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Clinical Study

Phase I/II trial of combined kyphoplasty and intraoperative radiotherapy in spinal metastases

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Abstract

BACKGROUND CONTEXT: Spinal metastases occur in 30%–50% of patients with systemic cancer. The primary goals of palliation are pain control and prevention of local recurrence.

PURPOSE: This study aimed to test the safety and efficacy of a combined modality approach consisting of kyphoplasty and intraoperative radiotherapy (Kypho-IORT).

STUDY DESIGN/SETTING: Kyphoplasty and intraoperative radiotherapy was a prospective, single-center phase I/II trial. Patients were enrolled in a classical 3+3 scheme within the initial phase I part, where Kypho-IORT was applied using a needle-shaped 50 kV x-ray source at three radiation dose levels (8 Gy in 8-mm, 8 Gy in 11-mm, and 8 Gy in 13-mm depth). Thereafter, cohort expansion was performed as phase II part of the trial. The trial is registered with clinicaltrials.gov, number NCT01280032.

PATIENT SAMPLE: Patients aged 50 years and older with a Karnofsky Performance Status of at least 60% and with one to three painful vertebral metastases confined to the vertebral body were eligible to participate.

FDA device/drug status: Approved (INTRABEAM System (Carl Zeiss Meditec AG).

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The sponsor of this trial was the University of Heidelberg, Mannheim Medical Faculty and it was conducted with institutional funds. Financial support was received by Carl Zeiss Meditec AG (the manufacturer of the IORT device) for radiobiological research associated with the trial and not reported here.

FAG serves as consultant and speaker for Carl Zeiss Meditec AG (the manufacturer of the device used for IORT in this trial), NOXXON Pharma AG, Merck Serono GmbH, Roche Pharma AG, and Siemens Healthcare Diagnostics GmbH, hold patents related with Carl Zeiss Meditec AG and is co-founder of pab^2 cancer solutions. GW received travel support from Carl Zeiss Meditec AG. FB, UO, ESp, FS and SC are on the Carl Zeiss Meditec AG speaker's bureau. FW is an advisor, consultant and speaker for Celgene GmbH, Roche Pharma AG, Eli Lilly and Company, and Ipsen Pharma GmbH, receives travel and research grants from Carl Zeiss Meditec AG and Elekta AB, is on the Carl Zeiss Meditec AG speaker's bureau and holds patents related with Carl Zeiss Meditec AG.

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OUTCOME MEASURES: The primary end point was safety as per the occurrence of dose-limiting toxicities. The secondary end points were pain reduction, local progression-free survival (L-PFS), and overall survival (OS).

METHODS: Pain was measured using the visual analog scale (VAS) and local control was assessed in serial computed tomography or magnetic resonance imaging scans.

RESULTS: None of the nine patients enrolled in the phase I part showed dose-limiting toxicities at any level and thus, 52 patients were subsequently enrolled into a phase II part, where Kypho-IORT was performed at various dose levels. The median pain score significantly dropped from 5 preoperatively to 2 at the first postoperative day ($p<.001$). Of 43 patients who reported a pre-interventional pain level of 3 or more, 30 (69.8%) reported a reduction of ≥3 points on the first postoperative day. A persistent pain reduction beyond the first postoperative day of ≥3 points was seen in 34 (79.1%) patients. The 3, 6, and 12 month L-PFS was excellent with 97.5%, 93.8%, and 93.8%. The 3, 6, and 12 months OS was 76.9%, 64.0%, and 48.4%.

CONCLUSION: Kyphoplasty and intraoperative radiotherapy is safe and immediately provided sustained pain relief with excellent local control rates in patients with painful vertebral metastases.

Keywords: Cement augmentation; Intraoperative radiotherapy; IORT; Kyphoplasty; Metastatic spine tumor; Vertebral metastases

Introduction

The spine is the most common site of bone metastases in systemic cancers [1]. Around 40% of patients with bone metastases will suffer from vertebral metastases [2,3], 90% of them with severe axial pain. Initial management of metastases confined to the vertebral body includes radiotherapy, kyphoplasty/vertebroplasty or other minimal invasive techniques, all with the goal of palliation and local control.

External beam radiotherapy (EBRT) resembles a commonly and broadly applied first-line option in vertebral metastases. Depending on the availability of techniques, there are regional variations in fraction schedules. Most common regimens include a single dose of 8 Gy (most common in the United States) and 30 Gy in 10 fractions [4]. External beam radiotherapy may provide acceptable local control rates, but pain relief occurs rather slowly within several weeks to months after treatment [5–7]. Stereotactic body radiotherapy (SBRT) also provides excellent local control and pain response comparable or even better than standard EBRT [8,9]. However, as these high single doses also deplete osteoblasts, roughly 40% of patients treated with SBRT will in the long run encounter vertebral compression fractures [10].

Minimally invasive techniques like kyphoplasty or vertebroplasty have substantially improved care of palliative patients. However, although the impressive analgesic and stabilizing effect of kyphoplasty could be shown in several studies [11,12], these approaches have no anticancer effect and postintervention EBRT is mandatory, causing a prolongation of the overall (local) treatment time as well as a delay in the application of efficient systemic therapies.

A possibility to shorten treatment time are one-stop-shop procedures that combine kyphoplasty with other locally active anticancer methods, such as kyphoplasty combined with intravertebral administration of ^{153}Samarium or interstitial implantation of ^{125}I seeds [13,14]. However, both techniques require handling of nuclides and specific dosimetric prerequisites.

We developed a novel approach that combines kyphoplasty with intraoperative low-energy x-ray radiotherapy (Kypho-IORT) [15–17] and here report on the outcome of a prospective phase I/II trial of this technology.

Material and methods

Study design

This prospective study was designed as a single-arm dose escalation phase I/II study, consisting of a phase I dose escalation part and a phase II cohort expansion. The protocol was approved by the local institutional review board (2009-338Str.-MA) and the Federal Office for Radiation Protection (Z5-22462/2-2010-010). It is registered at clinicaltrials.gov, number NCT01280032. All patients provided written informed consent at least 24 hours before treatment. General eligibility criteria were described in detail before [17]. In brief, patients aged 50 years or older with a known primary cancer disease (largest diameter <4 cm) and spinal metastases between T4 and L5 were eligible for Kypho-IORT. Tumors needed to be confined to the vertebral body (Tomita 1). Patients with fractured or instable vertebrae were not excluded (stability was estimated with Taneichi and spinal instability neoplastic scores). Spinal canal involvement (including cord compression) or metastatic growth into more dorsal structures like pedicle or lamina was an exclusion criterion, whereas an involvement of the posterior wall was rated as uncritical.

Technique and procedures

Kyphoplasty and intraoperative radiotherapy was described in detail before (14, 15, 16). All patients were placed in prone position under general anesthesia. Kyphoplasty was performed with minor modifications to adapt for IORT, which requires placement of the irradiation device through the metallic sleeves. The device (Intrabeam System, Carl Zeiss

Meditec, Oberkochen, Germany) resembles a miniature x-ray generator that accelerates electrons through a drift tube that then hit a gold target at the tip. The braking radiation generated is of low energy (10–50 kV) and is emitted spherically around the tip. A needle-applicator with an outer diameter of 4.2 mm that fits into the transpedicular kyphoplasty sleeve (5.0-mm inner diameter) is then plugged onto the drift tube and inserted into the vertebral body (ideally the center of the metastasis). After verification of the applicator position by biplanar x-ray and calculation of the distance to the spinal canal, irradiation was applied for a total of 2–5 minutes. Thereafter, the system was removed and a standard kyphoplasty with inflation of the balloon followed by bipedicular cement injection was performed.

Dose escalation and safety

Dose escalation was performed in a classical 3+3 dose scheme with 3 patients entering each dose level (level I: 8 Gy in 8-mm, level II: 8 Gy in 11-mm, and level III: 8 Gy in 13-mm depth, calculated from the isocenter of the radiation source). All patients were monitored for dose-limiting toxicities (DLTs) for at least 90 postoperative days, whereas DLTs included wound-healing difficulties or infections, osteoradionecrosis, nerve or spinal cord injury, and pathologic fractures.

Phase II part (cohort expansion)

In parallel to the phase I part, we performed a cohort expansion for data consolidation and treated 52 patients at various dose levels. In this part of the trial, patients younger than 50 years and patients with vertebral tumors ≥4 cm were also eligible to participate.

Efficacy parameters

Local progression free survival (L-PFS), overall survival (OS), and pain control were secondary end points that were indicative for efficacy of the IORT part. Local PFS was measured from the date of Kypho-IORT until the date of local recurrence as per computed tomography or magnetic resonance imaging scanning or date of last follow-up (death was not considered as an end point for L-PFS). Distant PFS was measured from the date of Kypho-IORT until the day of any cancer progression or death by any cause. Overall survival (OS) was defined as time span from the date of Kypho-IORT until death by any cause. Pain was scored using the visual analog scale (VAS). The Kaplan-Meier method was used to estimate OS and PFS, and the Friedmann test for non-normally distributed data was used to assess changes in pain over time. The paired-samples *t*-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data were used to compare different time points. All tests of significance were two-tailed, and the level of significance was set at 0.05. All statistical analyses were performed with IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics, safety

In sum, 61 patients (76 vertebrae) were treated with Kypho-IORT, 9 (13 vertebrae) thereof within the phase I trial and 52 (63 vertebrae) within the phase II cohort expansion part (Table). The median age was 62 years (18–86), the median follow-up of all patients was 6.7 months (range 0–41 months), whereas 19 patients had a follow-up of more than 1 year.

Most spinal metastases originated from breast (45.9%) and lung cancers (18.0%). In the absence of DLT, the dose was safely escalated within the phase I part. Minor complications included temporary symptomatic radiculopathy (1 patient) and asymptomatic perivertebral leakage of bone cement in 55 cases (72% of all treated vertebrae), which is in the expected range after standard kyphoplasty of metastases [18,19]. Of 74 lesions treated, 1 compression (re-)fracture occurred (1.4%) in a patient with a locally progressive tumor. No treatment-related deaths were observed. There was no change

Table
Patient characteristics

Characteristics	N (range)	%
Gender		
Female	34	
Male	27	
Age (median)	62 (18–86)	
KPS (initial)	80 (60–100)	
Primary tumors		
Breast cancer	26	42.6%
Lung cancer	11	18.0%
Prostate cancer	6	9.8%
Gastrointestinal cancer	6	9.8%
Genitourinary cancer	4	6.6%
Multiple myeloma	2	3.3%
Gynecologic cancer	2	3.3%
Others	4	6.6%
Location		
Total number of vertebrae	76	
Thoracic spine	49	64.5%
Lumbar spine	27	35.3%
IORT dose		
8 Gy in 8 mm	48	63.1%
8 Gy in 10 mm	20	26.3%
8 Gy in 13 mm	8	10.5%
Other therapies after Kypho-IORT*		
Surgery to vertebrae treated with Kypho-IORT	2	3.3%
EBRT to vertebrae treated with Kypho-IORT	2	3.3%
EBRT to other locations	14	23.0%
Chemotherapy	28	45.9%
Antihormonal therapy	14	23.0%
None	17	27.9%

KPS, Karnofsky Performance Status; IORT, intraoperative radiotherapy; kypho-IORT, kyphoplasty and intraoperative radiotherapy; EBRT, external beam radiotherapy.

* Sums up to more than 100% as patients may have received multiple therapies after Kypho-IORT.

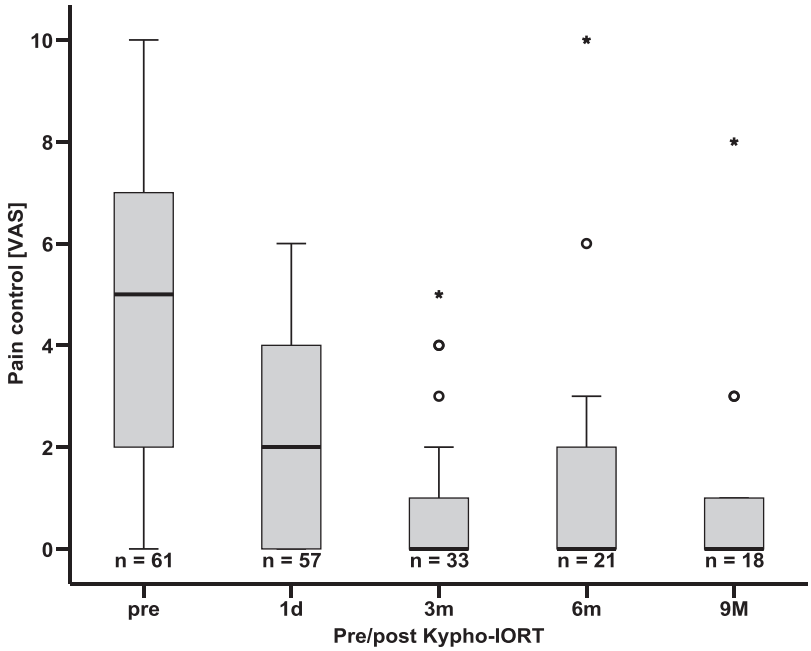

Fig. 1. Pain scores measured at various time points. Shown are box-and-whisker plots of all patients treated with Kypho-IORT (n=61). Data were collected at 5 time points (preoperative pain scores, scores at day 1, and scores during the follow-ups at 3, 6, and 9 months post Kypho-IORT). Points are outliers, the box indicates the interquartile range, the whiskers indicate the range, and the horizontal line within the box is the median. Extreme values are plotted as asterisks. Kypho-IORT, kyphoplasty and intraoperative radiotherapy; VAS, visual analog scale.

in motor strength over time (the median strength at the first postoperative day, at 6 months, and at 12 months was 5/5 [range 3–5], 5/5 [4–5], and 5, respectively). Median surgical time was 65 minutes (range: 38–173 minutes) which is roughly 10 minutes longer than a regular kyphoplasty.

Pain control

Kyphoplasty and intraoperative radiotherapy caused a significant reduction of pain with a drop in the median preoperative pain score of 5 of 10 to a median score of 2 of 10 ($p<.001$) at the first postoperative day (Fig. 1). No difference in pain control could be detected in patients of the dose escalation part compared with the cohort expansion. We also separately analyzed 13 patients who reported pain scores at all 5 time points (data not shown). Consistent with the pooled data, pain significantly improved from a median score of 3 of 10 to a median score of 0 of 10 (Friedman test: $p<.001$). Of note, 30 of 43 patients (69.8%) who had a preoperative pain score of ≥3 reported a reduction of 3 or more points at the first postoperative day. Sustained pain control of 3 or more points at any postoperative time point was seen in 34 of these 43 patients (79.1%). Of 51 patients with a pre-interventional pain score ≥1, 27 showed a complete response (52.9%) over all time points.

Local and distant tumor control, overall survival

The overall 3-, 6-, and 12-month L-PFS was excellent with 97.5%, 93.8%, and 93.8% (Kaplan-Meier estimates; Fig. 2). The 3-, 6-, and 12-month distant (off-target) PFS was 52.5%, 29.2%, and 20.0%. In total, three patients were failing locally (two with breast cancer, one with colorectal cancer). Two of these patients received second (open) surgery, with tumor debulking and posterior fixation followed by postoperative EBRT to a total dose of 40 Gy (applied in 20 fractions). The median OS was 11.8 months (95% CI: 6.2–17.5 months). The 3-, 6-, and 12-month OS was 76.9%, 64.0%, and 48.4%.

Discussion

Patients with progressive metastatic cancers commonly await a timely initiation of systemic therapies and thus, logically, local palliative approaches should be limited to only few days of treatment time. Furthermore, in the light of more effective systemic therapies gaining clinical impact (including targeted therapies and immunomodulators), the portion of patients that will achieve long-term systemic tumor control will increase [20]. This in consequence requires modern local palliative approaches for spinal metastases to fulfill three criteria: they have to be short, guarantee sustained local tumor control, and provide instantaneous vertebral stability.

External beam radiotherapy is an integral part of local therapy, with several studies revealing fair pain control within weeks to months, whereas the various regimes appear to be equally effective [4,6,7,21]. Nielsen et al. enrolled 239 patients with bone metastases receiving either fractionated radiotherapy (4×5 Gy) or a single treatment (1×8 Gy) [22]. Pain relief was seen in 60%–70% of patients 3–5 months after therapy in both arms with no significant differences. In line with this, Koswig and Budach showed similar pain response

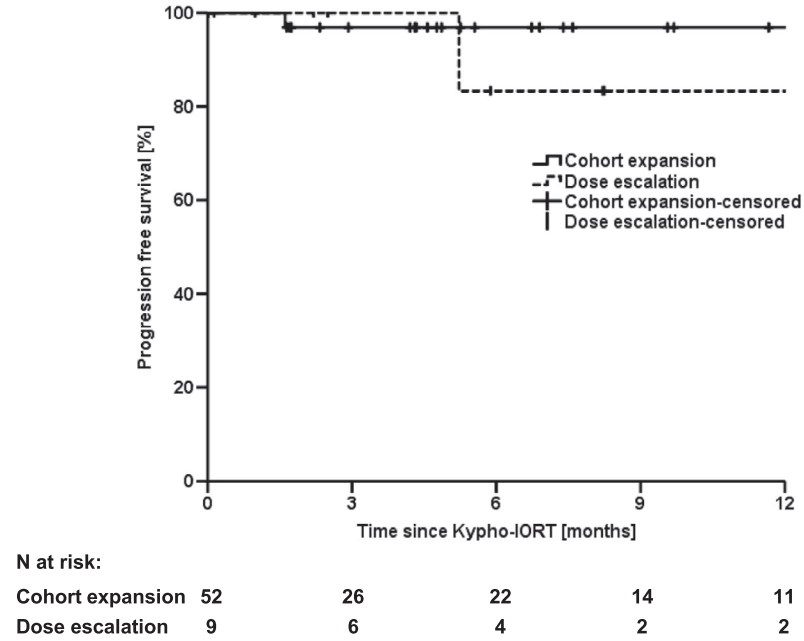

Fig. 2. Local progression-free survival. Shown are Kaplan-Meier plots for 52 patients treated within the (phase I) dose escalation part and for 9 patients treated in the (phase II) cohort expansion part of the trial. Kypho-IORT, kyphoplasty and intraoperative radiotherapy.

rates after single-fraction (1×8 Gy) or fractionated (10×3 Gy) radiotherapy, also without significant differences in both treatment arms [23]. However, high single doses appeared to provide faster responses: 50% of the patients who received fractionated EBRT showed a response after 10 days, whereas patients treated with a single fraction responded after a median of 5 days.

In addition to all time-consuming radiation therapy planning necessities, treatment time is further prolonged by fractionation. Hence, specifically in cases where metastases are confined to the vertebral body, SBRT has become a widespread option to considerably shorten treatment times. A recent systematic review by Husain et al. suggested a 1-year local control rate of 85%–90% [24]. Chang et al. reported radiological control of spinal metastases in 90% of patients at 6 months and in 80% at 12 months [25], which was similar to data from Sheehan et al. who obtained a decreased or stable tumor volume in 82% of the patients at follow-up (mean 12.7 months) [9].

However, high single doses to vertebrae illicit local inflammatory responses, and roughly 70% of patients will require steroids to manage pain "flares" which emerge hours to days after SBRT [26]. High single doses will also deplete osteoblasts, which are essential to re-mineralize and re-stabilize the bone, leading to vertebral compression fractures in as much as 4 out of 10 patients treated with SBRT, resembling a risk that is 8 times higher than with fractionated radiotherapy [27] [10,28,29]. In particular, patients with single lesions (the odds ratio is 3.5), pre-existing, or impending fractures are at highest risk [30]. Of note, with a median time to fracture of 2.5 months, even highly palliative patients are likely to experience this considerable side effect with the necessity of further salvage interventions (typically cement augmentation procedures) [28], and approaches to combine SBRT with subsequent kyphoplasty suggested a >90% likelihood of pain control [31].

A limitation of this study is the "basket" design, with patients suffering from cancers of different histologies and thus receiving various other therapies after Kypho-IORT. Roughly half of our patients had spinal metastases of breast or prostate cancers, where antihormonal therapy or chemotherapy may have contributed to local control at the site of Kypho-IORT. However, roughly 20% suffered from lung cancers, which are generally more aggressive and less responsive to systemic therapies [32], and none of the patients who failed locally had cancers of these histologies, suggesting a high efficacy of the procedure.

The technique we prospectively evaluated here, Kypho-IORT, can be performed in a standard operating room [33] and resembles a one-stop-shop treatment option for patients who would be eligible for SBRT. Yet in contrast to SBRT, the immediate stabilization after sterilization of the tumor eliminates the risk of a subsequent compression fracture and provides instantaneous pain relief, with similar outcomes in terms of complete pain response rates (50%) and local tumor control (almost 94% at 1 year) [24].

Conclusion

Kypho-IORT is a minimally invasive procedure with immediate and sustained pain relief, excellent local control rates, and a low toxicity profile. The procedure has the potential to become a valuable treatment option in the palliative setting, where treatment times should be minimized and palliation ef-

ficiency is key for preserving quality of life. A prospective randomized phase III study comparing Kypho-IORT versus EBRT (1×8 Gy or 10×3 Gy) has in consequence been initiated.

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