Author’s response to reviews

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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Author’s response to reviews:

We greatly thank the reviewer for his/her time in reviewing the manuscript and for the positive comments. We have worked to address each facet of the revision suggested by the reviewer and are happy to address any further issues at any point in time. Thanks very much.

Reviewer #1:

It is not clear to which of the vertebra area will be performed the SIB. It is necessary to specify it.

Thanks for this comment. We have completed and specified the SIB definition.

Reviewer #2:

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.

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.

Patients with MSCC are excluded from participating in the study. We included this point in the exclusion criteria. If intraspinal metastases are suspected, an MRI examination is performed beforehand.

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.

Patients with lymphoma, multiple myeloma or sarcoma are excluded. Both radiosensitive and radioresistant solid tumors are included in this study. Different responses to radiosensitive and radioresistant solid tumors can be examined in more detail in the subgroup analysis.

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.

Patients with MSCC are excluded from participating in the study. We included this point in the exclusion criteria.

The potential added effects of systemic therapy/targeted therapy are not specifically detailed in the methodology. Are these allowed before or concurrent with RT?

Radiotherapy is performed in systemic/targeted therapy free interval.

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?

If intraspinal metastases are suspected, an MRI examination is performed beforehand.

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.

1. **SIB: GTV includes the osseus metastasis, CTV= GTV+3 mm safety margin, CTV=PTV**

2. **Without SIB: GTV includes the metastasis, CTV covers the entire WK including posterior structures (pedicles, processi and arcus). CTV+3 mm safety marging= PTV.**

It is not clear why the protocol stipulates coverage of only the osteolytic component with the SIB volume.

SIB is generally applied to the visible osteolysis respectively macroscopic tumor. The response can then be clearly assessed by means of recalcification.

4) Technique-wise, the manuscript states that IMRT will be delivered using either tomo or step-and-shoot IMRT. However, these 2 techniques, ie. 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?

We expect that differences in the conformity and homogeneity of different techniques (helical IMRT using Tomo vs. VMAT/S&S using Linac) should not affect local response.

We have followed up on your point and will search for any differences within the framework of a subgroup analysis.

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.
Among the preconditions for participation in the study is the condition that no metastatic spinal cord compression (tumor distance of more than 3 mm to spinal cord) of the metastasized vertebral body be detected in the MRI recorded during the planning procedure.