Reviewer’s report

Title: Intensity-modulated radiotherapy with integrated-boost in patients with bone metastasis of the spine: study protocol for a randomized controlled trial

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Reviewer: Chia-Lin Tseng

Reviewer’s report:

The authors of this manuscript proposes a prospective, randomized, single-centre exploratory intervention study consisting of 4 arms for patients receiving palliative spinal radiotherapy for bone metastases. The arms consist of IMRT with 30 Gy in 10 fractions to the whole vertebral body, IMRT with 30 Gy in 10 fractions to the whole vertebral body with the application of a SIB to 40 Gy, 20 Gy in 5 fractions to the whole vertebral body or IMRT with 20 Gy in 5 fractions to the whole vertebral body with the application of a SIB to 30 Gy. The primary aim is to evaluate local control with secondary objectives being QoL, pain response, and toxicities. The proposed is interesting and of relevance to the literature as there are currently no randomized prospective data addressing the value of SIB in IMRT spine irradiation. There are, however, several concerns/questions that deserve mentioning:

1) The protocol describes assessment of the primary endpoint (local control) using CT. However, it is well recognized in the literature and in clinical practice that the sensitivity of CT alone in the assessment of spinal metastases is suboptimal, especially within the epidural space, which is likely going to be under-reported in the current design. The protocol as it is written does not mandate the use of MRI and I do question this decision.

2) The inclusion/exclusion criteria excludes hematologic malignancies but do not make any mention of traditional radiosensitive histologies (ex. SCLC and other neuroendocrine tumors), which may significantly affect the local control rates. Further, are cases of acute cord compression excluded? I would presume these cases would not permit sufficient planning time as proposed in this study and are likely inappropriate for inclusion. The potential added effects of systemic therapy/targeted therapy are not specifically detailed in the methodology. Are these allowed before or concurrent with RT?

3) With respect to OAR delineation, specifically, the delineation of the spinal cord, it would be extremely difficult if not impossible to contour the spinal cord in the absence of an MRI or CT myelogram. It is not clear based on the manuscript whether an MRI will be consistently acquired for this purpose. The GTV is defined as the entire vertebral body but makes no mention of inclusion of posterior spinal elements if involved? Furthermore, how would involvement of posterior spinal elements be determined if an MRI is not acquired? It is not entirely clear what is meant by CTV "is confirmed with PTV". The authors state that the SIB volume will be limited by bone posteriorly and will not extend into the canal, but this will omit coverage of any epidural
disease component, which may be the most important region in terms of threat to the neurological structures. It is not clear why the protocol stipulates coverage of only the osteolytic component with the SIB volume.

4) Technique-wise, the manuscript states that IMRT will be delivered using either tomo or step-and-shoot IMRT. However, these 2 techniques, i.e. one delivered by tomo and another delivered by linac may result in very different dose distribution and homogeneity. How will these differences be reconciled with any differences that may be observed in the outcomes?

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