Peer Review File

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Reviewer A:

Comment 1: There may be a typo line 34: “patient response and opioid use we reassessed”. Should “we” be “were”

Reply 1: This was a typo, thank you.

Changes in text: “patient response and opioid use *were assessed.*”

Comment 2: - Line 36: it is not clear what “both groups” of participants refer to

Reply 2: updated to clarify groups.

Changes in text: “these metrics were met for *patients and clinicians* over 8 weeks post-RT.”

Comment 3: - Line 39: it is unclear what early recruitment refers to. This is later inferred when reading the manuscript, but the abstract should be able to stand alone

Reply 3: updated to clarify.

Changes in text: “Recruitment was completed *quickly.*”

Comment 4: - Line 46: I would not include new information within the conclusion. The result that 6 patients required further pain management should be within the results. It is not clear when these 6 patients required further pain management (e.g. was this detected given the 8-week follow-up period, or subsequently later?)

Reply 4: This information is in the results, further details added for clarity.

Changes in text: “Six patients were referred back to their provider *for pain management.*”

Comment 5: I think manuscript clarity would be greatly enhanced if the number of patients were added to each of these time points. For example, 20 patients at week -4 to week -1, 14 patients at day 0, etc. This should also include the number of patients that fell into 1 of the 4 categories “no pain response”, “PR or CR sustained”, “PR or CR recurrence”, and “new site of pain”.

Reply 5: Thank you for this insight. This information has now been added to table 2, to provide clarity.

Changes in text:

Patient Outcome	Levels	Week 0	Week 1	Week 4	Week 8
Patients on study		14	14	13	6
Patients referred	Back to RT	0	0	5	1

	deceased	0	1	1	1
	hospice	0	0	2	1
Responded to call	No	0	3	3	1
	Yes	0	11	10	5
Pain Scores	Median (IQR)	9.5 (7.2 to 10)	4.0 (0.5 to 5.5)	5.0 (1.2 to 8.8)	1.0 (0.8 to 1.2)
Opioid Use	Median (IQR)	28.8 (0.0-132.0)	NA	15 (0.0 to 82.5)	52.5 (16.9 to 103.1)

Comment 6: Line 120: Could the authors provide examples of what "alternative" pain management options were discussed for those that had NR at week 4?

Reply 6: Additional information added for clarity.

Changes in text: "*including additional drug management, re-irradiation, surgical management or referral to hospice services.*"

Comment 7: - It would be helpful for the authors to comment why an 8 week time point was thought to be adequate for follow-up? What is considered an adequate surveillance time?

Reply 7: Eight weeks was chosen to balance the level of progression patients were experiencing and the impact of RT on the specific site treated. Whilst 90 days post RT is normally considered the end of the "acute" period, preliminary data suggested many of the patients treated for specific sites of bony mets and progressed or moved to hospice care by week 12.

Changes in text: *"An 8-week study period was chosen to allow for resolution of RT related side effects on the treated site, while acknowledging the advanced nature of disease progression for these patients."*

Comment 8: - Line 156: Though "physician satisfaction with the protocol" was listed as an outcome measure, this wasn't reported within the manuscript.

Reply 8: This was included in error.

Changes in text: *removed.*

Comment 9: - Please provide more information on the time frame (month/year) that the 20 patients were identified. Were they consecutive patients?

Reply 9: All patients who were referred to Rad Onc by other oncology services for pain over a two-month period in 2023 were initially screened. Not all patients were candidates for RT, and only once a treatment plan had been created were those patients formally screened.

Changes in text: *"These patients were referred to Radiation Oncology for acute pain over a period of two months in 2023, from both outpatient and inpatient oncology services."*

Comment 10: - Table 1: For primary disease and primary insurance, there are only 13 (out of the 14) patients accounted for

Reply 10: Thank you for noticing this, a patient was missed. Updated.

Changes in text: *Patient 14 was added (primary site lung(1), Medicaid insurance (9)).*

Comment 11: Table 2: I would clarify within the table that "pain score" reported is at the treated site. This can be gleaned from the Appendix, but on first pass, it otherwise is a little confusing why the pain score dropped at week 8 but there was an increase in OME

Reply 11: Thank you for this helpful information. Table description updated.

Changes in text: *Table 2- Call response, pain score at treated site and opioid use.*

Comment 12: Line 190: What is defined as "end of the study period"? The numbers do not seem to add up, as if there were 5 patients that died, 1 patient that did not answer, and 5 patients that answered the call at 8 weeks, this is only 11 out of the 14 patients.

Reply 12: These numbers are not cumulative, as when patients were referred back to their provider, they were taken off the study and did not receive a further call. Even when patients missed their previous call, the nurses would attempt the next call. We agree that this is not clear in this table and have updated accordingly.

Changes in text: *Table updated to include how many patients were on study at each time point, how many calls were made, and how many were answered.*

Comment 13: - Line 232: Would separate that you met your response feasibility endpoints, but not sure whether outside of the feasibility endpoints, that feasibility of "nurse-led palliative surveillance is strong" given the results under qualitative feedback, specifically about availability of the nursing team to conduct this.

Reply 13: This has been clarified.

Changes in text: that *from the* patients perspective, *enhanced palliative surveillance is feasible*.

批注 [SK1]: Do you mean "from" the patient's side? Or maybe "from the patient's perspective?"

Comment 14: - Line 235: "This suggests that patients were eager for additional nurse-led contact." I don't think this can be concluded from the early recruitment goals and lack of withdrawals. I would consider removing this sentence.

Reply 14: This sentence has been removed.

Comment 15: - Line 243: It would be helpful to understand what were the instances/outcomes in which the follow-up changed management. To this end, I would consider including details regarding the 2 outside healthcare visits for pain – e.g. who were the visits with, was the pain related to the irradiated site, timing of the visits with respect to RT? Also would provide info on the 6 patients that were referred back to radiation oncology, including timing of referral back (this may be able to helpful to inform what is a useful "time period" to offer surveillance for)

Reply 15: Thank you for this insight. We have updated the text to highlight this important point.

Changes in text:

Two outside healthcare visits were associated with pain *to untreated sites*,

Six of the 14 patients were referred back to their radiation oncology provider for pain, *with 4 of the 6 referrals taking place after the week 4 call*, with a variety of outcomes from discussions of adherence to prescribed medications through to additional RT treatments. *It may be appropriate in future studies to target calls around 4 weeks post-treatment*.

Comment 16: - Could you comment on why a 8 week period for FU was entertained, versus something longer?

Reply 16: Explanation added above, please see comment 7.

Comment 17: - I would include discussion of the 6 out of 20 (30%) patients that were deemed ineligible given hospitalization/death within 1 week of RT end or not completing treatment. Presumably did all those that did not complete treatment died or were hospitalized in 1 week? One could argue that if a patient did not complete treatment but survived >1 week, these would be patients that may be an ideal group to follow up, since presumably they did not receive the full intended dose and may benefit from additional fractions if they did not achieve an adequate response

Reply 17: Patients who did not complete treatment were moved to hospice care. Current insurance limitations mean that RT cannot be given whilst a patient is in hospice. Given that these patients were transitioning to end-of-life care, the decision was made to stop unnecessary calls. The numbers of patient in each of these categories were updated in results.

Changes in text: Results: Patients who *transitioned to hospice care (4 patients) and those who died (2 patients)* prior to the week one calls were excluded.

Discussion: *Six patients who were identified as eligible and consented to the study were withdrawn prior to the week one call. The primary reasons for this were further progression of disease or death. In the case of further progression, these patients were transitioned to end of life care. Radiation therapy is not given once a patient has entered hospice services, and as such additional calls were felt to be unnecessary.*

Comment 18: - I agree with the co-authors that especially in lean times, it may be challenging to identify who within a department may be best suited to do follow-up for palliative RT patients. Though the numbers are small, are there ways to identify which subset of palliative RT patients may be best served with offering FU (e.g. it isn't a one FU system for all patients)? Again, this would be going back to your data of which were the patients in whom the 8 week FU period was associated with a meaningful change in patient management

Reply 18: The reviewer certainly brings up a very important question. The study is not powered enough to make these conclusions. The primary goal of this study was to determine feasibility and our ongoing efforts are focused on opening a larger scale to address these important questions raised by the reviewer. We have added this to the limitations section in the Discussion.

Comment 19: - Line 267: What does “supportive measures” refer to here? This seems vague (and unclear whether this is outside the scope of what was presented within the manuscript)

Reply 19: This has been clarified.

Changes in text: there is a clear need for *improved* follow up *after* palliative radiation therapy for painful bone metastases.

Reviewer B

Comment 1: -in table 2 it may be better to put baseline or time 0 instead of just zero, may also want to consider changing patient outcomes to outcome measures and levels to metrics recorded or something else. The table is not clear.

Reply 1: This table has been redone to improve clarity.

Changes in text: Please see new table 2.

Comment 2: -How do you account for the 6 patient drop off from consented to actual enrollment?

Reply 2: These patients were moved to hospice care (which does not allow for palliative RT) or died. We have updated the text to include this.

Changes in text: Results: Patients who *transitioned to hospice care (4 patients) and those who died (2 patients)* prior to the week one calls were excluded.

Discussion: *Six patients who were identified as eligible and consented to the study were withdrawn prior to the week one call. The primary reasons for this were further progression of disease or death. In the case of further progression, these patients were transitioned to end of life care. Radiation therapy is not given once a patient has entered hospice services, and as such additional calls were felt to be unnecessary.*

Comment 3: What happened to the 6 who were referred back to Rad Onc? More RT, new pain strategy, something else? I think this is an important number since it is over 40% (6/14). Is this typical after treating bone mets with RT or is this just because you were looking closer than typical surveillance?

Reply 3: The patients who were referred back to RT covered a range of interventions from further radiation to more simple conversations around drug regimens. Patients were also referred on to hospice. With the closer follow up implemented on this study compared to standard practice surveillance, we were able to identify more opportunities treatment. These patients all had widespread metastatic disease and had originally been referred for radiation for pain crisis, refractory to narcotics. We have updated the text to reflect this.

Changes in text: *These patients were referred to Radiation Oncology for an acute pain crisis over a period of two months in 2023, from both outpatient and inpatient oncology services.*

Comment 4: good to add age, disease status/extent and prior treatments to the demographics. Would intervention be more feasible in younger patients or those with less disease.

Reply 4: All patients enrolled in this study had advanced disease and were in a pain crisis on enrollment. This information has been included within the text. There was no hypothesis generated by looking at age or disease status by our statistician.

Changes in text: We have further clarified the situation by which patients were referred to the RT clinic.

Comment 5: Is this intervention feasible if the staff feel that it is too much of a burden?

Reply 5: From a current staffing perspective, no, especially during COVID. What our study points to in an unmet need in palliative care need and identifies staffing feasibility as a rate limiting step. Importantly, it underscores the necessity of health care systems investment in nursing support as a key potential intervention to overcome these hurdles. This study also highlights the impact such nursing-driven surveillance has on patients' palliative experience at end of life. Such nursing-driven intervention offers a process to identify patients who will benefit from further pain management and as such sets a platform to test the intervention in a larger scale trial, which are part of our ongoing efforts.

批注 [SK2]: Can you please integrate into text of paper?

Changes in text: From a current staffing perspective, this study is not feasible, especially followinging COVID. This study points to an unmet need in palliative care need and identifies staffing feasibility as a rate limiting step. Importantly, it underscores the necessity of health care systems investment in nursing support as a key potential intervention to overcome these hurdles. This study also highlights the impact such nursing-driven surveillance has on patients' palliative experience at end of life. Such nursing-driven intervention offers a process to identify patients who will benefit from further pain management and as such sets a platform to test the intervention in a larger scale trial, which are part of our ongoing efforts.

Comment 6: The discussion lacks any references to similar initiatives or other studies using nurses to evaluate palliative outcomes. What has been done previously and how does it relate to this feasibility study? This would improve the discussion and better establish relevance.

Reply 6: Thank you for this valuable comment. This has been addressed in the discussion.

Changes in text: *Previous studies of nurse-led palliative care follow-up have been found these interventions to be feasible on both the patient and healthcare provider metrics, however no study has taken place in the post-Covid time period.*[8, 14-15]

Comment 7: The compliance of having calls within 3 days of the target time was poor. Were there other reasons other than staffing to explain this?

Reply 7: There were no reasons beyond staffing. When the calls could be added into the standard nursing call schedule, there was high compliance. However, for the days where nursing was understaffed, it was reportedly too challenging to add in the time.

Comment 8: Could the authors comment on patient selection for this intervention? Could the outcomes and number of consented patients who received treatment and were available for calls have been better by better refining the target population? Are there some patients whose prognosis is so poor that this type of an intervention is not reasonable? I mean only 5 patients had calls at 2 months. It seems like a lot of work for very little gain

Reply 8: All patients who were referred to Rad Onc by other oncology services for pain over a two-month period in 2023 were initially screened. Not all patients were candidates for RT, and only once a treatment plan had been created were those patients formally screened. This has been updated in the text. Additionally, the number of calls made by week 8 is only 5 because we removed those who were referred back to their treating MD. While the number of calls was low, we feel the impact of helping those with further pain management is the endpoint, rather than calls made. We have updated table 2 in order to clarify this further.

Changes in text: *Updated table 2*

These patients were referred to Radiation Oncology for an acute pain crisis over a period of two months in 2023, from both outpatient and inpatient oncology services.

Comment 9: How was the number of 20 patients decided upon? Was there consideration for drop off? There is a 20 consented vs 20 evaluable patients, especially with such high drop off.

Reply 8: The number of 20 patients was decided by statistical analysis by the oncology biostatistician (Dr. Hu, coauthor), and was in line with phase 1 trials. In retrospect, there could have been more consideration for drop off, but given the challenges with staffing the calls, especially during COVID, this may have been impractical. As this feasibility study was to serve as a platform for future studies, the small number has provided insight into where such studies and interventions must focus.

Reviewer C

Comment 1: It is mentioned that only 20 patients were included in this trial. Would it be possible to elaborate more on the recruitment? With the trial being organized in an academic hospital, I assume that these patients were recruited in a very short time (maybe even within one to two weeks). I wonder why so little patients were recruited and how long it took to recruit these patients, as patients dropping out of the trial is to be expected and was shown in the results with only 14/20 patients completing treatment. Wouldn't it be more logical to recruit over a set time period to see how many patients agree to be included in the trial; how many patients are missed and how follow-up of a larger set of patients is organized. With only 14

patients to follow-up feasibility is expected to be high, but this may not be the truth in reality (as is already briefly touched upon in the discussion). With such a small number of patients I'm not sure if the feasibility of this undertaking was really discovered. Would it be possible to discuss some of the choices that were made on the number of recruited patients/time of recruitment in the methodology and maybe the discussion.

Reply 1: All patients who were referred to Rad Onc by other oncology services for pain over a two-month period in 2023 were initially screened. Not all patients were candidates for RT, and only once a treatment plan had been created were those patients formally screened. The inclusion criteria were then applied, which reduced the number of eligible patients. The double-sided nature of the feasibility study meant that the inclusion of patients had to be balanced with the availability of nursing staff. Given the uncertainty of feasibility based on nursing availability, a set number was decided upon with statistician input, rather than a time frame.

Changes in text: *"These patients were referred to Radiation Oncology for acute pain over a period of two months in 2023, from both outpatient and inpatient oncology services."*

Comment 2: Regarding pain medication the opioids used were measured, but is there also information available on other pain medications often used for boneM+, such as NSAIDs?

Reply 2: While we did collect information on what concurrent pain medications were taken by patients, this was not included in the paper as these medications were taken PRN, so there was not a consistent way to confirm dose, which varied greatly on a day-to-day basis for each patient, making qualitative metrics challenging. Opioid doses were more closely followed by the patient and their caregivers, making it a more reliable metric.

Changes to text:

Comment 3: If I understand correctly, the calls were made by a trial nurse. Is these trial nurses experienced in radiation oncology or were they dependent on the study checklist during the phone calls?

Reply 3: All nurses involved in the trial were experienced Radiation Oncology nurses with experience in research studies.

Changes to text:

Comment 4: In line 95 it says: information was preferentially obtained from the patient, but where necessary, data were also obtained from a family member or other caregiver. It has been shown that by-proxy information is not always reliable. Is there data on how many patients relied no a proxy to answer their telephone calls?

Reply 4: While we had made provisions for information to be obtained by proxy, there was only 1 call where some questions were answered by proxy. However, in that case, the patient themselves took over the call and the answers to the proxy questions were clarified.

Comment 5: From line 177 it is about the call response rates. Are these patients called whenever there is time for a call? Wouldn't planned calls (telephone consultations) be more logical in

increase response and to keep an overview of patients that need to be called? Please elaborate on this a bit.

Reply 5: The calls made to the patients were scheduled for a specific day, and patients and nurses were given this in advance for the entire trial period. To allow flexibility for nursing staff, a specific time was not arranged.