period of time (<3 month) prior to study entry.

Change in text: Table 1 was deleted (to allow for a new table on univariate analysis), inclusion/exclusion criteria added in text methodology section page 7, Line 119

Comment C4: line 90 have there been patients with MAO bronchial obstruction which could be one of the causes of haemoptysis?

Reply C4:

We unfortunately did not capture this data prospectively

Comment C5: line 94 specify radiotherapy technique used (3dCRT / VMAT / IMRT). Write what was used as image guided (CBCT?)

Reply C5:

We specified the radiotherapy techniques used

Changes in text: Methodology section page 7 line 134

and image guidance used

Changes in text: Methodology section page 7 line 136

Additionally, we described the techniques used in the study results

Changes in text: Results section page 9 line 196

Comment C6: line 123 Statistical consideration : specify in the paragraph what is meant by OS, CSS , Blending related survival and freedom from hemoptysis .(example : for OS from the date of diagnosis or end of RT ….)

Reply C6:

We revised the manuscript as advised and added the definitions
Changes in text: methodology section page 8 line 166

Comment C7: Lne 135 specify clearly the number of patients with locally advanced lung or metastases and from which primary tumor. Specify how many patients had already undergone radiotherapy.

Reply C7:

We modified the text as advised on primary breakdown
Changes in text: results section page 9 line 185
We described prior radiation of our cohort on
Changes in text: results section page 9 line 192

Comment C8: Line 145 add range median pre treatment hemoglobin

Reply C8:

We modified the text as advised
Changes in text: results section page 10 line 199

Comment C9: Line 147 add range PTV cc

Reply C9:

We modified the text as advised
Changes in text: results section page 10 line 202

Comment C10: Line 156 add range median post treatment hemoglobin

Reply C10:

We modified the text as advised
Changes in text: results section page 10 line 200

Comment C11: Line 159 add data for Blending related survival and freedom from hemoptysis with percentages and confidence interval as OS.

Reply C11:

We added the data on survival as requested in the results section
Changes in text: results section page 10 line 219

Comment C12: Line 162 Results unclear. Having used COX regression as a statistical method, insert a table with which and how many variables were used and specify Hazard ratio and 95% CI for each variable and describe them in the text. For a sample of 40 patients as in your study it is appropriate to use a maximum of 4 variables to avoid statistical bias. Add new table “Univariate analysis”

Reply C12:

We agree, text was modified as advised

A new table for univariate analysis was added

Changes in text: Results section page 10 line 225

Comment C13: Line 168 Discussion : add the proposed references in the previous comment and describe it.

Reply C13:

Added the proposed references in discussion section

Changes in text: Discussion section page 12 line 260

Reviewer D

While I applaud the authors of this article to focus on hemostatic radiotherapy, I do have some concerns about their paper.

Comment D1: The primary endpoint of this trial is a self-developed PROM. The use of unvalidated PROMS is generally advised against, as there are many PROMs available already. The for me it is unclear how this PROM is of additional value or what the goal of the PROM was exactly, as it is not further described in this publication. The authors could also have opted to use the PRO-CTCAE or the EORTC symptom bank, which are both validated.

Reply D1:

We thank review D for his valuable insights, comments, and feedback

We agree with avoiding unvalidated tools, however at the time of study design (2015), there were limited available options to consider for specific bleeding evaluation (such as quality of coughed sputum, frequency of bleeds, amount of blood in sputum).

For example, The EORTC 'Quality of life Questionnaire' (QLQ-LC13) validated tool evaluates various chest-related symptoms with only 1 out of 13 questions related to bleeding. Specifically asking "did you cough up blood?" without further details. We did include CTCAE grading, however, PRO-CTCAE was not considered at the time. The current PRO CTCAE library only contains nosebleeds, and vaginal bleeding symptoms.

Thus, the authors decided to develop an in-house tool. This study collected the necessary preliminary data for validation testing (including face validation, content, construct validation, and internal consistency) following the COSMIN guidelines. However, describing this was out of scope for this paper and as such will be published in a separate manuscript.

Comment D2: At least a example of the questionnaire should be provided for the reader to review the scoring in order to review how the primary endpoint of this trial was assessed.

Reply D2:

We were instructed to not include the PROM tool for copyright reasons.

Comment D3: Under results, some of these results are reported with numbers (eg. only 1 patient had a history of bleeding disorder line 141) and others are with percentages (eg. 5% underwent a bleeding intervention, line 142-143) this is confusing. With this limited number of patients 15% is only 2 patients in absolute numbers. Please be consistent in your manner of reporting.

Reply D3:

We agree with your comment on consistent reporting of results, text modified as advised

Changes in the text: results section page 9 line 191

Comment D4: From line 149 forward the bleeding response is reported. The presentation of the results suggests, especially in the abstract, that the effect of RT increases overtime, but in reality the number of patients decreases. Are the 8 patients who have a bleeding response 6 months, included in the 17 patients at 2 weeks post RT or were there late responders? At 2 weeks there was only a 53% response rate - where there bleeding related deaths?

Reply D4:

We agree that the data may be interpreted differently than intended, we added a new figure diagram demonstrating patients' response throughout the study

Changes in text: Added new figure, added text result section page 10 line 208

Comment D5: From line 157 satisfaction with the RT is reported, but this is not mentioned anywhere in the methodology? How and when was this asked?

Reply D5:

We modified the methodology section as advised, patients were asked a yes/no question if they were satisfied, and why not if not satisfied

Changes in the text: Methodology section page 8 line 145

Comment D6: In line 171 it is mentioned that the hemostatic control rate is 80% (as in the rest of the article), in line 176 this is >75%, please be consistent.

Reply D6:

Text was modified as advised to reflect the bleeding related survival and freedom from hemoptysis rate instead of CR rates

Changes in the text: Results section page 11 line 240

Reviewer E

This is a single center, single arm, prematurely closed prospective study on RT for haemoptysis. In the absence of a pre-existing specific haemoptyis PROM tool, the authors developed an in-house tool, currently undergoing validation. I think this work is potentially a useful addition to the literature but there appears to be a need for more statistical input in the analysis and reporting of results. Specific comments:

Comment E1. Highlight box, fifth dotpoint - "…and no re-treatment requirements." is too strong as a summary statement. Suggest "…and no re-treatment was required in this cohort" (or similar).

Reply E1:

We thank reviewer E for his valuable comments and recommendations.

We have reconciled the highlight box entirely based on the received feedback

Comment E2. Abstract, line 23 - this should read ECOG greater than or equal to 2.

Reply E2:

Changes in text: Abstract line 51 corrected as advised

Comment E3. Lines 120-122 - with treatment duration varying between 1 day and 2 weeks, it would have been more sensible (and conventional) to base the assessments and survival from the start of RT rather than the end and to evaluate initially at one month. In any event, the primary endpoint needs to be defined and reported at the first assessment (not at all three), and with 40 as the denominator (not 32). With so many deaths, the stated CR percentages at 3 and 6 months are quite misleading. Similarly, it is not valid to state an 80% control rate at line 171.

Reply E3:

We agree with your comments; to clarify, survival was calculated from the time of treatment

We revised the manuscript and added the definitions for all survival rates

A new figure diagram was added to reflect and track the response of all patients on study

We also refrained from using the CR rate in our discussion section and used the bleeding related survival and hemoptysis free survival rates instead.

Changes in text: methodology section page 8 line 166, added a new figure diagram

Comment E4. Methods - how was the sample size determined?

Reply E4:

For this observational study, we estimated that our center could accrue roughly 25 patients with hemoptysis per year based on historical data, the study was approved for 3 years so a sample size of n=75 was determined

Unfortunately, we did not perform any statistical calculations to determine the sample size at the time of design

Changes in text: Methodology section page 6 line 112

Comment E5. Line 138 - the age range conflicts with Table 2.

Reply E5:

The age range in Table 2 is the correct one, we modified accordingly

Changes in text: Results section page 9 line 184

Comment E6. Line 145 - baseline Hb is reported differently in Table 2.

Reply E6:

We reported the mean, this was modified to the median as reflected in Table 2

Changes in text: results section page 10 line 200

Comment E7. Line 150 - please explain why 10 patients were assessable at 6 months, but the four survival curves appear to show only 6, 6, 6 and 4 patients at risk at that time point, respectively.

Reply E7:

The survival curve figure numbers represent subjects at risk that did not have an event and would be included in the analysis past the 6-month endpoint. We did not run the curve past that point

Comment E8. Line 157 - patient satisfaction is not mentioned in Methods. How was it assessed?

Reply E8:

We modified the methodology section as advised, patients were asked a yes/no question if they were satisfied, and why if not satisfied

Changes in the text: Methodology section page 8 line 145

Comment E9. Lines 215-19 - this information would sit better in Results.

Reply E9:

We have adjusted the discussion section (then relocated to results) to reflect the following:

We included 3 patients with elevated PROM scores (not necessarily massive hemoptysis) all of the 3 patients passed away from disease progression as per death certificate reports.

Changes in text: Discussion section then relocated to results section page 11 line 228

Comment E10. Discussion - the premature closure information is not previously mentioned. It should also be in Results.

Reply E10:

We added the premature closure

Changes in text: Results section page 9 line 182

Comment E11. There are several typos and grammatical errors, most notably in the Conclusion.

Reply E11:

We have reconciled the typos and grammatical errors throughout the paper