

### Reviewer A

Comment 1: This is an interesting paper covering a topic that has not been widely examined to my knowledge. The data are quite old (2008-18) and I am not aware if significant changes in radiotherapy practices occurred in this time period.

**Response 1: While there may have been national trends in increasing stereotactic radiotherapy treatment nationally, within the single institution studied there were few changes in the approach to palliative treatment in the time period studied in the analysis. While there have been increasing use of more focused stereotactic radiation for palliative bone metastases over time, it is unclear the extent to which these increases have impacted pain control, with results from a recently reported randomized trial reporting similar rates pain control for spinal metastases with stereotactic radiosurgery and more conventional radiotherapy techniques.**

**Change 1: This has been added to Page 3, Line 99.**

Comment 2: If the data sample were bigger it would be worth some analyses at different time points. The results section is quite short and although results are provided in a table I suggest that the stats will not be accessible to some practitioners. It would be helpful to see the results explained in the main body and the statement about co-morbid depression expanded in such a way that readers can assess its value.

One minor comment: I found percentages alone without the actual data to be quite unhelpful.

**Response 2: We have expanded the results section and included additional explanation of co-morbid depression. All percentages are accompanied by the absolute numbers.**

**Change 2: This has been added to Page 3, Line 99.**

### Reviewer B

Comment 3: The authors provide further evidence that pain derived from cancer is extremely complex and possibly understudied by the medical community. They demonstrate an increase of opioid requirements after what is expected to be a pain alleviation procedure (radiation), they fail to correlate pain relief or increase with regards to treatment, and this is the major shortcoming as in their discussions and conclusions they attribute a higher post radiotherapy MME to "looser prescribing guidelines in this population set forth by the CDC in this population. Thus, higher

prescription rates at the later time points may not necessarily be due to an increased pain burden, but rather, out of an abundance of caution and ease of access.” And other factors such as disease progression or treatment failure could not be ruled out. If this relation (Visual Analog Scale [VAS]) for example and MME could be demonstrated this could increase the impact of this study.

**Response 3: Thank you for your comment. We have included the fact that because pain measurements were not included, the observation of increasing MME prescription after palliative radiotherapy may in fact be secondary to other factors such as disease progression, more aggressive pain management, or changes in provider behaviors.**

**Change 3: We have added this discussion on page 3, line 184.**

### **Reviewer C**

The authors report an interesting research describing relationship between palliative radiotherapy and opioid among patients with metastatic cancer.

As shown below, there are some aspects of the current paper that need to be addressed.

Comment 4: I thought the definition of data (Pre-RT MME 30 days, 60 days, 90 days) difficult to follow; I suspect a reader less familiar with the topic might have even greater difficulties. Are they 30 days, 60 days, 90 days before the start of radiation therapy respectively? please describe them clearly.

**Response 4: We have clarified the definition of the 30, 60, and 90 days pre- and post – radiation therapy.**

**Change 4: This is added to page 4, starting at line 120**

Comment 5: In method, it described that patients with more than 15 treatment fractions, patients who expired 6 months or less after radiation therapy were excluded from this analysis. This Exclusion Criterion may be caused lack of representativeness. If possible, I think that those should be analyzed without excluding them. If it is difficult, you should describe that point as a limitation.

**Response 5 : Thank you for your comment. We felt that the 6 month cutoff was useful, as we were concerned about interpretation data as patients approached the end of life. For instance, if a patient enrolls in hospice care (which by definition requires a life expectancy of 6 months or less), this may fundamentally change prescription practices. It would be practically very difficult to analyze these data, so as per your suggestion, we have included this as a limitation.**

**Change 5: This is added to page 4, starting at line 115, and as a limitation on page 7, line 190**

Comment 6: There is not enough consideration for the increase in MME after radiation therapy. Radiation therapy is a topical treatment and opioids are used for systemic pain or dyspnea. It is unclear whether the increase in opioid dose after radiation therapy is an increase in pain at the irradiated site or an increase in pain in other lesions, or other causes. In Discussion and Conclusions, the lack of data in certain aspects are described as a limitation, is it possible to evaluate these by referring to images and medical records?

**Response 6: Unfortunately, as the data is de-identified, there is no way to link radiology or other clinical or pathologic patient characteristics not otherwise reported. The general practice of palliative radiation oncology is to direct the radiation to the most painful sites of disease. However, we have noted that as a limitation it is impossible to know if any increase in subsequent pain is secondary to lesions within our outside the irradiated field.**

**Change 6: This is addressed in Comment 3, as raised by reviewer B.**

Comment 7: This study shows that the factors about the increased opioid MME requirements after radiotherapy are younger age, head and primary cancer site, and comorbid anxiety and back pain depression. But the reason about that doesn't described. please discuss and add about that.

**Response 7: We have added additional discussion about potential mechanisms that may explain some of the correlations reported in the multivariate analysis.**

**Change 7: This has been reported on line 158.**

Comment 8: Although multivariate OLS is used in this research, the number of cases might be small compared to the number of variables. I recommend consulting to a biostatistics expert if you can.

**Response 8: Our number of cases vastly exceed the number of variables; as such, we feel that our OLS model is producing consistent estimates.**

**Change 8: N/A**

Comment 9: Please refine the tables a little more overall. They are a little bit difficult to understand.

**Response and Change 9: We have refined the tables to the best of our ability for formatting and clarity.**