Peer Review File

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Reviewer A

This editorial on Gillespie et al's recently published Phase II RCT examining the use of prophylactic RT for high-risk asymptomatic bone metastases cautions against acceptance of the positive result at face value. The counterpoints are well argued in my opinion, and the implications in terms of use of resources are significant indeed. I have only a couple of comments:

1. More could be made of statistical issues. Although randomized (not Phase III) and multi-centred (3 affiliated institutions), this was a relatively small trial with limited power (78 patients, 73 evaluable for the primary endpoint). Further, the authors have inflated the sample size by allowing multiple sites per patient (122 treated lesions). Although it is commonly employed in the literature, some statisticians would argue strongly against this practice because it can bias the results towards patients with larger numbers of treated sites (their outcomes may potentially be unrepresentative of the overall eligible population).

Reply: Thank you for the helpful suggestions. We added the following to the second last paragraph:

"Lastly, this study was a relatively small phase 2 trial with limited power, with 78 patients enrolled and 73 evaluable for the primary endpoint. Further, the authors had inflated the sample size by allowing multiple sites per patient (122 treated lesions in total). Although it is commonly employed in the literature, this may bias the results towards patients with larger numbers of treated sites, as their outcomes may potentially be unrepresentative of the overall eligible population."

2. Pain flare para (line 192) - whilst a reasonable issue to consider, has pain flare actually been reported after RT for asymptomatic bone metastases?

Reply: We added the following to the pain flare paragraph

"… though there are little data regarding the incidence of pain flare after radiotherapy for asymptomatic bone metastases."

Reviewer B

The authors are commended for their insightful analysis of a potentially practice changing trial.

As highlighted, a confirmatory phase III trial is needed to elucidate the key points and questions brought forth in this editorial surrounding diagnostic imaging, standardized fracture risk tools, BMAs, dose/fractionation, and clarification regarding baseline characteristics which may have impacted survival.

Prior to publication, they authors may consider additional discussion surrounding the features considered 'high-risk' and whether a dedicated stratification or subset analysis should be performed in the phase III trial to confirm the benefit of prophylactic RT for all indications (junctional spine and bulky lesions descriptively had more SREs in the current trial).

Reply: Thank you for the helpful suggestions. We added the following in page 6, second paragraph:

"In addition, Gillespie et al. reported that the time-to-SRE at the bone metastasis level varied significantly on the basis of the enrolled lesion's definition of high risk, with descriptively more events in junctional spine and bulky sites of disease. A dedicated subset analysis might be warranted in future trials to evaluate the magnitude of benefit of radiotherapy across the different indications."

We also changed to the first sentence of the last paragraph to the following:

"…a future phase III trial… perform subgroup analyses for… **and the indications of radiotherapy**,"

Reviewer C

Well written overview of recent trial and potential limitations that need to be addressed in future inquiries.

Only potential suggested changes: At line 150, consider changing "Gillespie's trial" to "The trial by Gillespie et al."

Reply: Thank you for the helpful suggestions. The amendment was made as suggested.

With respect to discussion of optimal dose/fractionation, I think it may be worth mentioning the LC (1) and CR (2) results of SC.24 showing a benefit in favor of SBRT for symptomatic spinal metastases and with dose escalation above 24/2 (3) as well as the results of Nguyen et al. (4) of SBRT vs conventional RT in the context of non-spinal symptomatic bone metastases, though as noted by the authors that these techniques likely should only be considered in patients with more favorable prognoses who would live to see this potential long-term benefit. These dose/fractionations might be ones to consider to start with for prospective trials but also agree that fractionation in theory may help with mineralization/repair and lower risk of iatrogenic fracture.

1. https://pubmed.ncbi.nlm.nih.gov/35675854/
2. https://pubmed.ncbi.nlm.nih.gov/34126044/
3. https://pubmed.ncbi.nlm.nih.gov/36309076/
4. https://pubmed.ncbi.nlm.nih.gov/31021390/

Reply: Thank you for the helpful suggestions. We added the following to p.5, second paragraph.

"In painful spine metastasis, SBRT has been shown to provide superior local control compared with cEBRT, with dose escalation beyond 24Gy in 2 fractions providing further benefit (15–17). In painful non-spine metastasis, SBRT can also achieve a higher local control compared with cEBRT (18). SBRT may be especially suitable for patients with good prognosis and live long enough to see this potential long-term benefit in local control."