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Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy

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ABSTRACT

Background: To report the primary endpoint of a randomized trial comparing pain response following palliative stereotactic body radiation therapy (SBRT) versus conventionally-fractionated 3D-conformal radiotherapy (3DCRT) for previously untreated spinal metastases.

Methods: Fifty-five patients with histologically/radiologically confirmed painful spinal metastases were analyzed in this single-institutional, non-blinded, randomized explorative trial. Participants were randomly assigned (1:1) to receive single-fraction SBRT (24 Gy) or 3DCRT (30 Gy in 10 fractions). The primary endpoint was pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months following radiotherapy completion. Other recorded parameters included pain response (per International Bone Consensus response definitions), use of concurrent medications and opioid usage (oral morphine equivalent dose, OMED). All parameters were assessed at baseline and at three and six months after RT. Intention-to-treat analysis was applied. This trial is registered with ClinicalTrials.gov, number NCT02358720.

Findings: Despite no significant differences for VAS at 3 months between groups ($p = 0.13$), pain values decreased faster within this time period in the SBRT arm ($p = 0.01$). At 6 months following RT, significantly lower VAS values were reported in the SBRT group ($p = 0.002$). There were no differences in OMED consumption at 3 ($p = 0.761$) and 6 months ($p = 0.174$). There was a trend toward improved pain response in the SBRT arm at 3 months ($p = 0.057$), but significantly so after 6 months ($p = 0.003$). No patient in the SBRT group experienced grade $\geq$3 toxicities according to the Common Terminology Criteria for Adverse Events v.4.03.

Conclusions: This randomized trial demonstrates the utility of palliative SBRT for spinal metastases, which was associated with a quicker and improved pain response. Larger ongoing randomized studies will assist in further addressing these endpoints.

Abbreviations: CR, complete response; CT, computed tomography; CTCAE, common terminology criteria for adverse events; CTV, clinical target volume; 3DCRT, conventional 3D conformal radiotherapy; EBRT, external body radiotherapy; Gy, gray; IMRT, intensity-modulated radiotherapy; IP, intermediate pain; MRI, magnetic resonance imaging; MV, megavolt; OAR, organ at risk; OMED, oral morphine equivalent dose; OS, overall survival; PP, pain progression; PR, Partial response; PTV, planning target volume; QoL, quality of life; RT, radiotherapy; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; VAS, visual analog scale; VMAT, volumetric modulated arc therapy.

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Approximately one third of cancer patients will develop bone metastases, approximately two thirds of which involve the vertebral column, most commonly at the thoracic and lumbar levels [1,2]. Conventionally fractionated 3D-conformal radiotherapy (3DCRT) is a well-recognized palliative treatment for painful bone metastases [3–14]. Comprehensive meta-analyses by Sze et al. and Wu et al. have provided consistent data regarding pain response after conventional external beam radiotherapy [13,14]. The overall (pain) response (OR) was up to 60% and complete (pain) response (CR) around one third [13,14]. A systematic review by Chow et al. yielded similar results in respect to OR, but lower CR rates of approximately 23% [3].

It has long been questioned whether an increase in radiation dose may lead to increased pain control while maintaining few toxicities. Although 3DCRT is limited in its capacity to dose-escalate owing to spinal cord dose constraints, stereotactic body radiation therapy (SBRT) is a highly conformal technique that does allow for safe dose-escalation [15–19]. These notions have been supported by phase I–II data demonstrating a clinical benefit of SBRT in the primary or salvage treatment of stable spinal lesions [20]. Phase II results of the RTOG 0631 study showed stereotactic radiosurgery to be feasible and accurate [21]. The latter is the basis for the currently ongoing RTOG 0631 phase III assessment, which aims to compare pain response and quality of life (QoL) between SBRT (single dose of 16 Gy) and EBRT (external beam radiotherapy) (single dose of 8 Gy).

To date, no randomized trials are available comparing SBRT with conventional 3DCRT in terms of pain relief. Furthermore, the interaction between ablative doses and pain response remains unclear. The aim of this randomized trial was to analyze pain response after high-dose SBRT versus conventional 3DCRT for this patient population.

Materials and methods

Subjects, recruitment strategy, and eligibility for enrollment

From November 2014 to March 2017, 60 patients with histologically confirmed cancer and painful bone metastases of the thoracic or lumbar vertebral column were randomized in both arms: high-dose single-fraction SBRT (24 Gy) versus standard fractioned 3DRT (10×3 Gy).

Inclusion criteria were ages 18–80, a Karnofsky performance score [22] $\geq$70, ability to provide written informed consent, a maximum of two irradiated vertebral bodies per region, a maximum of two different vertebral regions affected, and tumor distance >3 mm to the spinal cord. Exclusion criteria were subjects with significant neurological or psychiatric disorders precluding informed consent, previous RT to the given irradiation site, contraindications for MRI, multiple myeloma or lymphoma histology, or involvement of the cervical spine.

In total, five patients were duly excluded. Four patients in the SBRT arm had an insufficient distance between tumor and spinal cord. One participant from the control arm was excluded because of the confirmed diagnosis of multiple myeloma after randomization. 55 patients met the inclusion/exclusion criteria and were enrolled into the trial (Fig. 1).

The randomized trial, registered on clinicaltrials.gov (NCT02358720), was approved by the Heidelberg University Independent Ethics Committee (Nr. S-431/2013). Additionally, approval was given from the German Federal Office of Radiation Protection (BfS).

Design, randomized allocation, and procedures

This was a randomized, single-institutional, explorative study with the intention to compare pain response after high-dose single fraction SBRT versus conventional 3DCRT in patients with painful untreated spinal bone metastases. Details of the study design have been published previously [23]. A block randomization approach (block size of 6) was used to ensure that the two groups were balanced.

Two different techniques were evaluated on a 1:1 basis according to the randomization list: high-dose, single-fraction (24 Gy to the 80% isodose line) SBRT versus 30 Gy in 10 fractions of conventional radiotherapy.

The randomization procedure was carried out by a central office. Prior to their enrollment into the study, patients underwent staging of the vertebral column in connection with planning computed tomography (CT) and MRI to measure the spinal cord dimension. The prerequisite for participation in the study was the exclusion of spinal cord compression, along with a sufficient distance (>3 mm) between the metastasized vertebral body and spinal cord on MRI.

The primary endpoint-related parameters were measured at the start of RT (t_0), at the end of RT (t_1), 3 months post-RT (t_2), and 6 months post-RT (t_3). These parameters included the following: documentation of pain according to the Visual Analog Scale (VAS), neuropathic pain, OMED [5], and as well as individual patient-specific data such as use of concurrent medications.

During therapy, treating physicians documented each of these parameters; subsequently, patients continued complete documentation by means of pain diaries. VAS (collated as weekly mean values) and concurrent medication usage were documented daily for 3 months, and once after 6 months. In addition, use of basic pain medications and other concurrent medications (or medication changes) were continuously recorded from the start of RT to 6 months. In addition to patient-reported neuropathic pain use, opioid analgesic usage was converted into an oral morphine equivalent dose (OMED), and any non-opioid analgesics were also recorded.

Patient records were collected by the authors. The evaluation included all recorded data up to the 6-month follow-up interval. The baseline data of the patient characteristics are presented in summary (Table 1).

Assessment of the primary endpoints

The primary endpoint of this randomized, single-institutional, phase II trial was pain response after high-dose single-fraction SBRT versus conventional 3DCRT in patients with painful, previously untreated spinal metastases. The primary endpoint was defined as pain relief >2 points according to the visual analog scale (VAS) measured at the irradiated region three months after RT (t_2). The pain response was assessed according to the International Bone Consensus response categories by Chow et al. [5] as complete response (CR), partial response (PR), pain progression (PP), and intermediate pain (IP) at 3 and 6 months after RT. Complete response (CR) was defined as VAS = 0 after 3 months and partial response (PR) as an improvement by at least two score points after 3 and 6 months. CR was defined as VAS = 0 at the treated site with no concurrent increase in analgesic intake (stable or reducing analgesics in daily OMED). PR was defined as pain reduction of 2 or more at the treated site without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain. PP was defined as increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline. Any response not covered by the complete response, partial response, or pain progression definitions was called "intermediate pain". Responders were defined as having CR or PR, non-responders as having PP or IP.

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