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ORIGINAL ARTICLE

Effective local control of vertebral metastases by simultaneous integrated boost radiotherapy

Preliminary results

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Abstract
Background The primary endpoint was to improve local tumour control of patients with metastatic spinal tumours by stereotactic body radiotherapy (SBRT) and dose escalation by simultaneous, integrated boost (PTV-boost). We used a whole vertebral body (PTV-elective) contouring approach. Secondary endpoints were severity of acute and chronic adverse effects and overall survival.
Methods In all, 33 patients with metastases of the vertebral column were treated at Erlangen University Hospital. SBRT was given in 12 or 10 fractions. The metastatic lesion (PTV-boost) received 3.6 Gy (range 3.0–4.51 Gy) per fraction for a total of 42.0 Gy (24.36–48.0 Gy) and the whole vertebra (PTV-elective) received 2.85 Gy (range 1.8–3.6 Gy) per fraction for a total of 32.39 Gy (range 21.60–38.0 Gy). Patients were followed up every 3 months.
Results Local control rate of all patients was 93 % at 12 and 24 months. The overall survival rate was 54 % at 12 months, 38 % at 24 months and 18 % at 36 months. No radiation myelopathy occurred. The most frequently observed adverse events in 3 cases was oesophagitis grade 2.
Conclusion SBRT with simultaneous, integrated boost was associated with excellent local control of 93 % after 24 months. This result shows the possibility of delivering escalated doses to the target while still keeping the incidence of side effects low. This study forms the basis for a future randomised controlled trial comparing conventional radiotherapy (10 fractions of 3 Gy) with hypofractionated dose intensified SBRT (12 fractions of 3 Gy + integrated boost 12 fractions of 4 Gy) for improvement of local tumour control and pain.

Keywords Spine · Radiotherapy · Integrated boost · Dose escalation · Neoplasm metastasis

Stabilität von Wirbelsäulenmetastasen bei Brustkrebs nach Radiotherapie

Eine retrospektive Analyse von 157 Fällen

Zusammenfassung
Hintergrund und Ziel Das primäre Ziel der Studie war die Verbesserung der lokalen Tumorkontrolle von Patienten mit Wirbelkörpermetastasen mittels stereotaktischer Radiotherapie (SBRT) mit Dosiseskalation durch einen simultan integrierten Boost (PTV-Boost). Dabei wurde der ganze Wirbelkörper konturiert (PTV-Elektive). Zu den sekundären Endpunkten der Studie gehörten der Schweregrad von akuten und chronischen Nebenwirkungen sowie das Gesamtüberleben.
Patienten und Methoden 33 Patienten mit spinalen Metastasen wurden am Universitätsklinikum Erlangen behandelt. SBRT wurde in 12 oder 10 Fraktionen appliziert. Die erreichte Maximaldosis in der Metastase (PTV-Boost) war 42,0 Gy (24,36–48,0 Gy) bei einer Einzeldosis von 3,6 Gy (Spanne 3,0–4,51 Gy). Die mediane Referenzgesamtdosis im Wirbelkörper (PTV-Elektiv) betrug 32,39 Gy (Spanne 21,60–38,0 Gy) bei einer Einzeldosis von 2,85 Gy (Spanne 1,8–3,6 Gy). Die Nachsorge der Patienten wurde in 3-monatigen Abständen durchgeführt.

Dorota Lubgan and Anke Ziegaus contributed equally to this work.

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Ergebnisse Nach einer Beobachtungszeit von 12 und 24 Monaten waren 93 % der Läsionen lokal kontrolliert. Das Gesamtüberleben belief sich nach einem Jahr auf 54 %, nach 2 Jahren auf 38 % und nach 3 Jahren auf 18 %. In keinem Fall trat eine Myelitis auf, in 3 Fällen wurde eine Ösophagitis (Grad 2) als akute Nebenwirkung berichtet.
Schlussfolgerung Die SBRT von Wirbelkörpermetastasen mit integrierter moderater Boostbestrahlung zeigt exzellente Ergebnisse. Die lokale Kontrolle beträgt 93 % nach 24 Monaten. Dies Daten belegen, dass es möglich ist, die Dosis zu eskalieren, ohne die Nebenwirkungsrate zu erhöhen. Diese Arbeit bildet die Basis für eine randomisierte, kontrollierte Studie, die eine konventionelle Radiotherapie (10 × 3 Gy) mit einer hypofraktionierten, dosisintensivierten SBRT (12 × 3 Gy + integriertem Boost 12 × 4 Gy) vergleicht, um so die lokale Tumorkontrolle zu verbessern und Schmerzen zu verringern.

Schlüsselwörter Wirbelsäule · Strahlentherapie · Integrierter Boost · Dosissteigerung · Tumormetastasierung

The spine is the third most common site for metastatic disease, following the lung and the liver [22]. Radiation therapy (RT) plays an important role in the treatment of vertebral metastases, including palliation of pain, control or prevention of neurological symptoms and prevention of pathologic fractures [6, 21].

It is generally accepted that patients with very short life expectancy should be treated with single-fraction (8–10 Gy) or short course RT (e.g. 20 Gy in 5 fractions) to keep overall treatment short [15]. The schedule 10 fractions of 3 Gy is recommended for patients with better prognosis [13].

In a multivariate analysis by Rades et al. [14], it was shown that local control remained significantly ($p = 0.018$) associated with the radiation schedule only, whereas the tumour type was not significant. In the patients who received short-course radiotherapy with 1 fraction of 8 Gy, the local control rates at 12 months were 59 % whereas after long-course radiotherapy with 10 fractions of 3 Gy, the 12-month local control rates were 83 %. The protracted schedule has resulted in fewer in-field recurrences, but nevertheless 17 % of patients showed local failure after 12 months [14].

Recently, new approaches such as intensity-modulated radiotherapy (IMRT) [8] or stereotactic body radiotherapy (SBRT) [6, 10] have been suggested for the treatment of vertebral metastases. Outcome data show high rates of local control and suggest better efficacy than with conventional palliative therapy [20]. Furthermore, it has been shown that the use of different contouring approaches—whole versus partial vertebral body contouring for stereotactic radiation therapy—has a beneficial effect on the local in-field recurrence [12].

The aim of our trial was to improve local tumour control by stereotactic body radiotherapy through an increase in total and single dose compared to the standard irradiation with 10 fractions of 3 Gy and contouring using the whole vertebral body approach (PTV-elective). Dose escalation was realized by simultaneous, integrated boost by means of image-guided stereotactic radiotherapy (IGRT and hfSRT). Secondary endpoints were severity of acute and chronic adverse effects and overall survival.

Material and methods

Study design

Patient selection

Between February 2010 and March 2013, 33 patients with metastases of the vertebral column were treated at Erlangen University Hospital by stereotactic radiotherapy with an integrated boost.

Eligible patients were aged 18 years or older with vertebral metastasis confirmed via radiology or biopsy. Further inclusion criteria were pain in the involved spinal region, Karnofsky Index ≥ 60 % and a life expectancy > 6 months. Exclusion criteria included short life expectancy, > 3 involved vertebral levels, spine instability, metastatic neoplasms involving the spinal cord, previous radiotherapy at the involved metastasis and more than 6 distant metastases outside of the spine. The study was conducted in accordance with the current version of the Declaration of Helsinki [7] and according to Good Clinical Practice [3].

Treatment planning

Fractionated stereotactic radiotherapy was performed using the dedicated stereotactic radiosurgery system Novalis™ (BrainLAB, Feldkirchen, Germany). Intensity-modulated radiotherapy (IMRT) was used to treat 64.1 % of patients. Patients were treated on consecutive workdays, with one fraction per day.

PTV-boost was defined as involved parts of the vertebra based on T1 sequence with 1 mm margin in the x/y/z axes without spinal cord and PTV-elective as whole vertebra. The target volume concept can be seen in Fig. 1a, b. Organs at risk—the spinal cord and oesophagus—were contoured according to the MRI. The dose was prescribed according to the ICRU guidelines.

Outcome measurements and statistical analysis

Local progression-free survival (local control) was assessed through repeat MRI or CT imaging. Local progression was

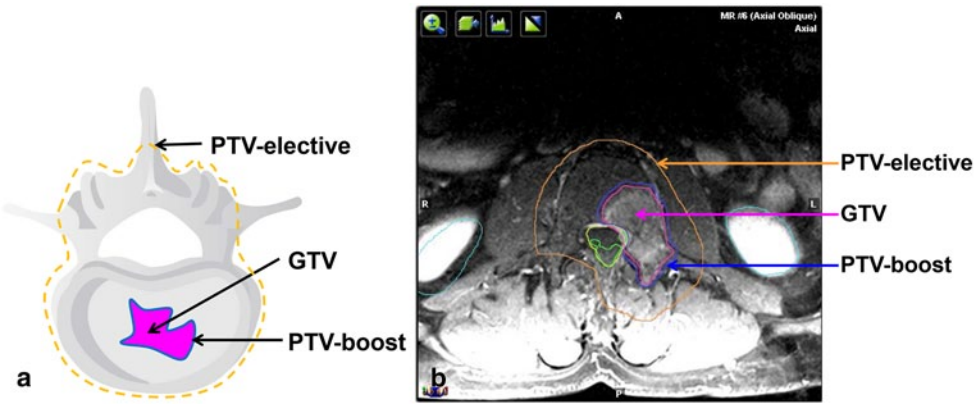

Fig. 1 Definition of irradiation planning. *GTV* (gross tumour volume) based on CT alone = metastasis; *PTV-boost* (planning target volume) based on T1 sequence MRI with 1 mm margin in x/y/z axes without spinal cord, *PTV-elective* whole vertebra (**a**, **b**)

evaluated using RECIST criteria as previously described [4]. In order to permit adequate analysis, the patients were examined according to the scheme in Table 2. The study used the International Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and adverse events reporting. An assessment of pain during and after irradiation was not documented due to the heterogeneous patient collective with extraspinal metastases, and with it the associated administration of diverse amounts of analgesia.

Continuous variables were evaluated using descriptive statistics, and unless indicated otherwise, results are presented as mean and/or median ± standard deviation (SD). Standard summary statistics and two-tailed 95% confidence intervals (CI) were calculated as appropriate. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp., Armonk, NY, USA). The level of significance for all analyses was set at $\alpha = 0.05$ (two-tailed).

Kaplan–Meier curves for local progression-free survival, progression-free survival (PFS) and overall survival (OS) were calculated starting from the first day of treatment. The date of progression was selected as the date of first event including local progression or distant metastases. OS was defined as the time from the first day of irradiation until death due to any cause. Surviving patients were censored at date of last contact.

Results

Patient characteristics

A total of 27 patients with one and 6 patients with two metastatic lesions of the vertebral column were enrolled in the study. Baseline characteristics were performed for all patient data sets (Table 1).

The types of cancer were as follows: 9 (27.3%) patients suffer from renal cell carcinoma, 6 (18.2%) breast cancer, 5 (15.2%) prostate cancer, 2 (6.1%) rectal cancer, 2 (6.1%) multiple myeloma, and 1 (3.0%) malignant melanoma, thyroid cancer, hypopharyngeal cancer, GIST of the duodenum and cancer of unknown primary respectively.

Spinal metastases of 10 patients (30.3%) were synchronous and of 23 patients (69.7%) were metachronous. The median interval from primary cancer diagnosis to irradiation was 29.57 months (range 0.36–166.79 months). Metastases occur most frequently in the thoracic spine (51.3%) followed by the lumbar (35.9%) spine, then the cervical (5.1%), sacrum (5.1%) and coccyx spine (2.6%). In all, 38.5% of spinal metastases involved the vertebral body and foramen, 30.8% vertebral body, foramen and the spinous process followed by the vertebral body (17.9%) and the spinous process alone (12.8%); 24 (72.7%) patients showed other extraspinal metastases.

Treatment

Two patients received a previous operation at the involved metastasis. Systemic therapy consists of chemotherapy, hormone therapy and immunotherapy, which was administered concurrently with the irradiation in 33.3, 17.9 and 10.3% of patients respectively. Radiotherapy was given in 12 (71.8%), 10 (25.6%) or 16 (2.6%) fractions. The PTV-boost received 3.6 Gy (range: 3.0–4.51 Gy) per fraction up to a total of 42.0 Gy (24.36–48.0 Gy). Radiotherapy on PTV-elective (whole vertebra) was delivered to a median total dose of 32.39 Gy (range 21.60–38.0 Gy) in single fractions of 2.85 (range 1.8–3.6) Gy daily (Fig. 1, Table 1). GTV and PTV-elective values were 23.60 cm^3 (0.60–157.30 cm^3) and 184.10 cm^3 (36.20–477.70 cm^3) respectively.

Outcome

Patients were followed up as described in Table 2. The median follow-up at the time of overall survival (OS) analysis was 13.01 months (range 1.08–41.77 months). OS rate of all patients was 54% at 12 months, 38% at 24 months

Table 1 Patient characteristics

General data/medical history (*N*=33 patients)	
Age (years)	
Mean ± SD	65.67 ± 11.910
Median (range)	70.00 (41–85)
Sex	
Male	18 (54.5%)
Female	15 (45.5%)
Primary cancer diagnosis	
Renal cell carcinoma	9 (27.3%)
Breast cancer	6 (18.2%)
Prostate cancer	5 (15.2%)
Rectal cancer	2 (6.1%)
Multiple myeloma	2 (6.1%)
Liposarcoma	2 (6.1%)
Chondrosarcoma	1 (3.0%)
Sacroma	1 (3.0%)
Malignant melanoma	1 (3.0%)
Thyroid cancer	1 (3.0%)
Hypopharyngeal cancer	1 (3.0%)
GIST of duodenum	1 (3.0%)
Cancer of unknown primary	1 (3.0%)
Metastases	
Spinal metastases	
Synchronous	10 (30.3%)
Metachronous	23 (69.7%)
Interval from cancer diagnosis to irradiation (months)	
Mean ± SD	47.68 ± 45.20
Median (range)	29.57 (0.36–166.79)
Other distant metastases (outside of spine)	
No	10 (30.3 %)
Yes	23 (69.7 %)
Number of other distant metastases (outside of spine)	
0	10 (30.3%)
1	13 (39.4%)
2	1 (3.0%)
3	4 (12.1%)
4	3 (9.1%)
> 5	2 (6.0%)
Number of spinal metastases/patient	
1	27 (81.81%)
2	6 (18.19%)
Total 39 metastases	
Site of spinal metastasis (*N*=39 metastases)	
Cervical	2 (5.1%)
Thoracic	20 (51.3%)
Lumbar	14 (35.9%)
Sacrum	2 (5.1%)
Coccyx	1 (2.6)
Site of metastasis in vertebra	
Vertebral body	7 (17.9%)
Vertebral body + foramen	15 (38.5%)
Spinous process	5 (12.8%)
Vertebral body + foramen + spinous process	12 (30.8%)
Therapy	
Previous therapy of spinal metastasis	
No	37 (94%)
Yes (surgery)	2 (5.1%)
Concurrent therapy during irradiation	
No	15 (38.5%)
Chemotherapy	13 (33.3%)
Hormone therapy	7 (17.9%)
Immunotherapy	4 (10.3%)
Irradiation	
Fractionation regimen	
10 × 3 Gy (total dose 30 Gy)	10 (25.6%)
12 × 3 Gy (total dose 36 Gy)	28 (71.8%)
16 × 2.5 Gy (total dose 40 Gy)	1 (2.6%)
IMRT	
Yes	25 (64.1%)
No	14 (35.9%)
PTV-boost dose to a reference point (Gy)	
PTV-boost total dose (Gy)	
Mean ± SD	41.49 ± 4.69
Median (range)	42.0 (24.36–48.0)
PTV-boost single dose (Gy)	
Mean ± SD	3.70 ± 0.29
Median (range)	3.6 (3.0–4.51)
Max total dose (Gy)	
Mean ± SD	45.56 ± 16.85
Median (range)	49.19 (29.64–58.48)
Max single dose (Gy)	
Mean ± SD	4.14 ± 0.47
Median (range)	4.15 (2.88–5.00)
PTV-elective dose to a reference point (Gy)	
PTV-elective total dose (Gy)	
Mean ± SD	30.99 ± 3.59
Median (range)	32.39 (21.60–38.0)
PTV-elective single dose (Gy)	
Mean ± SD	2.7 ± 0.30
Median (range)	2.85 (1.8–3.6)
GTV/PTV-elective (cm^3)	
GTV (cm^3)	
Mean ± SD	33.16 ± 34.47
Median (range)	23.60 (0.60–157.30)
PTV-elective (cm^3)	
Mean ± SD	210.63 ± 135.72
Median (range)	184.10 (36.20–477.70)
Organs at risk maximum dose (Gy)	
Spinal cord total dose (Gy)	
Mean ± SD	35.31 ± 4.06
Median (range)	32.39 (23.52–41.70)
Spinal cord single dose (Gy)	
Mean ± SD	3.02 ± 0.55
Median (range)	3.09 (0.0–3.59)
Spinal cord biological effective dose BED (Gy_2)	
Mean ± SD	87.32 ± 16.10
Median (range)	76.10 (0.0–114.15)

Table 1 (continued)

Spinal cord EQD_2 (Gy)	
Mean ± SD	43.64 ± 8.02
Median (range)	38.05 (0.0–57.08)
Oesophagus total dose (Gy) n = 26	
Mean ± SD	21.51 ± 13.15
Median (range)	26.48 (0.00–38.47)
Oesophagus single dose (Gy)	
Mean ± SD	1.87 ± 1.12
Median (range)	2.4 (0.0–3.21)

Data are number of patients (%) unless otherwise stated. *GIST* gastrointestinal stromal tumor, *SD* standard deviation, *IMRT* intensity-modulated radiotherapy, *PTV* planning target volume, *GTV* gross tumor volume, *BED* biological effective dose, *EQD_2* equivalent 2 Gy dose

and 18% at 36 months (Fig. 2a). Progression-free suvival rates were 48% at 12 months, 27% at 24 months and 9% at 36 months.

The major efficacy outcome measure of the trial was local progression-free survival. Of the 33 evaluable patients (39 irradiated metastases), 32 show no progression of their metastasis (Figs. 2b and 3a–c) and 1 patient experienced disease progression (Figs. 2b and 4a–c). The median follow-up for the cohort was 11.85 months (range 0–41.77 months). The local control rate of all patients was 93% at 12 and 24 months (Fig. 2b). At the last follow-up, all of the 9 surviving patients were disease-free.

Adverse events

Overall the incidence of adverse events (AEs) suspected to be related to the irradiation was low. No deaths occurred during irradiation. No cases of radiation myelopathy were observed. Patients received a median spinal cord maximum total dose of 32.39 Gy (range 23.52–41.70 Gy) at a 3.09 Gy (0.0–3.59 Gy) single dose per day. A median of maximum BED and EQD_2 values to the myelon assuming an alpha–beta ratio of 2 Gy were 76.10 (0.0–114.15) and 38.05 (0.0–57.08) respectively.

The most frequently observed AEs was oesophagitis grade 2 in 3 of 39 irradiated cases. The median oesophagus maximum total dose was 26.48 Gy (range 0.00–38.47 Gy). An MRI scan confirmed the presence of a pathological fracture in the L4 irradiated vertebra body of 1 patient. The pathological fracture occurred 4 months after irradiation with 10 fractions of 3 Gy (PTV-boost total dose: 38.00 Gy).

Discussion

The use of stereotactic body radiotherapy has been increasing in the management of metastatic spinal tumours [6, 17]. This study examined the effect of SBRT with simultaneous, integrated boost on local tumour control of patients with spinal metastases. Especially appealing is the possibility of

Table 2 Patient follow-up and assessment scheme

Assessment	Prior RT	Weekly during RT	1 month	3 months	6 months	Every 3 months
Physical examination	X	X	X	X	X	X
Karnofsky performance index	X	X	X	X	X	X
NCI CTCAE v4 toxicity	X	X	X	X	X	X
MRI/CT imaging	X	X	X	X	X	X

NCI CTCAE v4 National Cancer Institute Common Terminology Criteria for Adverse Events version 4, *MRI/CT* magnetic resonance imaging/computed tomography, *RT* radiotherapy

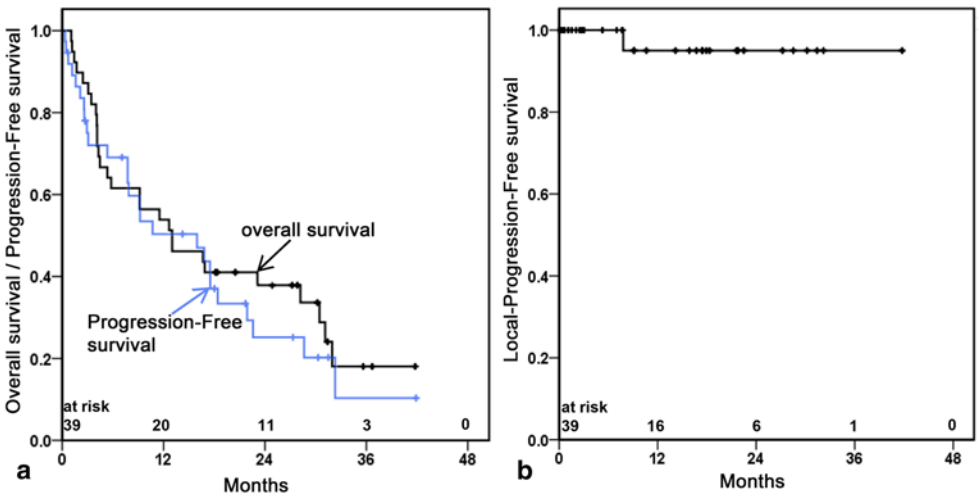

Fig. 2 Overall survival, progression-free survival (**a**) and local progression-free survival (**b**) rates of the complete study group. Survival rates are given in % for the 3-year survival (36 months)

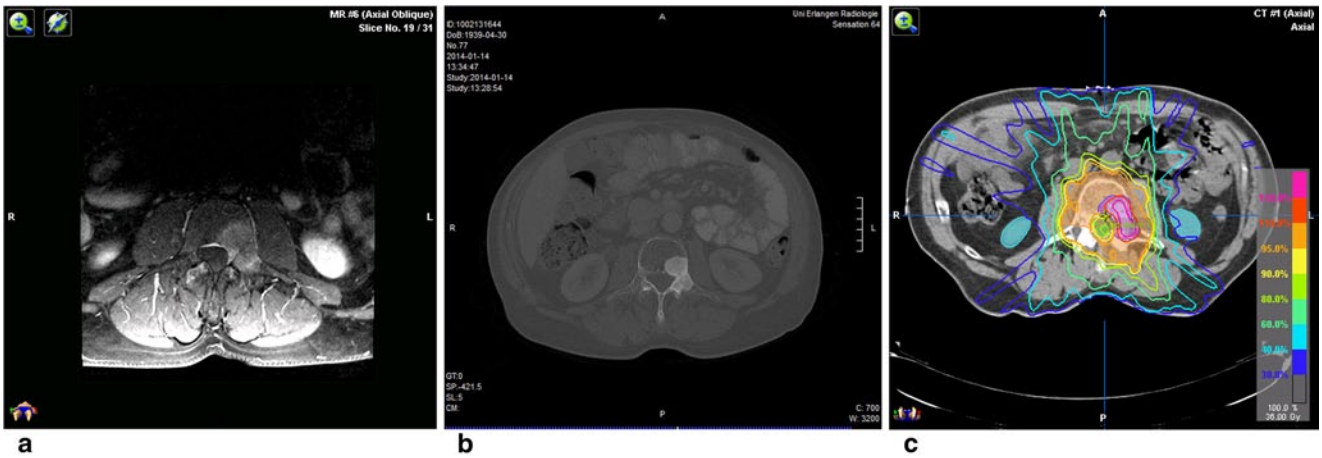

Fig. 3 Example: Local control after stereotactic therapy of a 52-year-old patient with prostate cancer metastasis in the L2 vertebral body. Bone metastasis prior to irradiation (**a**), sclerotisation of irradiated metastasis 20 months after stereotactic therapy (**b**), axial CT slice of the dose distribution (**c**), dosage: total dose 36 Gy to a reference point for the 12-fraction regimen, PTV-boost: total dose 45.60 Gy, single dose 3.8 Gy

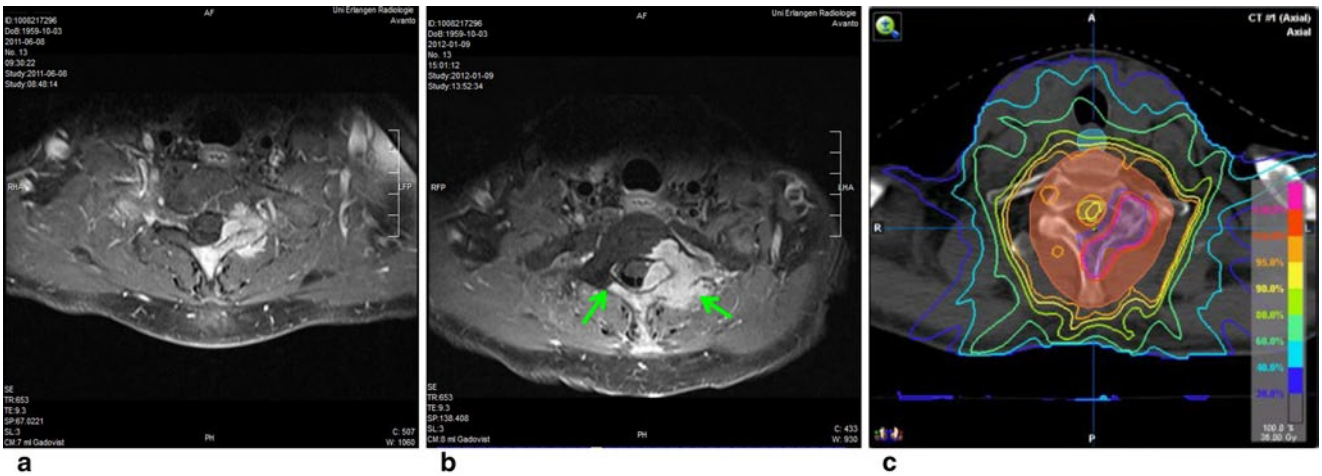

Fig. 4 Local progression 7 months after stereotactic therapy of a 51-year-old patient with liposarcoma metastasis in the T1 vertebral body. Bone metastasis size estimated by MR imaging with gadolinium-based contrast agents prior to (**a**) and 7 months after irradiation (**b**), axial CT slice of the dose distribution (**c**), dosage: total dose 36 Gy to a reference point for the 12-fraction regimen, PTV-boost: total dose 46.80 Gy, single dose 3.9 Gy

shaping the dose distribution within the target in such a way that areas with a high tumour cell load received increased doses (PTV-boost), while the whole vertebral body was contoured and also irradiated (PTV-elective).

The definition of PTV-boost presented here differs from the study of Guckenberger et al. [6]. The PTV-boost in our study based on T1 sequence MRI with 1 mm margin in the x/y/z axes without the spinal cord was considerably smaller (GTV 23.69 cm^3 and PTV-elective 184.10 cm^3) compared to that employed by Guckenberger al. [6]. As a result, patient selection has been typically oriented to those with fewer than six metastases outside the spine and patients with radioresistant histologies such as renal cell carcinoma, colorectal cancer and sarcoma.

Outcome data show high rates of local control for spine metastases treated with SBRT and suggest better efficacy than with conventional palliative radiotherapy [20]. For conventional irradiation, one of the largest series consisting of 603 patients with radiological follow-up showed a 1-year local control rate of 86 % for tumours located within the vertebral bone [11, 20]. No longer follow-up is reported up to day.

We have shown that 1-year local control was improved (93 %) in patients receiving 12 fractions of 3 or 10 fractions of 3 Gy as SBRT with integrated boost compared with findings of Rades et al. (86 %) after 10 fractions of 3 Gy conventional irradiation (standard regimen in Germany) [14]. The 2-year local control was 93 % too. No significant difference was found between the three fractionation schedules

(10 fractions of 3 vs. 12 fractions of 3 vs. 16 fractions of 2.5 Gy). Other outcome measures included progression-free survival (PFS) and overall survival (OS). OS rate of all patients was 54 % at 12 months, 38 % at 24 months and 18 % at 36 months. OS was predominantly limited by systemic progression.

Chang et al. [2] investigated patterns of failure after SBRT of 74 spinal metastatic lesion. The actuarial 1-year tumour progression-free incidence was 84 % for all tumours. Pattern-of-failure analysis showed two primary mechanisms of failure: (1) recurrence in the bone adjacent to the site of previous treatment probably due to in part to radiation underdosing in the region as a result of spinal cord constraints, and (2) recurrence in the epidural space adjacent to the spinal cord, probably due to the fact that these structures were not routinely included in the target volume unless visibly involved with tumour. In our study only a single patient had local progression 7 months after SBRT outside the previously irradiated PTV-boost but within PTV-elective.

A retrospective study for the clinical outcomes of 154 metastatic lesion of the spine treated with SBRT using either a whole (WB) or partial (PB) vertebral body contouring approach has shown that the WB group had a lower retreatment rate (11 %) versus 18 % in PB group [12]. Our findings confirm the analysis of Patel et al. [12] that contouring of whole vertebral body for PTV-elective shows potential benefits by reducing the risk of recurrence.

Moreover, no recurrence in adjacent vertebral after SBRT of 500 patients was observed [5]. This confirms that irradiation of the involved vertebra only, without the vertebrae above and below was an adequate treatment option in relation to the rate of local control and acute or chronic adverse effects.

Using higher doses in PTV-boost is a clinical decision in which tumour control is weighed against toxicity. Unfortunately, the higher biologically equivalent doses (BED) conferred by stereotactic body radiotherapy can also result in acute radiation toxicity such as oesophagitis [1] and late toxicity notably myelitis [16, 18, 19] or vertebral compression fracture (VCF) [20]. Overall, the observed incidence of radiation-induced oesophagitis is low in clinical trials and retrospective studies [9]. We reported three cases (3/39; 7.7 %) of oesophageal toxicity grade 2 associated with SBRT for spinal metastases.

Radiation myelopathy is one of the most serious late radiation-induced toxic effects after spinal SBRT and although rare, can cause both paralysis and death [19]. The maximal irradiation dose delivered to the spinal cord was about 32.5 Gy. Usually it was administered in 12 or 10 fractions, with a 3 Gy single dose per day. During a follow-up ranging from 1–42 months (median 13 months), there were no clinically detectable neurologic signs that could be attributed to radiation-induced myelopathy. We have shown that a higly conformal isodose distribution of SBRT sparing of the spine cord is possible.

A more frequent and yet serious late effect is spinal SBRT-induced VCF. Although VCF is a fairly low-risk adverse event (approximately 5 % risk) after conventional radiotherapy, crude risk estimates for VCF after spinal SBRT range from 11–39 % [20]. We have observed one pathological fracture 4 months after irradiation of renal cell carcinoma metastasis in the L4 vertebral body.

We recognize that the results of our study are based on a limited number of cases and that there are no reliable data concerning pain. In our institution, efforts have been made with the goal of increasing the local control rate and decreasing the irradiation-induced adverse effects after SBRT as compared to conventional irradiation. The excellent 2-year local control of 93 % was probably owed at least to some extent to our contouring of the whole vertebral body (PTV-elective) approach and dose escalation by simultaneous, integrated boost focused only on the involved parts of the vertebra.

Conclusion

Hypofractionated stereotactic body radiotherapy with simultaneous, integrated boost was associated with excellent local control of 93 % after 24 months, comparable to historical results of 61 to 81 % of conventional palliative radiotherapy of spinal metastases (1 fraction of 8 Gy, 10 fractions of 3 Gy). This raises the possibility of applying escalated doses to the target (PTV-boost), while still keeping the incidence of side effects low. The intention of this study was to form the basis for a future randomised controlled trial comparing conventional radiotherapy (10 fractions of 3 Gy) with hypofractionated dose intensified radiation by IGRT hfSRT mediated boost (12 fractions of 3 Gy + integrated boost 12 fractions of 4 Gy) for improvement of local tumour control and pain.

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Compliance with ethical guidelines

Conflict of interest D. Lubgan, A. Ziegaus, S. Semrau, U. Lambrecht, S. Lettmaier and R. Fietkau state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

References

1. Abelson JA, Murphy JD, Loo BW Jr et al (2012) Esophageal tolerance to high-dose stereotactic ablative radiotherapy. Dis Esophagus 25:623–629
2. Chang EL, Shiu AS, Mendel E et al (2007) Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine 7:151–760
3. E3 IT (1996) ICH Topic E3, Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95)
4. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
5. Gerszten PC, Burton SA, Ozhasoglu C et al (2007) Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine (Phila Pa 1976) 32:193–199
6. Guckenberger M, Hawkins M, Flentje M et al (2012) Fractionated radiosurgery for painful spinal metastases: DOSIS—a phase II trial. BMC Cancer 12:530
7. The World Medical Association (WMA) (2008) Helsinki Do. Declaration of Helsinki—ethical principles for medical research involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, Korea, October 2008
8. Inoue T, Oh RJ Shiomi H (2011) New approach for treatment of vertebral metastases using intensity-modulated radiotherapy. Strahlenther Onkol 187:108–113
9. Lo BM (2013) An evidence-based approach to acute aortic syndromes. Emerg Med Pract 15:1–23 (quiz 4)
10. Mantel F, Glatz S, Toussaint A et al (2014) Long-term safety and efficacy of fractionated stereotactic body radiation therapy for spinal metastases. Strahlenther Onkol 2014 DOI:10.1007/s00066-014-0706-1
11. Mizumoto M, Harada H, Asakura H et al (2011) Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at Shizuoka Cancer Center Hospital. Int J Radiat Oncol Biol Phys 79:208–213
12. Patel VB, Wegner RE, Heron DE et al (2012) Comparison of whole versus partial vertebral body stereotactic body radiation therapy for spinal metastases. Technol Cancer Res Treat 11:105–115
13. Rades D, Stalpers LJ, Veninga T et al (2005) Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. J Clin Oncol 23:3366–3375
14. Rades D, Lange M, Veninga T et al (2011) Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 79:524–530
15. Rades D, Weber A, Bartscht T et al (2014) A new prognostic factor for the survival of patients with renal cell carcinoma developing metastatic spinal cord compression. Strahlenther Onkol 190:667–670
16. Sahgal A, Ma L, Gibbs I et al (2010) Spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 77:548–553
17. Sahgal A, Bilsky M, Chang EL et al (2011) Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. J Neurosurg Spine 14:151–166
18. Sahgal A, Ma L, Weinberg V et al (2012) Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 82:107–116
19. Sahgal A, Weinberg V, Ma L et al (2013) Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. Int J Radiat Oncol Biol Phys 85:341–347
20. Sahgal A, Whyne CM, Ma L et al (2013) Vertebral compression fracture after stereotactic body radiotherapy for spinal metastases. Lancet Oncol 14:e310–e320
21. Schlampp I, Rieken S, Habermehl D et al (2014) Stability of spinal bone metastases in breast cancer after radiotherapy: a retrospective analysis of 157 cases. Strahlenther Onkol 190:792–797
22. Witham TF, Khavkin YA, Gallia GL et al (2006) Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nat Clin Pract Neurol 2:87–94 (quiz 116)