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Original Research Article

Remineralization of lytic spinal metastases after radiation therapy – A retrospective cohort study comparing conventional external beam radiation therapy with stereotactic ablative body radiation

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ABSTRACT

Introduction: Osteolytic spinal metastases (SM) have a higher risk of fracture. In this study we aim to confirm the remineralization of lytic SM after radiation therapy. Secondary the influence of SBRT compared to cEBRT and tumor type will be analyzed.
Methods: A retrospective cohort study was performed.
Results: 87 patients, 100 SM were included. 29 received SBRT, 71 cEBRT. Most common primary tumors were breast (35 %), lung (26 %) and renal (11 %). Both cEBRT and SBRT resulted in a significant increase of bone mineral density (BMD) (83.76 HU ± 5.72 → 241.41 HU ± 22.58 ($p < 0.001$) and 82.45 ± 9.13 → 179.38 ± 47.83$p = 0.026$). There was a significant increase in absolute difference of BMD between the SM and reference vertebrae ($p < 0.001$). There was no significant difference between SBRT and cEBRT. There was no increase of BMD in renal lytic SM after radiation therapy (pre-treatment: 85.96 HU ± 19.07; 3 m 92.00 HU ± 21.86 ($p = 0.882$); 6 m 92.06 HU ± 23.94 ($p = 0.902$); 9 m 70.44 HU ± 7.45 ($p = 0.213$); 12 m 98.08 HU ± 11.24 ($p = 0.740$)). In all other primary tumors, a significant increase of BMD after radiation therapy was demonstrated ($p < 0,05$).
Conclusion: We conclude that the BMD of lytic SM increases significantly after radiation therapy. Lytic SM of primary renal tumors are the exception; there is no significant remineralization of renal lytic SM after radiation therapy. There is no benefit of SBRT over cEBRT in this remineralization. These findings should be taken into account when deciding on surgery in the potentially unstable group defined by the spinal instability neoplastic score.

Introduction

The prevalence of spinal metastases (SM) in the oncologic population is increasing, due to the growing incidence of cancer and the improving survival [1–4].

SM can lead to metastatic epidural spinal cord compression (MESCC) in one out of 10 (9,8%) or pathologic vertebral compression fractures (pVCF) in 1 out of 8 patients (12.6 %) [1].

The spinal instability neoplastic score (SINS) provides an estimation of mechanical instability and need for therapeutic interventions [5]. One of the parameters determining this score is the type of SM: lytic lesions, compared to blastic or mixed lesions, result in a higher score, associated with a higher risk of instability and fracture. Pathologic fractures can cause pain (either mechanical local pain or radicular pain), spinal cord compression and/or radicular compression that may result in loss of function. These symptoms can lead to reduced quality of life (QoL) [6–8]. The benefit of surgery in patients with proven instability (SINS > 13 or SINS 7–12 with mechanical pain) is well-established [9]. In SINS 7–12, improving the bone quality of lytic SM could improve stability and prevent fractures or avoid the burden of surgical treatment.

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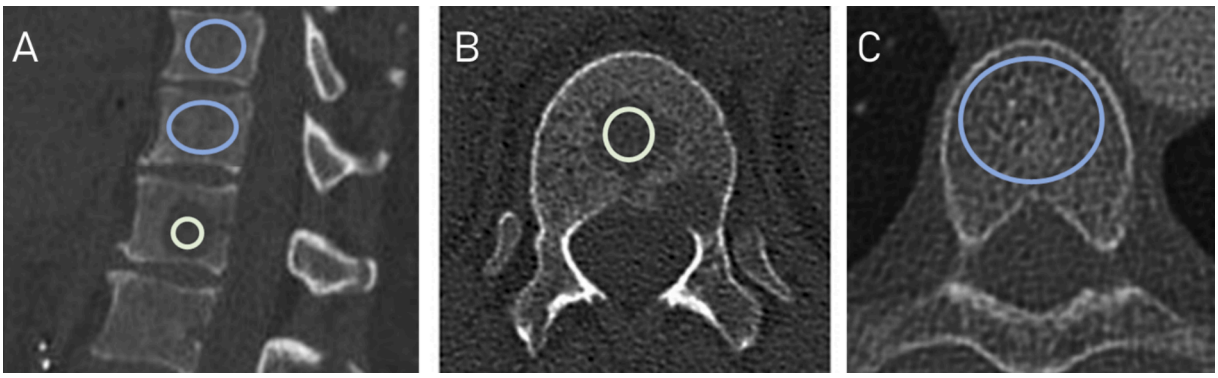

Fig. 1. Drawing of the region of interest (ROI) for BMD measurement in HU as described in methods. A: sagittal CT scan, sagittal ROI of the lytic lesion is shown in light green, sagittal ROI of reference vertebrae in blue. B: axial CT slide of the lytic lesion, axial ROI shown in light green. C: Axial slide through one of the reference vertebrae, axial ROI of the reference vertebra is shown in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Bone formation is a result of complex and interconnected processes. SM disrupt the equilibrium between osteoblast and osteoclast activity. Depending on the predominant activity within SM either osteolytic or osteoblastic lesions arise. In osteolytic SM, these processes form a complex vicious cycle with tumor growth and bone resorption stimulating each other. Local treatment of these metastases can disrupt this cycle and restore the equilibrium between osteoblasts and osteoclasts leading to remineralization [10]. Previous studies showed significant improvement in bone mineral density (BMD) of lytic SM after cEBRT [11,12]. One study showed a slight trend favoring 10 x 3 Gy in recalcification for all primary tumor sites, only in breast cancer this trend was significant [12].

BMD is linearly related to the strength of the vertebral body and fracture force [13–15]. The use of Hounsfield units measured on a computed tomography (CT) scan image is a well-described method to measure bone mineral density (BMD) [16], with a normal value for the vertebral body of 195.7 (95 % CI 171.4 − 220.0) [17]. [17,13–15].

Radiation therapy is primordial in the treatment of SM. Last decade, stereotactic body radiation therapy (SBRT) emerged and showed possible benefits compared to conventional radiotherapy (cEBRT) in local control (LC) and pain control [18–21]. Moreover, SBRT is an extremely promising treatment modality being integrated into the treatment algorithms of MESCC and seems to provide durable LC [22]. However the effect of SBRT on the remineralization of lytic SM is not well described.

With this study we aim to analyze if SBRT is superior compared to cEBRT in the remineralization of lytic spinal metastases after radiation therapy and confirm the remineralization of lytic SM after cEBRT. Secondly, the influence of primary tumor type and bone-modifying agents (Denosumab and bisphosphonates) will be analyzed.

Methods

The study was approved by the institutional ethics committee of GZA Hospitals (230703RETRO) and complied with the Declaration of Helsinki and good clinical practice guidelines.

Patient selection

All patients who underwent radiation therapy for SM within the Iridium Network, Belgium, between 01/01/2020 and 31/12/2022 were reviewed in a retrospective study. We included patients with (1) diagnosis of a solid malignant tumor, (2) at least one osteolytic SM (metastases were considered osteolytic when a region of bony destruction/disappearance (a visible decrease in HU) was observed within a vertebra on pre-radiation CT), (3) 18 years or older and (4) at least one CT-scan after radiation therapy. We excluded: (1) non-solid primary tumors (lymphoma, multiple myeloma, germ cell tumors) and primary bone tumors, (2) vertebral collapse of more than 50 % at the level of osteolytic metastasis pre-radiation and (3) osteosynthesis at the level of osteolytic metastasis pre-radiation.

Measurements

The following data were analysed: age, sex, primary tumor type, use of bone modifying agents (bisphosphonates, Denosumab), level of the vertebra, radiographic characteristics of SINS as measured on the pre-radiation CT-scan (location, alignment, posterolateral involvement, spinal body collapse), radiotherapy characteristics (cEBRT or SBRT, total dose (Gy), number of fractions), BMD: HU of the lytic SM and the reference vertebrae were recorded in each available CT scan, pre-treatment and at 3 months, 6 months, 9 months and 12 months after treatment. (+/- 4 weeks).

BMD was measured using a circular region of interest (ROI) in the sagittal and axial plane of the CT-scan images. The center point of the ROI was set manually on the estimated 3D centroid of the osteolytic lesion. The average between the sagittal and axial measurements was calculated. The ROI, as established in the first measurement, was used for the follow-up measurements. As a reference, the first two normal vertebrae cranial to the lesion were selected. If there were no appropriate vertebrae cranial to the lesion, the first two caudals were selected. The axial and sagittal ROI for the reference measurement was placed in the center of the vertebral body on the midsagittal CT image and in the center of the vertebral body on the axial image with a minimal diameter of at least 10 mm and as large as possible without including the endplates or ventral or posterior wall of the vertebra. The mathematical average between these 4 measurements (2 axial and 2 sagittal) was calculated to determine the reference value. The reference measurement is used to estimate the effect of osteoporosis/osteopenia, the use of bone-modifying agents or the effects of any systemic therapy on BMD Fig. 1.

All measurements were executed by two investigators (RVdB and MVK), a random sample of 10 % of patients was assessed again by the co-authors. In case of more than 10 % discrepancy in measurements, all cases would be double-checked and the average of the 2 measurements would be used. The investigators were not blinded to patients' characteristics and outcomes during the assessment.

BMD was assessed for the lytic SM on the planning CT pre-treatment, at 3-, 6-, 9- and 12-month intervals available follow-up CT-scan. The absolute difference with the reference vertebrae was calculated by subtracting the HU of the reference vertebrae from the HU of the SM.

All follow-up up CT-scans were assessed for the presence of pathologic fractures. Fractures were scored following the AO spine classification [23]. Additional spinal metastasis-related treatment was registered. For this registration, surgery including the level of the

Table 1
Demograpics. *Other primarytumors are thyroid, melanoma, bladder, cholangio and parotic.

	Overall	cEBRT	SBRT	p
Patients	87	59	28	
Lesions	100	71	29	
Mean diameter	18.45 mm (2–56)	18.25 mm (2–52)	18.93 mm (9–56)	0.771
Age	65.7 (42–90)	65.5 (42–90)	66.4 (42–86)	0.695
Gender	43 M / 57F	29 M / 42F	14 M / 15F	0.498
Localisation				
Cervical	9 (9 %)	6 (8.5 %)	3 (10.3 %)	0.888
Thoracic	52 (52 %)	39 (54.9 %)	13 (44.8 %)	0.357
Lumbar	37 (37 %)	26 (36.6 %)	11 (37.9 %)	0.450
Sacral	2 (2 %)		2 (6.9 %)	0.143
Primary tumor				
Breast	35 (35 %)	25 (35.2 %)	10 (34.5 %)	0.945
Lung	26 (26 %)	21 (29.6 %)	5 (17.2 %)	0.164
Prostate	12 (12 %)	7 (9.9 %)	5 (17.2 %)	0.347
Renal	11 (11 %)	6 (8.5 %)	5 (17.2 %)	0.257
Gastro intestinal	6 (6 %)	5 (7.1 %)	1 (3.4 %)	0.317
Other*	10 (10 %)	7 (9.9 %)	3 (10.3 %)	0.941
Medication				
Bisphosphonates	13 (13 %)	10 (14.1 %)	3 (10.3 %)	0.807
Denosumab	53 (53 %)	36 (50.7 %)	17 (58.6 %)	0.572
None	34 (34 %)	25 (35.2 %)	9 (31.0 %)	0.685
SINS				
Location				
Junctional	39 (39 %)	28 (39.4 %)	11 (37.9 %)	0.888
Mobile spine	24 (24 %)	16 (22.5 %)	8 (27.6 %)	0.601
Semirigid spine	35 (35 %)	27 (38 %)	8 (27.6 %)	0.301
Rigid	2 (2 %)	0 (0 %)	2 (6.9 %)	0.143
Posterolateral involvement				
Bilateral	10 (10 %)	7 (9.9 %)	3 (10.3 %)	0.942
Unilateral	51 (51 %)	37 (52.1 %)	14 (48.3 %)	0.728
None	39 (39 %)	27 (38.0 %)	12 (41.4 %)	0.757
Alignment				
De novo deformity/ kyfose	7 (7 %)	6 (8.5 %)	1 (3.4 %)	0.290
Normal alignment	93 (93 %)	65 (91.5 %)	28 (96.6 %)	290
Collaps				
>50 % collaps	1 (1 %)	1 (1.4 %)	0 (0 %)	0.314
< 50 % collaps	4 (4 %)	3 (4.2 %)	1 (3.4 %)	0.851
No collaps, >50 % involvement	19 (19 %)	15 (21.1 %)	4 (13.8 %)	0.361
None of the above	76 (76 %)	52 (73.2 %)	24 (82.8 %)	0.277
Radiotherapy				
1 X 8 Gy		64 (90.1 %)		
2 x 8GY		2 (2.8 %)		
5 X 4 Gy		5 (7.0 %)		
1 X 20 Gy			6 (20.7 %)	
5 X 8 Gy			13 (44.9 %)	
3 X 10 Gy			2 (6.0 %)	
3 X 8 Gy			5 (17.2 %)	
5 X 7 Gy			3 (10.3 %)	

pathologic vertebra, re-irradiation including the level of the pathologic vertebra or vertebroplasty was registered.

Statistical analysis

Data were summarized using descriptive measures with mean HU and standard error mean (±). The difference in mean HU between two points in time was analyzed with a paired T-test in subgroups of cEBRT and SBRT. The difference in mean HU between the lytic SM and respective reference vertebrae was analyzed with a Welch T-test. Subgroup analyses were performed per primary tumor, very low BMD (≤54 HU) vs other osteolytic SM and for the use of bone modifying agents. Data were analyzed by IBM SPSS statistics version 28.

Results

Demographic data

631 patients were reviewed; most prevalent primary tumors were breast (n = 117, 18.5 %), prostate (n = 184, 29.2 %), lung (n = 120, 19.0 %) and renal (n = 25, 4.0 %). We excluded 310 patients due to not available or existing post-radiation CT-scan. Of the remaining patients, 176 had osteoblastic SM, 52 were multiple myeloma, plasmocytoma or lymphoma patients and 6 had a vertebral body collapse, osteosynthesis or vertebroplasty at the level of the SM, resulting in exclusion for the analysis. Finally, 87 patients remained resulting in 100 SM included in this study. We included 71 SM treated with cEBRT and 29 with SBRT. Mean age was 65,7 years (42–90 y), primary tumors were breast (35 %), lung (26 %), prostate (12 %), renal (11 %), gastrointestinal (6 %) and others (10 %). There was no significant difference between cEBRT and SBRT groups regarding age, gender, mean diameter of the lytic SM, localization or attributes of the SINS or primary tumor type (Table 1.).

Bone mineral density

The mean BMD of all osteolytic SM at baseline was 83.39 HU (±4.83) significantly lower compared to the mean BMD of the reference vertebrae at baseline 187.82 HU (±10.12) ($p < 0.001$). There was no significant difference pre-treatment between SM treated with cEBRT and SBRT ($p = 0.901$) (Table 2., Fig. 2). The mean absolute difference between osteolytic SM and reference at baseline in the cEBRT group was − 108.48 HU (±10.60) and in the SBRT group − 94.53 HU (±16.37) ($p = 0.479$).

Three months post-radiation, both the cEBRT (n = 57) and SBRT (n = 21) showed a significant increase in BMD compared to pre-treatment with a mean BMD of respectively 241.41 HU (±22.58) ($p < 0.001$) and 179.38 HU (±47.83) ($p = 0.026$); there is no significant difference between cEBRT and SBRT ($p = 0.192$). Due to this increase, the absolute difference between the SM and reference vertebrae became positive (HU of the SM are higher than HU of the reference vertebrae) (cEBRT: 47.73 HU (±23.36) ($p < 0.001$); SBRT 16.29 HU (±47.20)($p = 0.012$), both cEBRT and SBRT showed significant improvements compared to the pre-treatment absolute difference.

Six months post-radiation there was a further increase of the mean BMD of the lytic SM (270.46 HU ± 25.17), without a significant difference between cEBRT (n = 52) and SBRT (n = 15) ($p = 0.106$). The absolute difference remained positive (70.11 HU ± 24.85), there was no significant difference between cEBRT and SBRT ($p = 0.175$).

Nine months post radiation, the mean BMD of the lytic SM treated with cEBRT (n = 43) was significantly higher compared to those treated with SBRT (n = 21) (319.37 HU ± 34.69 vs 163.91 HU ± 39.71; $p = 0.008$). This significant difference was not confirmed in the absolute difference (111.99 HU ± 37.48 vs 6.40 HU ± 41.58; $p = 0.057$). The mean BMD of the SM differed significantly from the BMD of the reference vertebrae (268.36 HU ± 28.07 vs 195.22 HU ± 12.64; $p < 0.001$).

One year post-radiation (cEBRT n = 39; SBRT n = 22) the mean BMD of the SM was significantly higher compared to the mean BMD of the reference vertebrae ($p < 0.001$) with an absolute difference of 110.64 HU ± 31.16 (significant improvement compared to pre-treatment (−104.43 HU ± 8.88) ($p < 0.001$). The mean BMD of the lytic SM treated with cEBRT was significantly higher compared to those treated with SBRT (363.05 HU ± 40.82 vs 200.84 HU ± 44.05; $p = 0.013$), when excluding renal metastases, this difference was non-significant (370.11 HU ± 41.27 vs 230.88 HU ± 55.08; $p = 0.058$). This significant difference was not confirmed in the absolute difference (153.22 HU ± 39.72 vs 35.17 HU ± 46.97; $p = 0.068$). (See Table 2.).

Table 2
Results:Hounsfield Units (HU) of the lytic lesion, reference vertebrae and HU absolute difference: HU reference vertebrae minus HU lytic lesion with the respective standard error mean (±). * P value paired samples T-test between follow-up and pre-treatment value. § P value paired samples T-test between HU lytic lesion compared and HU reference vertebrae for overall, cEBRT or SBRT respectively.ˆP value paired samples T-test between cEBRT and SBRT.

	HU lytic lesion				HU reference vertebrae				HU Absolute difference			
	Overall	cEBRT	pˆ	SBRT	Overall	cEBRT	pˆ	SBRT	Overall	cEBRT	pˆ	SBRT
Pre-treatment n = 100	83.39 ± 4.83	83.76 ± 5.72	0.901	82.45 ± 9.13	187.82 ± 10.12	192.25 ± 11.98	0.497	176.98 ± 19.12	− 104.43 ± 8.88	−108.48 ± 10.60	0.479	− 94.53 ± 16.37
cEBRT = 71 SBRT = 29	p < .001§	p < .001§		p < .001§								
3 months n = 78	224.71 ± 21.00	241.41 ± 22.58	0.192	179.38 ± 47.83	185.45 ± 9.80	193.68 ± 11.46	0.168	163.09 ± 18.50	39.26 ± 21.17	47.73 ± 23.36	0.514	16.29 ± 47.20
cEBRT = 57 SBRT = 21	p = 0.068 §	p = .046§		p = .734§								
p value*	0<.001	0<.001		0.026	0.824	0.521		0.234	0<.001	0<.001		0.012
6 months n = 67	270.46 ± 25.17	292.35 ± 28.61	0.106	194.57 ± 49.73	200.34 ± 12.75	204.04 ± 14.57	0.593	187.53 ± 26.97	70.11 ± 24.85	88.31 ± 28.63	0.175	7.03 ± 47.74
cEBRT = 52 SBRT = 15	p = .006§	p = .003§		p = .885§								
p value*	0<.001	0<.001		0.028	0.406	0.370		0.855	0<.001	0<.001		0.023
9 months n = 64	268.36 ± 28.07	319.37 ± 34.69	0.008	163.91 ± 39.71	195.22 ± 12.64	207.38 ± 16.37	0.170	170.31 ± 18.35	73.14 ± 29.30	111.99 ± 37.48	0.057	− 6.40 ± 41.58
cEBRT = 43 SBRT = 21	p = .15§	p = .005§		p = .879§								
p value*	0<.001	0<.001		0.048	0.108	0.010		0.303	0<.001	0<.001		0.019
12 months n = 61	304.54 ± 31.95	363.05 ± 40.82	0.013	200.84 ± 44.05	193.91 ± 13.45	209.83 ± 17.65	0.116	165.67 ± 19.36	110.64 ± 31.16	153.22 ± 39.72	0.068	35.17 ± 46.97
cEBRT = 39 SBRT = 22	p < .001§	p < .001§		p = .462§								
p value*	0<.001	0<.001		0.005	0.555	0.293		0.373	0<.001	0<.001		0.002

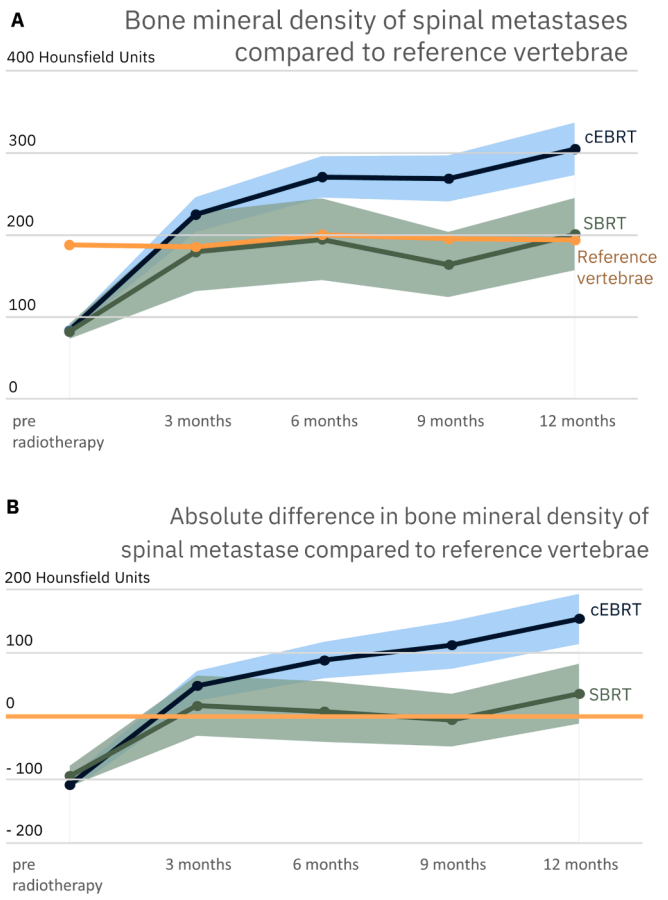

Fig. 2. Comparison of the pre-treatment, 3 month, 6 month, 9 month and 12 months measurements of the bone mineral density (BMD) of the lytic lesion in Hounsfield Units (HU) A) the bone mineral density of the lytic SM in Hounsfield Units and reference vertebrae and (B) absolute difference between the lytic SM and reference vertebrae in HU between cEBRT and SBRT.

Factors associated with remineralization

Primary tumor type

Subgroup analysis per primary tumor was performed for breast (35), lung (26), prostate (12) and renal (11) metastases (Table 3., Fig. 3.

Renal metastases showed no significant raise in mean BMD of the lytic SM after radiation therapy (pretreatment: 85.96 HU ± 19.07; 3 m 92.00 HU ± 21.86 ($p = 0.882$); 6 m 92.06 HU ± 23.94 ($p = 0.902$); 9 m 70.44 HU ± 7.45 ($p = 0.213$); 12 m 98.08 HU ± 11.24 ($p = 0.740$)). The absolute difference (− 101.33 HU ± 24.11) did not improve after radiation therapy, 3 months (− 112.93 HU ± 23.75 ($p = 0.342$)), 6 months (− 152.33 HU ± 41.31 ($p = 0.598$)), 9 months (− 170.53 HU ± 42.34 ($p < 0.001$)) or 12 months (− 105.54 HU ± 60.32 ($p = 0.829$)). The remineralization of lytic SM resulting from renal tumors after radiation therapy is significantly less compared to other spinal metastases (absolute difference 3 m: $p = 0.005$; 6 m $p < 0.001$; 9 m $p = 0.001$ and 12 m $p = 0.021$) with renal metastases being the only subgroup without improvement in HU of the lytic SM and absolute difference.

For lytic SM in breast cancer patients, there is a tendency to higher recalcification of the lytic SM with an absolute difference improving to 128.95 HU (±39.64) 3 months after radiation therapy, significantly better compared to other primary tumors ($p = 0.002$), even when excluding renal metastases ($p = 0.016$). In the measurements at 6 and 9 months this higher remineralization rate remains significant compared to other primary tumors ($p = 0.006$ and $p = 0.043$), when excluding renal metastases, this benefit is statistically non-significant ($p = 0.068$ and 0.238). The remineralization at 12 months post-radiotherapy is high with an absolute difference of 185 HU (±44.14), a significant improvement compared to the pre-treatment absolute difference of −106.84 HU ± 17.20 ($p < 0.001$). This improvement is larger compared to other primary tumor types, but not significant ($p = 0.068$ and $p = 0.184$ when excluding renal metastases).

Subgroup analysis for primary lung carcinoma showed no significant difference compared to the overall group. (Table 3.).

Denosumab and bisphosphonates

66 were treated with bone-modifying agents (53 with Denosumab and 13 with bisphosphonates) and 34 received neither one of these. Both groups showed a significant increase in BMD of the SM ($p < 0.001$ at 3, 6, 9 and 12 months). There was no significant difference in BMD of the SM between these groups. The reference vertebrae showed no significant change in BMD after 3, 6, 9 or 12 months compared to pre-treatment. A significant difference in BMD between the groups developed at 3 ($p = 0.037$), 6 ($p = 0.008$), 9 ($p = 0.006$) and 12 months ($p = 0.014$) with increased BMD if treated with bone modifying agents. In the absolute difference, both groups showed a significant improvement at 3, 6, 9 and 12 months; there was no significant difference between those with or without bone-modifying agents. (Table 4).

Bone mineral density

Subgroup analysis for BMD showed no significant difference between very low BMD (≤54 HU, n = 33) and other lytic SM (>54 HU, n = 67) in the remineralization and absolute difference. Both groups demonstrated a significant improvement in BMD of the lytic SM ($p < 0.001$) and comparable absolute differences at each time point between these groups. ($p = 0.131$).

Pathologic fractures

7 Pathologic fractures were documented after radiation. All AO spine A1 without a need for additional treatment. There is a non-significant increase in the incidence of pVCF in the SBRT group (4/29, 13,8%) compared to the cEBRT group (3/71, 4,2%)($p = 0.259$). No significant difference was demonstrated in subgroup analysis for tumor type

Discussion

Both cEBRT and SBRT result in a significant increase of BMD of lytic SM and an improvement of the absolute difference, due to the remineralization and sclerotic changes.

BMD is no exact measurement of strength. There is no in vivo way of measuring the strength of SM. BMD is well associated with bone strength, proven in different in vitro studies: BMD ultimate compressive strength was correlated ($r = 0.86$) and the strength was found to increase linearly with increasing amounts of bone mineral content [13]. This linear relation was confirmed in a recent in vitro model [14]. BMD is to our knowledge the best possible measurement for vertebral strength in a clinical study. These in vitro results are validated in clinical studies, a systematic review of these calculated that a 1 % increase in spinal BMD is associated with a 0.03 decrease in the relative risk of vertebral fracture [15].

Despite the well-documented potential benefits of SBRT compared to cEBRT in pain response and local control [18–21] this retrospective cohort study does not demonstrate a significant benefit in the remineralization of lytic SM when SBRT is compared to cEBRT. In neither of the outcome parameters, there is a significant benefit of SBRT over cEBRT and not even a tendency to such a benefit. SBRT does not lead to more rapid mineralization or does not lead to a higher BMD in time. cEBRT does not lead to a recurrent lytic SM within a year. Even when excluding the non-responding renal metastases, there is no tendency to a benefit for SBRT regarding remineralization in the investigated cohort.

Great variety in radiosensitivity exists between different primary tumor types [24]. This study demonstrates that lytic SM in patients with

Table 3
Subgroup analysis per primary tumor of the absolute difference in hu between mean bmd of lytic lesions and mean bmd of the reference vertebrae. * p value paired samples t-test between follow-up and pre-treatment value. § p value paired samples t-test between respective primary tumor absolute difference and overall absolute difference.ˆp value paired samples t-test between respective primary tumor absolute difference and overall excluding renal absolute difference.

		HU Absolute difference				
	Overall	Excluding renal	Breast	Lung	Prostate	Renal
Pre-treatment		n = 89	n = 35	n = 26	n = 12	n = 11
n = 100	− 104.43 ± 8.88	− 101.33 ± 9.51	− 106.84 ± 17.20	− 94.35 ± 14.88	− 114.63 ± 30.67	− 101.33 ± 24.11
cEBRT = 71						
SBRT = 29			p = .844§	p = .503§	p = .674§	p = .322§
			p = .644ˆ	p = .640ˆ	p = .670ˆ	
3 months		n = 68	n = 27	n = 25	n = 4	n = 10
n = 78	39.26 ± 21.17	61.64 ± 22.84	128.95 ± 39.64	23.39 ± 31.31	64.63 ± 180.34	− 112.93 ± 23.75
cEBRT = 57						
SBRT = 21			**p = .002§**	p = .610§	p = .783§	**p = .005§**
			p = .016ˆ	p = .204ˆ	p = .170ˆ	
P value*	**0<.001**	**0<.001**	**0<.001**	**p = 0.002**	p = 0.570	p = 0.342
6 months		n = 58	n = 24	n = 19	n = 6	n = 9
n = 67	70.11 ± 24.85	104.63 ± 25.16	159.1 ± 35.09	112.87 ± 47.42	16.21 ± 98.58	− 152.33 ± 41.31
cEBRT = 52						
SBRT = 15			**p = .006§**	p = .282§	p = .500§	**p < .001§**
			p = .068ˆ	p = .822ˆ	p = .558ˆ	
P value*	**0<.001**	**0<.001**	**0<.001**	**p = 0.001**	p = 0.281	p = 0.598
9 months		n = 56	n = 24	n = 17	n = 7	n = 8
n = 64	73.14 ± 29.30	107.95 ± 30.25	149.48 ± 40.65	121.60 ± 62.87	17.04 ± 101.19	− 170.53 ± 42.34
cEBRT = 43						
SBRT = 21			**p = .043§**	p = .324§	p = .507§	**p < .001§**
			p = .238ˆ	p = .769ˆ	p = .369ˆ	
P value*	**0<.001**	**0<.001**	**0<.001**	**0.008**	0.318	0.052
12 months		n = 89	n = 23	n = 17	n = 7	n = 6
n = 61	110.64 ± 31.16	134.23 ± 32.48	185.46 ± 44.14	136.15 ± 64.74	18.00 ± 101.83	− 105.54 ± 60.32
cEBRT = 39						
SBRT = 22			p = .061§	p = .615§	p = .288§	**p = .021§**
			p = .184ˆ	p = .969ˆ	p = .665ˆ	
P value*	**0<.001**	**0<.001**	**0<.001**	**0.005**	0.299	0.829

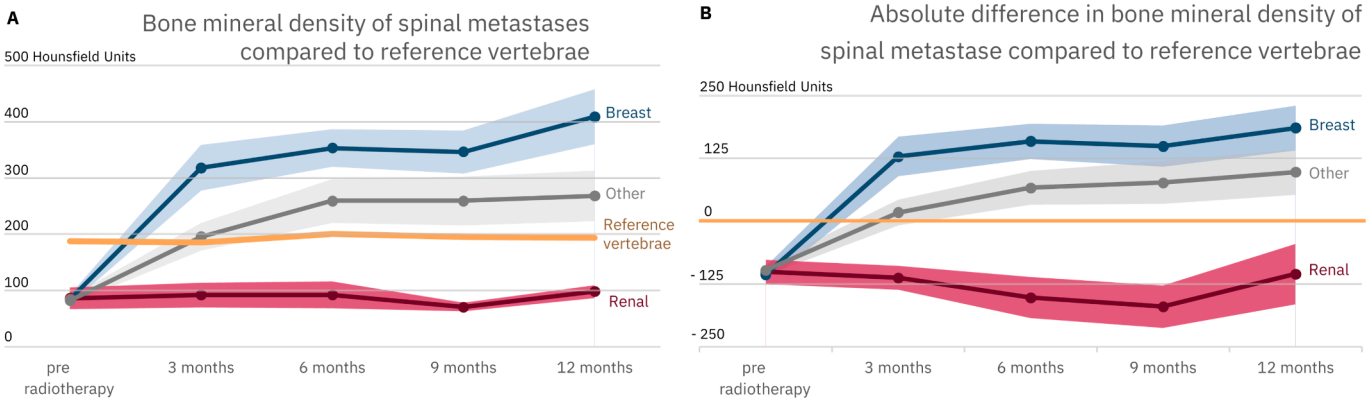

Fig. 3. Subgroup analysis (mean and standard error mean) of the pre-treatment, 3 month, 6 month, 9 month and 12 months measurements of (A) the bone mineral density of the lytic SM in Hounsfield Units and reference vertebrae and (B) absolute difference between the lytic SM and reference vertebrae in HU for breast cancer, other primary tumor type and renal cancer.

renal cancer do not have the ability of remineralization after radiation therapy. Both cEBRT and SBRT fail to reach improvement in BMD and absolute difference of renal lytic SM. In contrast to other primary tumor types, radiation therapy does not lead to remineralization of renal lytic SM. Therefore we cannot count on this remineralization process in renal cell SM with a potential spinal instability to downgrade the SINS score by remineralization of the lytic SM. Renal SM require adequate stabilization if there is a (potential) spinal instability. Additional instrumentation or vertebroplasty should therefore be considered in the surgical strategy of renal SM [9,25–28].

On the other hand, lytic SM in breast cancer patients showed a tendency towards higher remineralization and larger improvement of absolute difference compared to other primary tumor types. This confirms previous findings [12]. In this subgroup, there was no significant benefit of SBRT over cEBRT nor a tendency towards it. These results advocate that radiation therapy can rapidly improve the BMD of lytic SM in breast cancer. In the absence of mechanical pain and/or neurological signs and symptoms, upfront radiotherapy can be considered in patients with a potentially unstable spine (SINS 7–12) [5,9] Nonetheless, informing these patients on signs and symptoms of increased instability or fractures and close monitoring is mandatory.

All lytic SM (except for renal SM) had improvement in BMD after radiation. There is no significant difference between very low BMD (defined as $\leq$ 54 HU) and the other lytic SM. Osteolytic SM have the ability to increase the mineralization after radiotherapy, even if the mineralization is very low. Therefore, very low BMD alone does not exclude the possibility of regaining mineralization which leads to increased BMD.

Table 4
Influence of denosumab and bisphosphonates (bp) on hu of the lytic lesion, hu of reference vertebrae and absolute difference. * p value paired samples t-test between follow-up and pre-treatment value. § p value paired samples t-test between HU lytic lesion and HU reference vertebrae for none or bone modifying agents respectively. ° P value paired samples T-test between none and bone modifying agents.

	HU lytic lesion			HU reference vertebrae			HU Absolute difference		
	None	p°	Bone modifying agents	None	p°	Bone modifying agents	None	p°	Bone modifying agents
Pre-treatment	n = 34	0.573	n = 66	n = 34	0.102	n = 66	n = 34	0.120	n = 66
n = 100	79.57 ± 6.78		85.36 ± 6.44	164.76 ±		199.70 ± 12.90	− 85.19 ±		− 114.34 ± 11.64
cEBRT = 71				15.59			12.64		
SBRT = 29	p < .001§		p < .001§						
3 months	n = 25	0.756	n = 53	n = 25	0.037	n = 53	n = 25	0.520	n = 53
n = 78	215.12 ±		229.24 ± 25.11	155.85 ±		199.41 ± 12.05	59.27 ± 35.02		29.83 ± 26.55
cEBRT = 57	38.88			15.54					
SBRT = 21	p = 0.068 §		p = .266§						
p value*	0<.001		0<.001	0.824		0.738	0<.001		0<.001
6 months	n = 18	0.314	n = 49	n = 18	0.008	n = 49	n = 18	0.752	n = 49
n = 67	228.31 ±		285.94 ± 31.78	145.08 ±		220.64 ± 16.15	83.22 ± 36.41		65.30 ± 31.41
cEBRT = 52	35.35			10.02					
SBRT = 15	p = .006§		p = .043§						
p value*	0<.001		0<.001	0.406		0.441	0<.001		0<.001
9 months	n = 19	0.070	n = 45	n = 19	0.006	n = 45	n = 19	0.572	n = 45
n = 64	190.08 ±		301.41 ± 36.15	142.67 ±		217.41 ± 15.55	47.41 ± 39.52		84.01 ± 38.33
cEBRT = 43	35.23			16.33					
SBRT = 21	p = .15§		p = .034§						
p value*	0<.001		0<.001	0.108		0.054	0<.001		0<.001
12 months	n = 21	0.175	n = 40	n = 21	0.014	n = 40	n = 21	0.731	n = 40
n = 61	244.45 ±		336.10 ± 40.29	148.77 ±		217.60 ± 17.89	95.68 ± 44.08		118.50 ± 41.83
cEBRT = 39	50.87			15.25					
SBRT = 22	p < .001§		p = .007§						
p value*	0<.001		0<.001	0.555		0.118	0<.001		0<.001

Subgroup analysis of bone modifying agents demonstrated a benefit for these medications in increasing the BMD of both the reference vertebrae (p = 0.006) and lytic SM (p = 0.070). Nonetheless, bone modifying agents do no lead to significant larger improvement in the absolute difference compared to those without these medications. The benefit of bone-modifying agents has been well proven before [29–32].

There is a non-significant increase in the incidence of pVCF in this cohort in the SBRT group (4/29, 13,8%) compared to the cEBRT group (3/71, 4,2%)(p = 0.259). Previous studies demonstrated similar (non-significant or significant) increases in pVCF after SBRT compared to cEBRT [21], with an incidence of pVCF of approximately 10 % in SBRT [33–35]. Less than 2 % of these fractures require surgical treatment [34]. This cohort shows that there is no improved remineralization after SBRT compared to cEBRT, consequently SBRT does not reduce the risk of pathologic fractures, in contrast there is a tendency to increase the risk of fracture.

Strengths and limitations

The BMD was measured on objective CT-scan data, due to the method of measuring we limited the risk of bias as much as possible.

The retrospective study design is a limitation of this study. We excluded 310 patients due to non-existing or non-accessible post-radiation CT-scan. The nature of the metastatic disease is associated with limited survival. Many patients of the reviewed cohort were lost in follow-up (mainly because of death). This resulted in limited access to their medical records across the different hospitals of the Iridium Network. The quality of evidence is dependent on the accessibility and completeness of these records. Some subgroups have only a small sample size, therefore the power of the findings in these groups is limited.

To our knowledge, this is the first study that compared the effect of cEBRT and SBRT on the remineralization of lytic SM.

Conclusion

The BMD of lytic SM increases significantly after radiation therapy. There is no benefit of SBRT over cEBRT in this remineralization. Lytic SM of primary renal tumors are the exception; there is no remineralization of renal lytic SM after radiation therapy. These findings should be taken into account when defining a surgical strategy in the potentially unstable group as defined by the SINS.

CRediT authorship contribution statement

Ruben Van den Brande: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maxim Van den Kieboom:** Data curation, Formal analysis, Investigation. **Marc Peeters:** Supervision. **Charlotte Billiet:** Conceptualization, Supervision, Methodology. **Erik Van de Kelft:** Conceptualization, Supervision, Methodology.

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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