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Original Article

Risk factors for vertebral compression fracture after spine stereotactic body radiation therapy: Long-term results of a prospective phase 2 study

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ABSTRACT

Purpose: To identify frequency, clinical relevance and risk factors for vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT) with long-term follow up (FU).
Methods: From 2012 to 2015, 61 lesions (56 patients) were treated within a prospective multicenter phase 2 study (NCT01594892) of SBRT for painful vertebral metastases. Post-SBRT VCF were identified. Anatomical segments, normal and tumor tissue of treated vertebrae were segmented for volumetric analyses. Predictive factors for VCF were identified by logistic regression.
Results: Median clinical and radiological FU for all patients was 16.2 months (range, 0–68.2) and 7.8 months (range, 0–66.9), respectively. Local metastasis control was observed in 82% of lesions at last imaging FU. Post-SBRT VCF occurred in 21 lesions (34.4%): 16.4% showed a progressive VCF, while a new VCF occurred in 18.0%. 3/56 (5.4%) patients developed painful VCF defined as pain increase by $\geq$2 on the visual analogue scale (VAS) and 2 (3.6%) patients required surgical stabilization. Pre-SBRT VCF, localization in the thoracic spine, Bilsky score >0, SINS score, pre-SBRT osteolytic volume and metastatic vertebral body (VB) involvement were predictive factors for VCF on univariate analysis. Relative VB involvement, osteolytic volume and pre-SBRT VCF remained in the multivariate logistic regression model that had AUC = 0.930, 83.3% sensitivity and 96.6% specificity.
Conclusion: Spine SBRT resulted in favorable long-term pain and local metastasis control. Despite post-SBRT VCF being observed after one third of treatments, this was symptomatic in only 5% of patients. Predictive factors for developing VCF were identified which could contribute to better selection of patients for spine SBRT.
 Radiotherapy and Oncology 141 (2019) 62–66

Bone metastases frequently occur in metastatic cancer patients and the spine is a common site of tumor spread [1]. Palliative radiation therapy (RT) is an effective therapy for painful spinal metastases [2]. Stereotactic body radiation therapy (SBRT) to the spine has been implemented in the last decade as a highly efficient approach [3,4]. By multimodality imaging for target volume definition, modern intensity-modulated treatment planning, radiotherapy delivery with image-guidance and nearly rigid patient immobilization, SBRT enables safe treatment with escalated doses to the affected parts of the vertebra whilst sparing the spinal cord. Spine SBRT achieves favorable rates of local metastasis control of approximately 90% at 1 year, and complete pain response in approximately 50% of patients, with overall low rates of serious adverse events [5].

However, vertebral compression fracture (VCF) is frequently reported as a potential adverse event following SBRT, with highly variable incidence rates [6–9]. Although most fractures are asymptomatic, vertebral compression fractures may be associated with pain aggravation, neurological dysfunction and the need for surgical interventions. Herein we report a secondary endpoint on the long-term outcome of VCF from a prospective, multicenter, non-randomized, single-arm, phase-2 study cohort of dose-intensified hypofractionated SBRT for painful spinal metastases.

Methods

This prospective, multicenter, phase 2 nonrandomized clinical trial was approved by the local ethics committees, registered at

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ClinicalTrials.gov (NCT01594892), and conducted in accordance with the ethical standards set forth by the Declaration of Helsinki [10]. Study population, SBRT treatment planning and delivery techniques as well as study endpoints have been reported in detail before [11]. All macroscopically involved anatomical segments (body, pedicles, transverse process, and spinous process) of the affected vertebra were treated with an escalated dose. The entire vertebra including the spinal canal was electively treated with a lower dose. Patients were stratified to their life expectancy using the modified Mizumoto score [12]. Patients with intermediate life expectancy were treated with 5 fractions (total dose for the high-dose PTV, 35 Gy [biologically effective dose at $\alpha/\beta = 10$ Gy (BED_{10}), 59.5 Gy]; total dose for the low-dose PTV, 20 Gy [BED_{10}, 28 Gy]). Patients with long life expectancy were treated in 10 fractions (total dose for the high-dose PTV, 48.5 Gy [BED_{10}, 72 Gy]; total dose for the low-dose PTV, 30 Gy [BED_{10}, 39 Gy). SBRT was delivered with a 6 to 18-MV linear accelerator with onboard imaging cone-beam CT using volumetric modulated arc therapy or step-and-shoot intensity-modulated radiation therapy.

The primary endpoint of the study was pain response 3 months after treatment at the treated site. Secondary endpoints of the study were local control, overall survival and cancer specific mortality, quality of life and acute and late toxicity documented according to NCI CTCAE v 4.0. Patient-reported worst and average pain during the last week was scored on a visual analogue scale (VAS) from 0 to 10 (0 = no pain; 10 = most severe pain) before SBRT, on the last day of SBRT treatment, at 1, 2, 3, 4, 5, and 6 weeks and 3, 6, 9, 12 months after SBRT and every 3 months thereafter.

During radiological follow-up local lesion control and appearance of VCF were assessed. Local failure was defined using RECIST criteria as an increase of the target lesion in tumor dimension equivalent to >20% increase in the largest dimension (LP), in the case of a partial remission initially, or the presence of measurable tumor after an initial complete remission [13]. Post treatment MRI and contrast-CT was performed 6 and 12 weeks after SBRT and every 3 months thereafter in the first year of FU, then every 6 months from the second year. 61 lesions (56 patients) were treated between 2012 and 2015 in 5 international radiation oncology departments. 7 lesions (6 patients) were surgically stabilized before SBRT and therefore excluded from the analyses of predictive factors for VCF. 3 patients (3 lesions) were lost to follow-up immediately after SBRT completion and thus excluded. Baseline CT and MR images were assessed to identify pre-SBRT VCF. On the follow up images, patients were evaluated for a worsening of a pre-existing VCF or occurrence of a new VCF. Post-SBRT VCF was defined as any fracture occurring after SBRT including both progressive and new fractures. Progressive VCFs were defined as worsening pre-SBRT VCFs. Characteristic imaging findings as well as any decline in the vertebral body (VB) height was rated as VCF. Imaging findings did not have to be associated with clinical symptoms for classification as a VCF. The Spine Instability Neoplastic Score (SINS) was retrospectively identified using pretreatment available clinical information and planning CT and MR images [14]. The anatomical segments, normal tissue, osteolytic and osteoblastic tissue of treated vertebrae were segmented manually by an experienced radiation oncologist and their volumes were calculated using Pinnacle (Philips Radiation Oncology Systems, Milpitas, CA, USA). Hounsfield units were measured in the vertebra cranial and caudal of the affected spine level. Time intervals were calculated from the date of SBRT completion.

SPSS version 25 (SPSS, Inc.) and R version 3.5 were used for statistical analyses. Univariate analysis was performed to identify predictive factors for VCF using logistic regression. For treatment- and lesion related variables (e.g., volume of high and low dose PTV, SINS score, Bilsky score, volume of affected vertebral body), receiver operating characteristic (ROC) analyses were performed for determination of optimal cut-off values maximizing the area under the ROC curve (AUC). For building a multivariate logistic regression model, the variables found to be significant in univariate analysis ($p < 0.05$) as well as other variables judged as potentially related to the outcome were investigated. Given the large number of those variables compared to the number of events, we conducted variable selection using the LASSO method, which shrinks regression coefficients of less important variables to 0 and typically yields lower estimation variance than stepwise selection methods. The optimal LASSO penalty parameter was determined based on 10-fold cross validation and used for selecting the three most important predictor variables, that were then used to build the final multivariable model. We chose to select only three variables to avoid overfitting and its potentially negative consequences for generalizing our results to other datasets.

Results

Median follow-up for all patients was 16.2 months (range, 0–68.2 months). Median radiological follow-up was 7.8 months (range, 0–66.9 months). The median overall survival of all patients was 19 months (0.2–68.3). At the time of last imaging follow-up local metastasis control was observed in 82% of treated lesions. Table 1 shows pretreatment patients and tumor characteristics.

Table 1
Patient and tumor characteristics.

Parameter	
Age, median (range)	64 (26–85)
Sex, No. (%)	
Female	25 (45)
Male	31 (55)
Karnofsky Performance Status, No. (%)	
>70	46 (82)
≤70	10 (18)
Primary tumor site, No. (%)	
Breast	14 (23)
Non-small cell lung cancer	11 (18)
Colorectal	5 (8)
Kidney	4 (7)
Melanoma	1 (2)
Prostate	12 (20)
Other	14 (23)
Location of spine metastasis, No. (%)	
Cervical spine	6 (10)
Thoracic spine	35 (57)
Lumbar spine	18 (30)
Sacral spine	2 (3)
SBRT fractions, No. (%)	
5	27 (44)
10	34 (56)
Epidural spinal cord compression (Bilsky Score), No. (%)	
0	19 (31)
1a	10 (17)
1b	10 (17)
1c	6 (10)
2	13 (22)
3	2 (3)
Type of metastasis, No. (%)	
Osteolytic	43 (71)
Osteoblastic	6 (10)
Mixed	12 (19)
Solitary metastasis, No. (%)	24 (39)
Presence of visceral metastasis, No. (%)	24 (36)
Prior surgery at RT-treated spinal segment, No. (%)	
Stabilization	7 (12)
Decompression	11 (18)
Pre-SBRT vertebral	
Compression fracture, No. (%)	17 (28)

SBRT = stereotactic body radiation therapy.

Pre-SBRT VCF was present in 17 lesions (27.9%). Post-SBRT VCF developed in 21 lesions (34.4%): of these, 10 lesions (16.4%) showed a progressive VCF, while a new VCF occurred in 11 lesions (18.0%). 7 lesions with a pre-SBRT VCF (41%) were stabilized by SBRT. Median time to VCF for progressive and new VCF was 1.6 months (1.3–6.4) and 1.9 months (0–40.2), respectively.

The mean maximum visual analog scale (VAS) pain score was 2.3 (standard deviation, 2.6) at the last follow-up before VCF and 2.6 (SD, 2.9) at the first follow up with a diagnosed VCF. 3/21 (14%) VCFs were associated with a pain increase ≥2 on the VAS (increase of 3, 3 and 8, respectively). 2/56 (3.6%) patients had to be treated surgically due to a VCF, including one patient with a neurological deficit.

Univariate analysis was performed to identify factors predictive for any fracture (new and progressive) after SBRT (Table 2). Pre-SBRT VCF, a localization of the treated vertebra within the thoracic spine, a Bilsky score >0, the SINS score, the volume of pre-SBRT osteolysis and the proportion of metastatic involved vertebral body (VB) were predictive factors for VCF. SBRT dose did not show a significant correlation with regard to VCF in the univariate analysis.

ROC analysis revealed that a relative involvement of ≥34.5% of the VB best predicted a post-SBRT VCF with an AUC of 0.864, a sensitivity of 77.8% and a specificity of 89.7%. A SINS >8 reached a sensitivity of 83.3% and specificity of 75.9% (AUC 0.82).

The following variables were used to build a LASSO model: Age [years], gender and their interaction; body mass index [kg/m^2]; metastasis location (C/T/L); relative VB involvement (≥34.5%/<34.5%), osteolytic and osteoblastic volume [ml]; Bilsky score (0/>0); number of fractions received (10/5); PTV high dose volume [ccm]; pre-SBRT VCF (yes/no). Of these 13 regression variables, relative VB involvement, osteolytic volume and occurrence of a pre-SBRT VCF were selected by the LASSO algorithm. The resulting logistic regression model based on these three variables is given in Table 3. This model had AUC = 0.930 and, at a prediction probability threshold of 50.5%, achieved 83.3% sensitivity and 96.6% specificity. Fig. 1 demonstrates the ROC curves for uni- and multivariate models.

Table 2
Univariate analysis of factors predictive for VCF.

Variable	p-value
BMI ≥26,5	0.056
Location in thoracic spine	**0.05**
Volume PTV Boost ≥37 cm^3	0.065
Pre-SBRT VCF	**0.02**
Bilsky Score >0 (yes)	**0.03**
SINS	**0.01**
SINS >8 (yes)	**0.0003**
Infestation of vertebral body (%)	**0.002**
Infestation of vertebral body >34,5%	**0.00004**
Vertebral volume >79 cm^3	**0.04**
Volume vertebral body >31,5 cm^3	**0.05**
Volume osteolysis (absolute)	**0.002**
Volume osteolysis >7,9 cm^3	**0.00008**

BMI = body mass index; PTV = planning target volume; SBRT = stereotactic body radiation therapy; VCF = vertebral compression fracture; SINS = spinal instability neoplastic score.

Table 3
Regression coefficients of the multivariate logistic regression model.

Coefficients	Estimate	Standard error	p-value
Intercept	−3.547	0.963	0.00023
Involved VB volume (≥34.5%)	3.138	1.047	0.00273
Osteolytic volume [ccm]	0.207	0.110	0.0595
Pre-SBRT VCF (yes)	1.304	1.109	0.240

VB = vertebral body; SBRT = stereotactic body radiation therapy; VCF = vertebral compression fracture.

Discussion

Herein, we present data of a prospective trial with, to our knowledge, the longest clinical and imaging FU evaluating the safety of spine SBRT with respect to VCF. SBRT achieved excellent long-term local metastasis control and resulted in favorable low rates of symptomatic VCF: 2/56 patients required post-SBRT surgical stabilization and 3/56 treated patients had a clinically relevant increase in pain associated with VCF. The majority of patients with post-SBRT VCF were asymptomatic. SBRT achieved a stabilization of 41% of preexisting VCFs. The high rate of long-term local metastasis control was accompanied with a lasting pain response [11]. We conclude that the majority of treated patients had a long-term benefit from the SBRT treatment.

These data of our prospective phase-2 clinical trial contribute to the evaluation of risk factors for VCF following spinal SBRT. A location of the treated lesion within the thoracic spine was predictive for VCF. This is in accordance with published studies on SBRT related VCF [6,15]. As anticipated, a pre-SBRT VCF was predictive for a VCF post SBRT, suggesting a destabilized vertebra being at higher risk for fracture. We found a Bilsky score >0 being predictive for post-SBRT VCF in univariate analysis, indicating a lower risk of bone only disease. A Bilsky score >0 indicates a destruction of the posterior vertebral bone cortex and consecutively invasion of the epidural space by the tumor. A higher Bilsky score is therefore not only associated with epidural disease but also with a destabilization of the trailing edge [16]. Remarkably, two third of the lesions in this trial had epidural disease grade >0; 51% of lesions had grade ≥1b (deformation of the thecal sac), 34% showed spinal cord abutment or even compression and would have been excluded from the practice of single fraction radiosurgery [17]. This proportion of lesions with high-grade epidural disease is, to our knowledge, higher than in most published spine SBRT series reporting on VCFs, and has to be considered when interpreting the VCF rates in this study. In these patients with high risk of neurological impairment, dose-intensified hypofractionated SBRT was able to achieve the same pain and local tumor control outcome than in the patients without epidural disease [11]. However, the Bilsky score was not selected into the multivariate model.

The Spinal Instability Neoplastic Score (SINS) was developed as a consensus of best evidence to help clinicians in predicting spine instability of metastatic lesions. This comprehensive classification system is based on lesion characteristics, patient symptoms and radiographic criteria. In a multi-institutional analysis of the SINS in 410 spinal metastases treated with SBRT, Sahgal et al. were able to identify three of the six original SINS criteria as significant predictors of VCF in a multivariate analysis. The authors concluded that SINS can be useful for predicting patients at high risk of SBRT-induced VCF [18]. By scoring the treated lesions in our study cohort by all original six SINS criteria, we were able to validate the original SINS as a highly effective instrument for prediction of VCF after SBRT. A SINS >8 showed the most precise cut off value for prediction of a VCF in this cohort.

However, a better prediction of post-SBRT VCF could be achieved in our study by quantification of the vertebral body involvement. The latter has consistently been described as an independent risk factor for VCF throughout the literature. Thibault et al. described a lytic disease threshold of ≥11.6% to be most predictive for VCF in their cohort [8]. Rose et al. reported on VCF after single fraction IMRT and found lytic disease involving more than 40% of the vertebral body and location at or below T10 to be associated with a high risk for fracture [15]. Faruqi et al. performed a systematic literature review for studies that addressed risk factors for

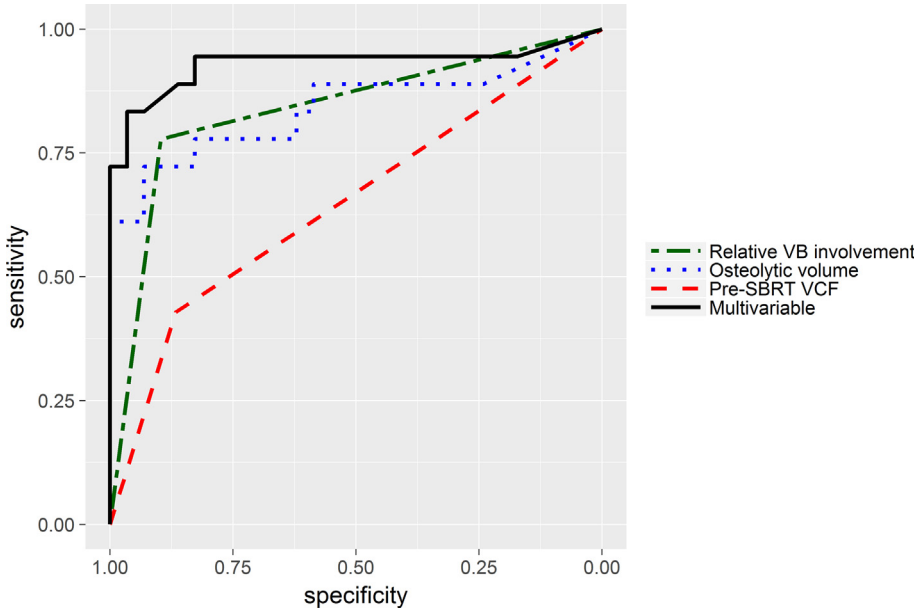

Fig. 1. ROC curves for uni- and multivariate models. ROC = receiver operating characteristic; VB = vertebral body; SBRT = stereotactic body radiation therapy; VCF = vertebral compression fracture.

post-SBRT VCF and reported more than 40% to 50% of vertebral body involved by the tumor among the most frequent risk factors on multivariate analysis [19].

Moreover, in this study, we were able to build a multivariate model based on osteolytic volume, relative vertebral body involvement and pre-SBRT VCF that was superior to the univariate models in our patient cohort (AUC 0.930). Future validation of this model is warranted in other patient cohorts.

In contrast to the metastatic burden of the VB, volumetric quantification of the remaining vertebral anatomic segments (transverse process, laminae, spinous process) as well as their metastatic infestation did not result in any predictive value with regard to post-SBRT VCF. This could be explained by the lower relevance of the posterolateral elements of the spine for its mechanical stability.

Radiologically detected post-SBRT VCF developed quite frequently in our patient cohort with a proportion of 34.4% of treated lesions. Thus, our results lie in the upper range of VCF rates following spine SBRT of 6–39% reported in the literature [7,8,15,18,20]. For a reasonable comparison of our data, several conditions should be considered: any decline in the vertebral body (VB) height was rated as VCF without using any threshold and despite of coexisting clinical symptoms. Also, the lesion characteristics in this study showed a preponderance of established risk factors for VCF, such as a high proportion of pre-SBRT fractures, thoracic spine lesions, osteolytic lesions and solitary spine metastases of oligometastasized patients that show improved survival [6,7]. Radiological follow up was considerably long for living patients. Finally, data acquisition in this study was conducted prospectively; in contrast, the VCF rates described in the literature most commonly were derived from retrospective analyses that inhere the risk of toxicity-underestimation.

While the high-dose treatment volume in our study was defined in accordance with current radiosurgery practice including the whole involved anatomical segment (as for example in the RTOG 0631 protocol [17]), the unaffected segments of the vertebra were additionally treated with a conventional radiation dose, leading to a higher total irradiated volume. This might have influenced the occurrence of VCF.

Possibly, a limitation of the high-dose volume to the gross tumor volume might lower the incidence of VCF as we could observe a trend towards significance for VCF of higher PTV Boost volumes. Whether this approach would result in comparable favorable local and pain control rates is unclear.

In this study, we were not able to identify an influence of the applied dose to the VCF probability. In this respect, the used SBRT fractionation and dose levels therefore seem to be safe. However, it should be noted that the study was not powered for the detection of differences in the outcomes of the five or ten fractions arm. Furthermore, an accurate identification of a dose response with regard to VCF would need a dose-escalation study design.

Most VCF occurred within the first two months after SBRT completion. Interestingly, no further progressive VCF were observed after 7 months, whereas new VCF showed a bimodal distribution with most VCF occurring early, but several VCF occurring late after more than 20 months post SBRT. One might speculate that the mechanisms leading to VCF differ in these early versus late VCF. This could be important for patients with good survival expectancy treated with spine SBRT. However, the sample size seems to be too small for a valid interpretation of this observation.

While the current study represents a robust data set with the strength of prospectively attained data and uniform planning, treatment and follow up procedures, there are limitations to this analysis. The patients treated within this study represent a selected cohort of patients with good performance score and limited metastatic tumor load. Together with a higher demand for technical and personnel resources than for conventional RT treatments, this resulted in a long recruitment time of nearly 3 years. The small number of lesions investigated in this study might inhere the risk of susceptibility to confounding factors. The specific treatment approach with an integrated boost, the fractionation up to 10 fractions and the high proportion of high-grade epidural disease lesions might limit the comparability especially to single-fraction radiosurgery series. It should be noted that a majority of treated lesions in our study was osteolytic or had an osteolytic component. Consequently, we cannot properly address the risk of osteoblastic lesions for VCF.

Nevertheless, our data is in accordance with prior publications about VCFs following spine SBRT and strengthens the knowledge about predictive factors for post spine SBRT VCFs.

VCF is a potentially relevant adverse effect following spine SBRT. Most radiologically detected VCFs were clinically

asymptomatic. Few patients suffered from painful and/or instable VCFs and had to be surgically treated. The SINS score could be validated as highly effective in prediction of post SBRT VCF. Quantification of the vertebral body tumor involvement separately, and a multivariate model based on osteolytic volume, relative vertebral body involvement and pre-SBRT VCF achieved an improved prediction of VCF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

MG, MF, RS, and FM designed the study. MG, RS, AT, FM, MH, JB, MA, BP performed the data acquisition. MG, RJK and FM performed the analyses and interpretation of the data. FM drafted the manuscript. All authors revised the manuscript critically for important intellectual content and finally approved the manuscript.

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