Response Assessment After Stereotactic Body Radiation Therapy for Spine and Non-spine Bone Metastases: Results From a Single Institutional Study

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Research

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Abstract

Background

The use of stereotactic body radiation therapy (SBRT) for tumor- and pain control in patients with bone metastases is increasing. Here, we report response assessment after bone SBRT using radiological changes through time and clinical examination of patients.

Methods

We analyzed retrospectively the oligo-metastatic/progressive patients with bony lesions treated with SBRT between 12/2008 and 10/2018 in our institution. Radiological data were obtained from imaging modalities used for SBRT planning and follow-up (FU) purposes in PACS and assessed by two independent radiologists blind to the time of treatment. Several radiological changes were described. Radiographic response assessment was classified according to University of Texas MD Anderson Cancer Center criteria. Pain response was captured pre- and >= 6 months post-SBRT.

Results

A total of 35 of the 74 reviewed patients were eligible, presenting 43 bone metastases, with 51.2% (n=22) located in vertebral column. Median age at the time of SBRT was 66 years (range, 38-84), and 77.1% (n=27) were male. Histology was mainly prostate (51.4%, n=18) and breast cancer (14.3%, n=5). Median total radiation dose delivered was 24 Gy (range: 24-42), in three fractions (range: 2-7), prescribed to 70 - 90% isodose-line. After a median FU of 1.8 years (range, 0.1-8.2) for survivors, complete-/ partial response, stable (SD), and progressive disease occurred in 0%, 11.4% (n=4), 68.6% (n=24) and 20.0% (n=7) of the patients respectively. Twenty patients (57.1%) died during the FU time, all from disease progression, yet 70% (n=14) from this population with local SD after SBRT. From patients who were symptomatic and available for FU, almost 50% reported pain reduction after SBRT.

Conclusions

Eighty percent of the patients showed local control (LC) after SBRT for bone metastases. Pain response was favorable. For more accurate response assessment, comparing current imaging modalities with advanced imaging techniques such as functional MRI and PET-CT is warranted.

Trial registration

Retrospectively registered.

Background

Many patients suffering from solid tumors develop metastatic cancer with single, limited or diffuse metastases. Besides lung and liver, bone is a common site of metastasis[1]. Caused in up to 70% by prostate and breast cancer, bone metastases are a major cause for morbidity[2]. Bone metastases are predominantly located in the vertebral column and it is estimated that over 10% of cancer patients develop symptoms at this site[3,4].

The role of radiotherapy to palliating pain for bone metastases is well established[5]. In the past, patients with painful bone metastases have a limited median overall survival (OS) of 7-9 months[6,7,8]. However, patients show increased OS in recent years due to improved treatment approaches, and therefore it is essential to provide a highly effective local therapy. SBRT is a promising modality to treat bone metastases with locally ablative intent[9] and has been used frequently in daily practice for more than a decade. Nevertheless, the results of prospective randomized trials comparing conventional radiotherapy to SBRT are very recent[10,11,12]. The pain response is the focus of these prospective randomized trials and none of them has reported the radiological response assessment yet. As the histological confirmation is challenging and costly in case of suspicious tumor progression after SBRT, an accurate radiological assessment is of utter importance and could avoid unnecessary interventions in asymptomatic patients. The SPIne response assessment in Neuro-Oncology (SPINO) group consensus uniforms the various criteria for radiological assessment of therapy response after spinal SBRT[13]. Nevertheless, few studies have evaluated the detailed radiological changes in bone metastases after SBRT[14,15,16]. For bone metastases, there are specific aspects to consider in interpretation of radiological changes after SBRT, including pseudo-progression, vertebral compression fracture (VCF), epidural progression, changes in bone density depending on the nature of metastasis and altered vascularization.

In this retrospective study, we aim to evaluate radiological changes after SBRT to osseous metastases at the last follow-up, thus reporting its oncological outcome with LC and pain response.

Methods

Patient selection

After approval of the study protocol by the institutional review board and ethic committee, patient informed consent was waived. We enrolled 74 adult patients (18 years-old or older) with a total of 103 spine or non-spine bone metastases, treated consecutively with SBRT between 12/2008 and 10/2018 in the radiation oncology department at Bern University Hospital, Switzerland. As shown in Figure 1, the exclusion criteria was the following: soft tissue component (n=1 metastasis), in-field re-irradiation (before or after SBRT, including overlapping of treatment fields) (n=28 metastases), different diagnostic imaging modality pre-/post-SBRT (n=8 metastases), patients with imaging less than six weeks after SBRT (n=17 metastases), and no diagnostic images from the treated site (n=5 metastases).

All patients had a histologic diagnosis of malignancy with either synchronous or metachronous bone metastasis. Diagnosis of bone metastasis was established by magnetic resonance imaging (MRI), computer tomography (CT), or less frequently positron emission tomography/computed tomography (PET/CT) and bone scintigraphy. Bone lesions were divided into osteolytic, osteoblastic, or mixed-form. No bone-targeted agents (i.e., denosumab, bisphosphonate, hydroxyapatite derivatives, or radioactive isotope therapy) have been administered.

SBRT Technique

Similar to what was previously described by Hwang et al.[17], the SBRT procedure consisted of: 1) image acquisition, 2) patient setup, and 3) SBRT planning and treatment. For planning, high-resolution thin-section MRI images were obtained (1.5 or 3 Tesla MRI). All MRI examinations included both turbo spin echo (TSE) T1-weighted (with and without contrast enhancement) and TSE T2-weighted sequences.

For accurate and precise treatment positioning and immobilization, patients were placed in a vacuum bag (BodyFix®). The DICOM data of the MRI and CT were transferred to workstations for stereotactic planning, where the MRI was fused, at the area of interest, onto the CT images.

The target volumes for spine metastases were delineated according to international spine radiosurgery guidelines[18]. For non-spine bone metastases, a gross tumor volume/clinical target volume (GTV-CTV) margin of 3-5mm and CTV-planning target volume of 3 mm were applied. Generally, patients with spinal metastases were treated at CyberKnife® using a spine-tracking system (SpineX®). For non-spine metastases, we have treated patients at NovalisTX using daily cone-beam CT. The median total radiation dose was 24 Gy (range 24 - 42 Gy) in median 3 fractions (range 2 - 7 fractions), prescribed to 80% isodose-line (range 70 - 90%).

Follow-Up Imaging Evaluation

As we analyze a retrospective cohort of patients, different imaging modalities have been used in order to assess the response to SBRT and evaluate the local control. Besides that, the intervals between SBRT and first FU-visit, as well as between following visits are inhomogeneous. For example, most of patients with metastatic prostate cancer were followed-up using prostate specific antigen (PSA) and the diagnostic imaging was done as the PSA raised from baseline after therapy. Despite all these inhomogeneity, we focused on MRI and CT-images and observed their changes through time. This assessment was done by two independent radiologists, blind to the time of treatment. Several radiological changes were described: alterations in mineralization of sclerotic/lytic bone metastases, vertebral compression fracture for spinal metastases, pathologic fracture for non-spine metastases, morphological size progression, and signal alterations on different MRI-sequences. Radiographic response assessment of metastases was classified according to University of Texas MD Anderson Cancer[19] as complete or partial response, and stable or progressive disease, based on the last follow-up imaging.

As MRI is the most recommended imaging modality for response assessment after bone SBRT, following changes were particularly observed on different MRI sequences: tumor volume, T2 signal intensity (SI) alterations and contrast enhancement patterns.

Considering pre- and post-treatment volumes, we categorized the tumors as decreased (group 1), unchanged (group 2), or increased (group 3). If the volumetric change was within 10% (ratio range 0.9 –1.1), the lesions were regarded as unchanged in volume. In case of absence of post-therapeutic MRI, we compared the volumes of the lesions in pre- and post-therapeutic CT. T2 SI changes of the tumors were categorized into four types: 1) no changes); 2) increase in T2 signal intensity; 3) increase in T2 signal intensity intermixed with dark signal intensity, and 4) totally dark signal intensity, based on the publication from Hwang et al.[17]. Enhancement patterns were divided into two groups: no change in contrast enhancement and decrease of contrast enhancement with or without non-enhancing foci.

The SPINO-consensus recommends FU-MRI every 3-6 months after spine-SBRT; however, as mentioned before, our retrospective cohort is inhomogeneous regarding radiological FUs. Besides MRI, computed tomography (CT), positron emission tomography/computed tomography (PET/CT), bone scintigraphy, or single-photon emission computerized tomography (SPECT) were also performed for some patients.

Pain response

Pain response was assessed before and at least six months after SBRT, using the numerical rating scale (NRS). We also captured the intake of painkillers.

Statistical analysis

Statistical analysis was performed with SPSS, version 22. Descriptive statistics were presented as means (M) and standard deviations (SD) for quantitative variables and frequencies (n) and percentages (%) for categorical ones.

Two-Way repeated measures ANOVA was conducted to evaluate the effect of SBRT on the quantitative parameters, along with the interaction of the effect of SBRT with the follow-up method. We also calculated the effect for the FU method but did not present these results due to lack of significant values. Effect sizes were assessed with eta squared (η2), considering Cohen's (1988) suggestion: 0.01, 0.06 e 0.14 for weak, moderate and high effect [20].

Then, we computed the difference between the two moments of assessment - *i.e.*, the last imaging before SBRT took place and the last follow-up imaging after SBRT (ΔSBRT= (after - before SBRT)), and built linear regression models adjusting not only for follow-up method, but also for type of lesion. This was done to reduce to number of estimated parameters and allow the computation of the effects when adjusting for these two variables. We computed unstandardized effect sizes (β), standard errors (SE) and p-values. Residual's normality was assessed and confirmed with Shapiro-Wilk test ($p>0.05$). No residuals were found above the threshold $Ri> |3|$.

For assessing the categorical parameters before and after SBRT, we calculated frequencies (n), percentages (%) and Cohen's kappa measure of agreement to assess the changes between these two moments.

Significance was considered for $p<0.05$. We also considered marginally significant results for $p<0.10$.

Results

Population

A total of 35 patients, 27 (77.1%) males and 8 (22.9%) females with 43 bone metastases were analysed in this cohort. Metastases were mainly from prostate cancer (n=18, 51.4%), followed by breast cancer (n=5, 14.3%). As shown in Table 1, the bony lesions are classified as spine (n=22, 51.2%) and non-spine (n=21, 48.8%) metastases. The spinal metastases involve mainly the lumbar spine (n=11, 50%) and non-spinal metastases are mostly located in pelvic/hip bones (n=15, 71.4%). The median age at the time of SBRT was 66 years-old (range: 38 - 84).

Table 1
Patient, treatment and follow-up characteristics.

Characteristics	**Value (range)**
Median follow-up, years	1.8 (<1 - 8.2)
Median age at SBRT, years-old	66 (38 - 84)
Dose Prescription	
Median total dose delivered, Gy	24 (24 - 42)
Median single dose, Gy	8 (5 - 12)
Median number of fractions	3 (2 - 7)
Median isodose prescription, %	80 (70 - 90)
Imaging Follow-up after SBRT	
3 months, range	1.3 - 4.3
6 months, range	5.1 - 9.8
12 months, range	9.3 - 19.3
	Nr. of Patients (%)
Sex	
Male	27 (77.1)
Female	8 (22.9)
Histology (primary tumor)	
Prostate	18 (51.4)
Breast	5 (14.3)
Melanoma	3 (8.6)
Non-small cell lung cancer	3 (8.6)
Other	6 (17.1)
Bone Metastases Location	**Nr. of metastases (%)**
Non-spine	21 (48.8)
Temporal bone	1 (4.8)
Scapula	1 (4.8)
Sternum	1 (4.8)
Rib	2 (9.5)
Pelvic/hip bones (6 ileum, 4 ischium, 4 pubis, 1 acetabulum)	15 (71.4)
Femur	1 (4.8)
Spine	22 (51.2)
Cervical	0 (0.0.)
Thoracic	9 (40.9)
Lumbar	11 (50.0)
Sacral	2 (9.1)

Radiological response

FU radiological assessment was performed with contrast-CT (n=17, 39.5%), MRI (n=26, 60.5%), and PET/CT (n=14, 32.6%), which took place mainly three, six, and 12 months after SBRT. After a median FU of almost 2 years (range: <1 - 8.2), complete-/ and partial response, stable-/ and progressive disease occurred in 0%, 11.4%, 68.6%, and 20% respectively. Twenty patients (57.1%) died, all from disease progression, yet 70% (n=14) with still local stable disease after SBRT.

No statistically significant difference on the radiological assessment of two independent radiologists was found. Table 2 presents results for paired comparisons regarding quantitative variables, compared by the imaging method. We found no significant differences for any of the quantitative parameters considering pre or post SBRT. Considering interactions, we found a statistically significant difference between the width parameter and the imaging method ($F=6.13$ ($p=0.004$), $\eta2=0.19$: increased only in contrast-CT, stable in MRI, while decreased in PET/CT (Figure 2). A marginally significant association was seen for the SBRT effect on the depth and height (respectively, $F=3.97$, $p=0.052$, $\eta2=0.07$ and $F=3.05$ ($p=0.056$) $\eta2=0.11$). There was a trend (depth: $F=3.12$, $p=0.053$, $\eta2=0.11$; height: $F=3.05$ ($p=0.056$) $\eta2=0.11$) to increase after SBRT in the contrast-CT follow-up, whereas it decreased in the PET/CT (Figure 2). Despite the absence of significance on the volume ($F=2.23$, $p=0.118$), moderate effect size was found ($\eta2=0.08$) after SBRT, similarly with a slight increase in contrast-CT, stable results in MRI, and decrease in PET/CT. No significant or marginally significant results were found for the effect of SBRT or its interaction with the imaging method in CT density native (CT-DN). ANOVA test was not done for the CT density contrast enhanced (CT-CE) because results were equal before and after SBRT. For the parameters T2-weighted images signal intensity (T2-SI), T2-weighted images turbo inversion recovery magnitude signal intensity (T2-TSI), T1-weighted images native signal intensity (T1-NSI), and T1-weighted images contrast enhanced signal intensity (T1-CESI) no significant results were found for the effect of SBRT.

Table 2
Repeated measures ANOVA for the quantitative parameters compared by the imaging method.

	CT contrast enhanced			MRI			PET/CT			Total			RM ANOVA effects	
	M	SD	n	M	SD	n	M	SD	n	M	SD	n	SBRT	Ima
Width														
Pre-SBRT	21.09	11.73	15	20.58	12.74	26	21.91	14.45	14	21.91	14.45	55	F=2.55 (p=0.116) η2=0.05	F=6 **(p=**
Post-SBRT	29.33	15.27	15	21.40	14.31	26	18.84	8.13	14	18.84	8.13	55		η2=
Depth														
Pre-SBRT	20.46	10.26	15	24.03	13.81	26	22.67	14.65	14	22.71	13.02	55	F=3.97 (p=0.052)† η2=0.07	F=3 (p= η2=
Post-SBRT	25.68	10.99	15	24.76	15.72	26	22.25	11.03	14	24.37	13.30	55		
Height														
Pre-SBRT	17.09	6.07	15	17.66	8.28	26	22.27	17.85	14	18.68	11.07	55	F=0.15 (p=0.701) η2=0.003	F=3 (p= η2=
Post-SBRT	20.94	5.05	15	18.55	7.85	26	18.83	7.64	14	19.27	7.09	55		
Volume														
Pre-SBRT	9997.74	13068.83	16	12775.66	15571.32	26	29478.44	74682.81	14	16157.66	39201.12	56	F=0.42 (p=0.502) η2=0.01	F=2 (p= η2=
Post-SBRT	17678.62	19147.79	16	14338.71	17120.47	26	10532.05	9453.02	14	14341.30	16164.13	56		
CT-DN														
Pre-SBRT	248.57	307.38	7	-	-	-	300.64	259.62	14	283.29	269.80	21	F=2.05 (p=0.168) η2=0.10	F=0 (p= η2=
Post-SBRT	300.14	324.13	7	-	-	-	377.93	337.06	14	352.00	326.76	21		
CT-CE														
Pre-SBRT	263.71	323.85	7										-	
Post-SBRT	263.71	323.85	7											
T2-SI														
Pre-SBRT	-	-	-	224.71	175.53	19	-	-	-	-	-	-	F=0.01 (p=0.947) η2=0.00	
Post-SBRT	-	-	-	222.74	206.11	19	-	-	-	-	-	-		
T2-TSI														
Pre-SBRT	-	-	-	214.82	194.65	8	-	-	-	-	-	-	F=0.06 (p=0.816) η2=0.01	
Post-SBRT	-	-	-	225.63	163.17	8	-	-	-	-	-	-		
T1-NSI														
Pre-SBRT	-	-	-	213.76	141.40	21	-	-	-	-	-	-	F=0.01 (p=0.945) η2=0.00	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/ computed tomography; RM, repeated measures; M, mean; SD, standard deviation; SBRT, stereotactic body radiotherapy; CT-DN, computed tomography density native in Hounsfield units; CT-CE, co tomography density contrast enhanced in Hounsfield units; T2-SI, T2-weighted images signal intensity; T2-TSI, T2-weighted images turbo inversion recovery magnitude signal intensity; T1-NSI, T1-weighted images native signal intensity; T1-CESI, T1-weighted images contrast enhanced signal intensity.

*statistically significant; †p<0.10

η2=0.01 weak, η2=0.06 moderate, η2=0.14 high effect, according to Cohen, J (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdal Erlbaum.

	CT contrast enhanced			MRI			PET/CT			Total			RM ANOVA effects
Post-SBRT	-	-	-	215.69	171.15	21	-	-	-	-	-	-	
T1-CESI													
Pre-SBRT				417.03	284.76	20	-	-	-	-	-	-	F=0.01 (p=0.945) η2=0.00
Post-SBRT				357.85	267.84	20	-	-	-	-	-	-	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/ computed tomography; RM, repeated measures; M, mean; SD, standard deviation; SBRT, stereotactic body radiotherapy; CT-DN, computed tomography density native in Hounsfield units; CT-CE, co tomography density contrast enhanced in Hounsfield units; T2-SI, T2-weighted images signal intensity; T2-TSI, T2-weighted images turbo inversion recovery magnitude signal intensity; T1-NSI, T1-weighted images native signal intensity; T1-CESI, T1-weighted images contrast enhanced signal intensity.

*statistically significant; †p<0.10

η2=0.01 weak, η2=0.06 moderate, η2=0.14 high effect, according to Cohen, J (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdal Erlbaum.

Table 3 shows the results of linear regressions for the difference before and after SBRT (ΔSBRT) adjusted for type of imaging method and type of lesion, not only showing that spinal metastases were associated with increased width (β = 4.89; p=0.031), but also confirming that contrast-CT is associated with increased width (β = 11.82; p<0.001), depth (β = 5.73; p=0.017), height (β = 7.27; p=0.012), and volume (β = 28347.15; p=0.026) compared with PET/CT.

Table 3
Linear regressions for the difference before and after SBRT adjusted for the type of imaging method and spinal lesion.

	ΔSBRT=(After – Before SBRT)								
	Δ Width	Δ Depth	Δ Height	Δ Volume	Δ CT-DN	Δ T2-SI	Δ T2-TSI	Δ T1-NSI	Δ T1-CESI
Imaging									
CT	11.82 (3.11) **p<0.001***	5.73 (2.39) **p=0.017***	7.27 (2.90) **p=0.012***	28347.15 (12743.88) **p=0.026***	-25.71 (85.02) p=0.762	-	-	-	-
MRI	3.87 (2.76) (p=0.162)	1.14 (2.13) p=0.592	4.34 (2.58) p=0.092†	20438.88 (11487.83) p=0.075†	-	-	-	-	-
PET/CT	Ref	Ref	Ref	Ref	Ref	-	-	-	-
Spine									
Yes	4.89 (2.27) **p=0.031***	0.93 (1.74) p=0.593	-0.20 (2.11) p=0.926	12841.73 (9358.37) (p=0.170)	-40.56 (80.99) p=0.617	19.16 (60.67) (p=0.752)	-124.38 (71.00) p=0.080†	88.54 (51.23) p=0.084†	112.05 (66.88) p=0.094†
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Abbreviations: SBRT, stereotactic body radiotherapy; CT-DN, computed tomography density native in Hounsfield units; T2-SI, T2-weighted images signal intensity; T2-TSI, T2-weighted images turbo inversion recovery magnitude signal intensity; T1-NSI, T1-weighted images native signal intensity; T1-CESI, T1-weighted images contrast enhanced signal intensity; CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/ computed tomography; Ref, reference.

*statistically significant; †p<0.10; results presented as unstandardized effect sizes β, standard errors (SE), and p-values.

When we assessed the spinal metastases without adjusting for the imaging method (only data for MRI was achievable), marginally significant results were found for their association with the parameters T2-TSI (β=-124.38; p=0.080), T1-NSI (β = 88.54; p=0.084), and T1-CESI (β = 4.89; p=0.031) after SBRT: lower in T2-TSI, while higher in T1-NSI and T1-CESI.

On Table 4, we present the assessment for the categorical variables' association with pre versus post SBRT, with Cohen's kappa measure of agreement to assess the changes between these two moments (k). CT appearance (k=0.84), soft component (k=0.72) and T2 turbo inversion recovery magnitude (TIRM) appearance (k=0.67) had moderate to high agreement between the two assessments. For CT appearance, proportion of agreement was 100% for osteolytic, 93.3% for osteoblastic and 71.4% for mixed-type lesions. For soft tissue component, 75% agreement for presence and 94.7% for non-presence were applicable. For SI on T2-TIRM sequence, agreement was 100% for homogenous hyper-intensity, 50% for dark spots, 50% for homogenous hypo-intensity, and 100% for intermediary. The other parameters showed low or very low agreement, with k varying from k=0.14 to k=0.40.

Table 4
Agreement of radiological categorical variables before and after SBRT.

Before SBRT	**After SBRT**				***k***
CT appearance	Osteolytic	Osteoblastic	Mixed		
Osteolytic	8 (100%)	0 (0.0%)	1 (14.3%)		0.84
Osteoblastic	0 (0.0%)	14 (93.3%)	1 (14.3%)		
Mixed	0 (0.0%)	1 (6.7%)	5 (71.4%)		
T2 appearance	Homogenous bright	Dark spots	Totally dark signal intensity	Intermediary	
Homogenous bright	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (25.0%)	-
Dark spots	0 (0.0%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	
Totally dark signal intensity	0 (0.0%)	3 (42.9%)	7 (87.5%)	1 (25.0%)	
Intermediary	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	
T2 TIRM appearance	Homogenous bright	Dark spots	Totally dark signal intensity	Intermediary	
Homogenous bright	2 (100.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0.67
Dark spots	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	
Totally dark signal intensity	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	
Intermediary	0 (0.0%)	0 (0.0%)	1 (50.0%)	2 (100.0%)	
T1 signal native appearance	Homogenous bright	Dark spots	Totally dark signal intensity	Intermediary	
Homogenous bright	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.30
Dark spots	0 (0.0%)	1 (33.3%)	1 (7.1%)	0 (0.0%)	
Totally dark signal intensity	0 (0.0%)	2 (66.7%)	11 (78.6%)	2 (50.0%)	
Intermediary	0 (0.0%)	0 (0.0%)	2 (14.3%)	2 (50.0%)	
T1 CE signal appearance	No enhancement	Slight enhancement	Bright enhancement		
No enhancement	0 (0%)	0 (0%)	0 (0%)		0.14
Slight enhancement	3 (75.0%)	9 (81.8%)	3 (60.0%)		
Bright enhancement	1 (25.0%)	2 (18.2%)	2 (40.0%)		
Contrast enhancement	Yes	No			
Yes	17 (100.0%)	6 (66.7%)			0.40
No	0 (0.0%)	3 (33.3%)			
Soft component	Yes	No			
Yes	9 (75.0%)	2 (5.3%)			0.72
No	3 (25.0%)	36 (94.7%)			
Abbreviations: SBRT, stereotactic body radiotherapy; CT, computed tomography; T2 TIRM, T2-weighted.					

Pain response

Considering the pain response, we observed that 22 (62.9%) patients remained asymptomatic on the treated metastases; four (11.4%) patients reported decreased pain (complete and partial); three (8.6%) had stable pain (two without regular analgesia and one stable after SBRT but requiring analgesia after surgery); two (5.7%) complained of increased pain, even though one of them without requiring analgesia; four (11.4%) had no available pain response follow-up, whereas one of them deceased before it was captured.

Discussion

Results of the current retrospective study present SBRT as an effective treatment for bone metastases. SBRT has been increasingly accepted as a valuable option for selective patients with metastatic disease. Using the appropriate imaging modality for treatment planning, SBRT offers an excellent local control with acceptable toxicity profile[21]. However, response assessment after SBRT is a challenging topic, which is not only limited to the bone, as we confront difficulties to interpret the changes in imaging modalities after stereotactic radiotherapy in other organs, like brain, liver and lung[22–24]. Appropriate evaluating of diagnostic images is a critical point in the process of the disease and can prevent the risks of unnecessary interventions. Besides that, pain response should be considered after RT for bone metastases, as pain relief is the most important goal in such patients. In this retrospective study, we report our institutional results regarding imaging-based local control and pain response after SBRT for bone metastases.

The SPINO-group published a report in 2015, focusing on response assessment after SBRT for spinal metastases[13]. The consensus is based on an international survey and not yet evaluated in clinical trials. We considered the recommendations from SPINO group for image-based tumor- and pain response, although we analyzed both spine and non-spine bone metastases in our study. The MRI is the preferred modality for response assessment after SBRT; however, we should be aware of some unique aspects such as pseudo-progression (PP) and vertebral compression fracture (VCF) when interpreting the post-SBRT images.

PP is a well-known phenomenon after SBRT in different organs. It was first reported for spine metastasis in a case report from 2015 and the authors described PP as subacute, post-radiotherapy reaction that mimics progressive disease (PD) with increased contrast enhancement and ultimate stabilization and regression[25]. Time is an important factor evaluating post-SBRT radiological changes, as PP present few weeks up to 6 months after radiation, in contrast to radio-necrosis (RN) which is a late effect and can occur even years after therapy[25]. Amini et al. did an analysis of osseous pseudo-progression in vertebral body following SBRT in patients from two prospective phase I/II clinical trials[26]. They defined the osseous pseudo-progression as “transient growth in signal abnormality centered at the lesion with a sustained decline on FU MRI that was not attributable to chemotherapy”. They reported the rates of PP and PD of 14% and 24% respectively. Furthermore, there was a significant association between single-fraction SBRT and development of PP[26]. The so far published randomized trials comparing SBRT versus conventional RT have not reported the rates of PP[12,27,28]. SPINO group defined any new or progressive tumor within the epidural space as local progression[13], but we have recently published a case report showing clear epidural involvement on radiological images after spine SBRT, however, the histological analysis revealed no tumor cells in epidural space[29]. Therefore, it is critical to distinguish between PP, PD and RN to avoid false patient management. In our study, we observed PP as a common finding after SBRT, however not all patients had MRI shortly after the therapy and therefore it was not possible to report the exact rate of PP.

VCF is a well-known and most common complication after spine SBRT. The rate of VCF after single fraction SBRT (SF-SBRT) with 18-24Gy was reported around 39%, and lytic lesions and location below T10 confer a high risk of fracture[30]. The median time to fracture was 25 months and VCF was seen earlier in patients with lytic lesions compared to sclerotic lesions[30]. Sahgal et al. reported 14% of new or progressing VCF after spine SBRT, using different fractionation and considering SINS-score to determine its predictive value[31]. They defined the high dose per fraction, lytic lesion and baseline fracture as significant predictors of VCF[31]. A review from 2017 reported a crude VCF rate of 13.9%[32]. Jawad et al. demonstrated low rates of VCF for 5.7% in their multi-institutional study, using 1-5 fractions for spine SBRT[33]. We report here the rates of new/progressive fractures for spine and non-spine metastases as 4.5% and 4.7% respectively. As half of our cohort had metastatic prostate cancer, one reason for our low rates of fractures could be the sclerotic nature of the metastases. Another reason might be related to our moderate SBRT schema with median total dose of 24Gy in three fractions.

As mentioned above, MRI is the most recommended imaging modality for radiological assessment of bone metastasis after SBRT. Hwang et al. reported the MRI changes after SBRT for osteoblastic spinal lesions, as these metastases usually show no obvious radiological volumetric alterations[17]. They classified signal intensity (SI) alterations on T2-MRI sequences as following: 1) no changes in SI; 2) increased SI; 3) increased SI intermixed with dark SI; 4) changed to complete dark SI. Most of our patients had prostate cancer as primary diagnosis; therefore, we assessed the T2 weighted MRI sequences for radiological response evaluation after SBRT for both spine and non-spine bone metastases as described above. According to recommendations from SPINO group, the routine use of contrast-enhanced T1-MRI sequences to visualize spinal metastases is controversial as both normal bone marrow and tumor are enhanced[13]. The interpretation becomes even more difficult after SBRT and therefore we considered the T1-MRI with gadolinium only for delineating the epidural and para-spinal tumor components. Although the patient population was heterogeneous in our cohort, SBRT achieved 80% of LC at almost 2 years. More than 40% of our patients survived and among the population who died in FU time, 40% had still SD at the irradiated sites. These results are in line with data from other studies, showing an excellent rate of LC after SBRT for osseous metastases[21].

Considering pain response, the randomized phase 2 trial from Germany reported significant improved pain values in SBRT group 6 months after the therapy in patients with spinal metastases[12]. However, as they chose the SF-SBRT with 24Gy, the rates of new pathological fracture were high in that study, with 8.7% and 27.8% at 3 and 6 months respectively[12]. Another randomized phase 2 trial from Netherlands compared SBRT versus conventional RT for bone metastases using different fractionations[28]. SBRT group did not show significant pain improve, but because of selective dropout, this trial was underpowered to detect the difference in pain response[28]. The NRG Oncology/RTOG 0631 trial initial results were presented at ASTRO annual meeting in 2019[34]. Randomizing patients with spinal metastases into SBRT and conventional RT groups, this study showed negative results for SBRT arm, as pain control was similar at 3 months between two groups. Finally, the Canadian randomized phase 3 trial compared spine SBRT with 24Gy in two daily fractions with conventional RT at a dose of 20Gy in five fractions[27]. The SBRT was superior to conventional RT and improved the complete pain response at 3 months. Interestingly, the incidence of VCF was equal between two groups, showing the safety of SBRT regimen[27]. In our retrospective study, the majority of patients (62.9%) had no pain prior to SBRT and the indication was mostly local ablation in oligo-metastatic/progressive disease. This group of patients remained asymptomatic after SBRT. In symptomatic group, only two patients experienced pain exacerbation following SBRT with only one of them required analgesic medication.

Conclusion

In conclusion, our results from a single institutional study show high rates of tumor- and pain control after SBRT for spine and non-spine metastases. We assessed the LC by analyzing the imaging modalities and hope that these results provide a better understanding of radiological changes, mainly on MRI after SBRT. The next step could be the comparison between different imaging modalities for response assessment, especially for solid tumors with specific tumor biomarkers as PSMA for prostate cancer.

List Of Abbreviations

SBRT Stereotactic Body Radiation Therapy

FU Follow-Up

SD Stable Disease

PD Progressive Disease

LC Local Control

OS Overall Survival

VCF Vertebral Compression Fracture

MRI Magnetic Resonance Imaging

CT Computed Tomography

PET Positron Emission Tomography

TSE Turbo Spin Echo

PSA Prostate Specific Antigen

SI Signal Intensity

SPECT Single Photon Emission Computer Tomography

NRS Numerical Rating Scale

SE Standard Error

DN Density Native

CE Contrast Enhanced

TIRM Turbo Inversion Recovery Magnitude

PP Pseudo-Progression

RN Radiation Necrosis

Declarations

Ethics approval: Study protocol was approved by the institutional review board and ethic committee (Berner Kantonale Ethikkommission für die Forschung – Project-ID 2018-01831)

Consent for publication: No individual person`data

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests: None

Authors` contributions: J. Cullmann and R. Heiss analyzed the whole imaging modalities as two independent radiologists. D. Correia, B. Moullet and H. Hemmatazad wrote the manuscript. D. Correia made also the tables and figures. D. M. Aebersold and Ekin Ermis did critical review of the manuscript. The project was supervised by H. Hemmatazad.

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Figures

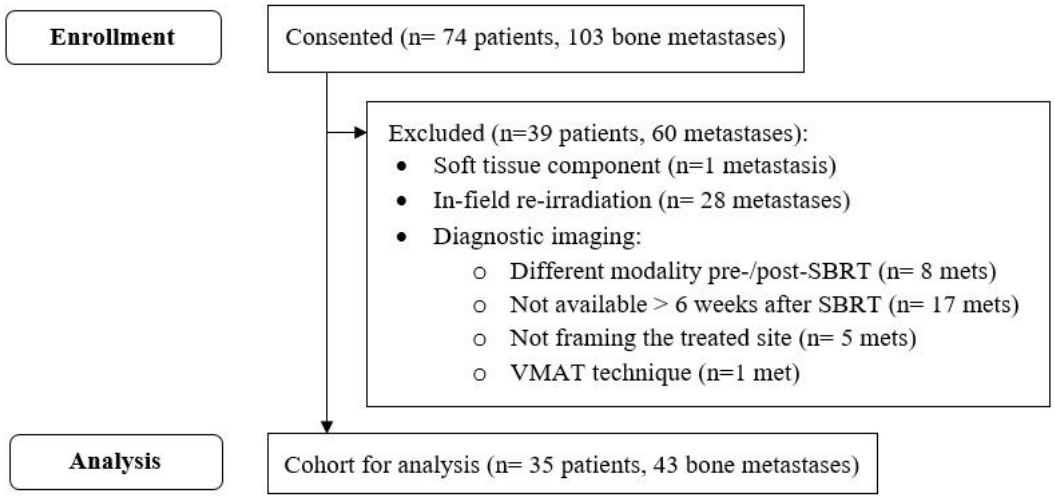

Figure 1

Study cohort flow diagram. Abbreviations: Mets, bone metastases; VMAT, volumetric modulated arc therapy.

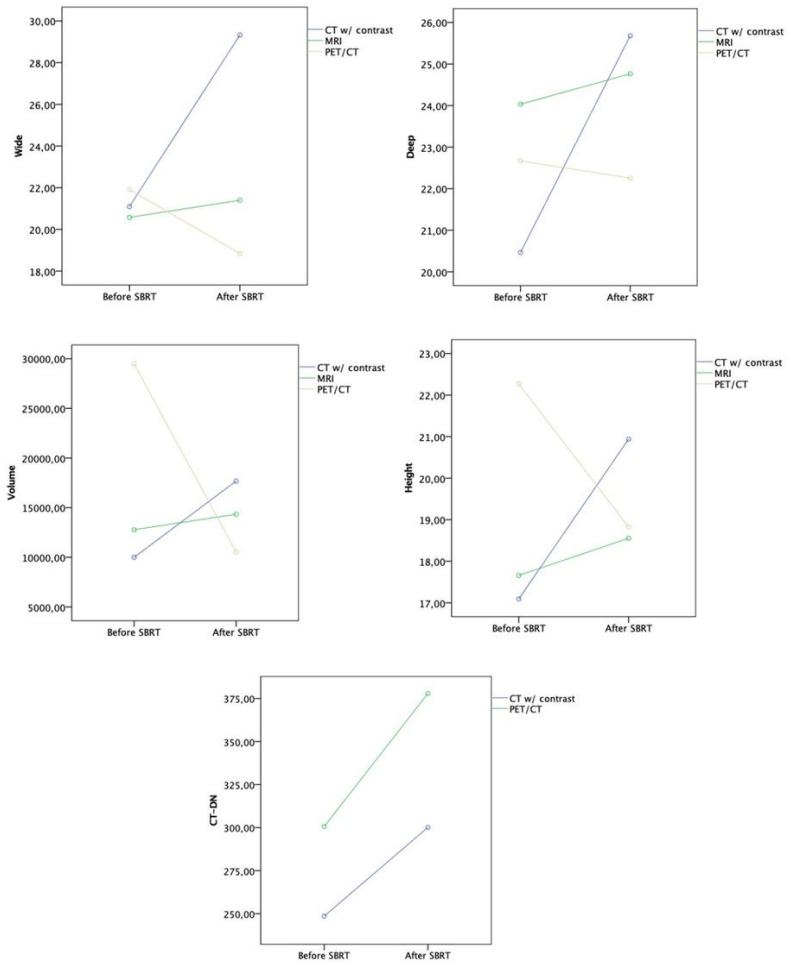

Figure 2

Quantitative parameters evolution and interaction with the imaging method. Abbreviations: SBRT, radiotherapy; CT w/ contrast, computed tomography contrast enhanced; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/ computed tomography; CT-DN, computed tomography density native in Hounsfield units.

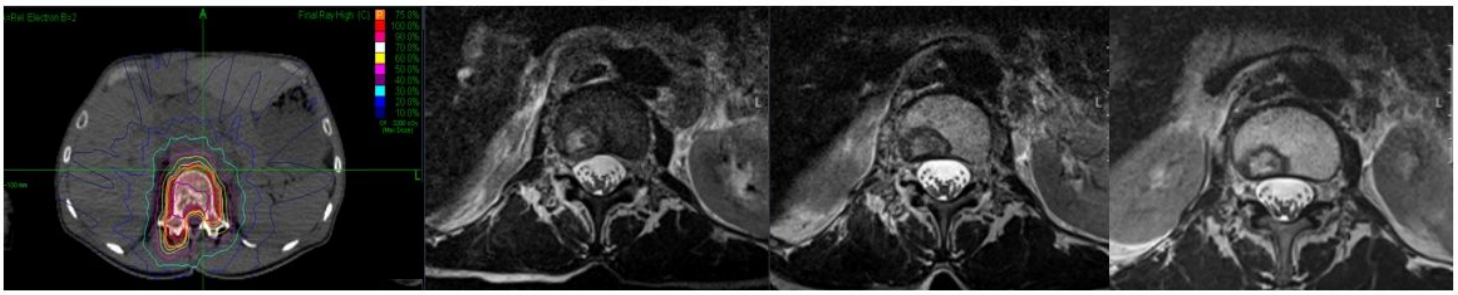

Figure 3

Example of radiological changes of a spine metastasis treated with SBRT (stable disease (C), yet initially classified as “pseudoprogression” (B)), and associated SBRT-plan (A1).