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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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: What does it mean the acronym WK?

Thanks for this comment. We have made the correction in the manuscript "vertebral body".

Reviewer #2

1) As the spinal cord will be primary dose-limiting structure, how will the spinal cord be delineated if an MRI is not necessarily acquired for every participant? The spinal cord or the thecal sac cannot usually be adequately be visualized on CT alone. Is the spinal canal going to be used as a surrogate for the thecal sac?
Thanks for this comment. In this case the GTV is always limited by the bone boundary. A drop in dose is accepted to avoid overdose in the myelon. The spinal canal is not equated with the thecal sac if it is clearly delimited.

2) The SIB arm defines the GTV as only the osteolytic (CT-visible) osseous metastasis. Therefore, presumably the authors recognize that potential osteoblastic metastases and/or marrow changes that are only visible on MRI will not be included in the GTV. This has implications in follow-up as local control will be difficult to define. Ideally, local control in follow-up should be defined by MRI as per SPINO recommendation (Lancet Oncol. 2015 Dec;16(16):e595-603).

The reviewer rightly highlights the potential uncertainties. The SPINO Group does not recommend the CT for assessment of spinal tumour response after SBRT. Despite the disadvantages of CT imaging, it does remain its role in assessment of bone integrity and VCF. MR imaging has excellent soft tissue resolution but is not appropriate in the measurement of bone density.

The primary endpoint of this study is defined by bone remodeling according to density. The quantitative measurement of bone density is only possible with CT.

Radiological response after radiotherapy is currently not clearly defined. In particular, the generally accepted radiological response criteria for the osteoblastic lesions are difficult to isolate and utilize.

Harada et al. (J.Radiat.Res., 51, 131-136; 2010) retrospectively researched the radiological response in 102 patients with femoral bone lesions after irradiation. The original criteria: recalcification and size change by plain radiographs were applied. Radiological response for initial sclerotic lesions were mentioned „normalization, complete filling in, regression in size and partial filling in“. CT imaging for radiological response was not performed.

The systematic review by Groenen et al. (Radiotherapy and Oncology, 119, 194-201; 2016) investigated the effect of irradiation alone or combined with bisphosphonates/RANK ligands inhibitors on bone quality. They found a high variability between studies in terms of measuring the radiological response. In eight studies seven unique definitions for radiological response were used. The authors concluded there was no sufficient evidence that radiotherapy had a positive effect on bone quality.

Therefore, for an evaluation of the response, only osteolytic metastases are included. The measured differences (in-/decrease bone density, sclerotic rim) between groups can be compared. This also enables an international comparison.

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.