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Vertebral compression fracture after stereotactic ablative radiotherapy in patients with oligometastatic bone lesions from hepatocellular carcinoma

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ABSTRACT

Background and purpose: Stereotactic ablative radiotherapy (SABR) is popularly used to treat bone metastasis. Despite its efficacy, adverse events, including vertebral compression fracture (VCF), are frequently observed. Here, we investigated VCF risk after SABR for oligometastatic vertebral bone metastasis from hepatocellular carcinoma.

Materials and methods: A total of 84 patients with 144 metastatic bone lesions treated at three institutions between 2009 and 2019 were retrospectively reviewed. The primary endpoint was VCF development, either new or progression of a pre-existing VCF. VCFs were assessed using the spinal instability neoplastic score (SINS).

Results: Among 144 spinal segments, 26 (18%) had pre-existing VCF and 90 (63%) had soft tissue extension. The median biologically effective dose (BED) was 76.8 Gy. VCF developed in 14 (12%) of 118 VCF-naïve patients and progressed in 20 of the 26 with pre-existing VCF. The median time to VCF development was 6 months (range, 1–12 months). The cumulative incidence of VCF at 12 months with SINS class I, II and III was 0%, 26% and 83%, respectively ($p < 0.001$). Significant factors for VCF development were pre-existing VCF, soft tissue extension, high BED, and SINS class in univariate analysis, and pre-existing VCF in multivariate analysis. Of the six components of SINS, pain, type of bone lesion, spine alignment, vertebral body collapse, and posterolateral involvement were identified as predictors of VCF development.

Conclusion: SABR for oligometastatic vertebral bone lesions from HCC resulted in a substantial rate of new VCF development and pre-existing VCF progression. Pre-existing VCF was significant risk factor for VCF development, which require special attention in patient care. Patients with SINS class III should be considered surgical treatment rather than upfront SABR.

1. Introduction

Reportedly, 5%–25% patients with metastatic hepatocellular carcinoma (HCC) develop bone metastasis [1]. Due to recent advances in diagnosis and treatment, despite improvements in survival, the incidence of bone metastasis in patients with HCC is expected to increase [2].

Radiotherapy (RT) is an effective treatment for cancer bone metastasis, with significant pain palliation at the irradiated site in approximately 60%–90% of patients [3]. Furthermore, the recent advancement in RT technique, ablative RT, which delivers high doses in few fractions, is widely used and expected to deliver more than just pain palliation [4]. In the SABR-COMET trial, some patients with oligometastasis (<5 metastatic lesions from various primary tumors) achieved long-term overall survival and progression-free survival with ablative RT [5]. We have also reported the clinical efficacy of ablative RT in improving survival in patients with bone metastasis from HCC [6].

However, a vertebral compression fracture (VCF) is not an infrequently occurring adverse event after RT, including stereotactic ablative RT (SABR) and conventional RT, for bone metastasis [7–9]. To the best

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of our knowledge, VCF after SABR for bone metastasis from HCC has not been investigated. In the current study, we evaluated the risk of VCF after SABR for oligometastatic bone lesions in patients with HCC.

2. Materials and methods

2.1. Study population

This study included three institutions belonging to the Korean Radiation Oncology Group. After receiving approval from the institutional review boards of each institution, we reviewed the data of 130 patients with bone metastasis from HCC who were treated with RT between 2009 and 2019. This study was approved by the Severance Hospital Institutional Review Board (IRB #4-2021-1101). Because this was a retrospective study, the need for written informed consent was waived. The inclusion criteria were age $\geq$18 years, $\leq$5 metastatic bone lesions in total, and bone metastasis treated with SABR with a fraction dose $\geq$6 Gy. When metastatic bone lesions were present consecutively, each spine segment was calculated as one lesion. The clinical data of 84 patients with 144 bone metastatic spine lesions were retrospectively reviewed. Patients with symptoms of spinal cord compression were excluded. All patients were radiologically diagnosed with HCC, and bone metastasis was confirmed using magnetic resonance imaging (MRI) and/or computed tomography (CT). Liver function was evaluated using the Child-Pugh classification. Controlled primary tumors were defined as no new lesions at least 3 months after the administration of definitive treatment for the primary tumor, with no progression at the primary site or no new lesions on follow-up enhanced CT and/or MRI. Performance status was graded at the time of treatment using the Eastern Cooperative Oncology Group (ECOG) score system. Before and after SABR, the patients received systemic therapy consisting of a tyrosine kinase inhibitor or chemotherapeutic agent.

Treatment-related toxicities were monitored at least weekly during the treatment and frequently if clinically indicated. Treatment-related toxicities were graded according to the Common Toxicity Criteria for Adverse Events version 4.0 [10]. Acute toxicities were defined as adverse events during RT and late toxicities as adverse events 3 month after RT. The data were assessed from patient records.

The procedures followed in the current retrospective study were in accordance with the tenets of 1975 Declaration of Helsinki, revised in 2000. All authors had access to the study data; they reviewed and approved the final manuscript.

2.2. Radiotherapy

All patients received SABR at all sites of metastatic bone disease with intensity-modulated RT (IMRT). The SABR protocol used in each institution has been widely accepted; however, doses ranged from 20 to 60 Gy in 3–8 fractions. In all cases, dose constraints to normal tissues were achieved, although the dose had to be reduced to all or part of the target. Using simulation CT fused with MRI or positron emission tomography (PET), gross tumor volume (GTV) was determined by radiation oncologists, and clinical target volume and planning target volume was determined according to consensus guidelines for spinal stereotactic radiosurgery [11]. Dose constraint for organs at risk was determined according to various guidelines [12,13].

Helical tomotherapy or volumetric modulated arc therapy (VMAT), an image guided IMRT system with megavoltage CT that allows precise delivery, was used. Patients were immobilized in thermoplastic head-shoulder masks for the cervical spine. A customized total-body vacuum bag was used for the thoracic and lumbar spine. When IMRT was administered, megavoltage or kilovoltage cone-beam CT was performed daily before each treatment for all patients for image guidance.

2.3. Assessment

Total doses were recalculated and normalized to obtain biologically effective dose (BED). The BED for the prescribed dose was calculated using a standard linear quadratic model with an α/β of 10 Gy for HCC, which is a commonly used value. The actual total dose was converted to BED as follows: $BED = nd\ [1 + d/(\alpha/\beta)]$, where n is the number of fractions and d is the dose per fraction.

To assess VCF, all spinal segments were evaluated in terms of baseline vertebral status and clinical variables, such as age, sex, body mass index, spinal level, and presence of pain. In addition, each spinal segment was evaluated according to the spinal instability neoplastic score (SINS) [8]. The SINS is a scoring system for the assessment of spinal instability based on six criteria: location, intensity of pain, type of bone lesion, spinal alignment, vertebral body collapse, and posterolateral involvement. The scores range from 0 to 18 points. The SINS classifies the status of metastatic spinal elements into three categories: class I, stable (0–6 points); class II, potentially unstable (7–12 points); and class III, unstable (13–18 points). The type of metastatic bone lesion (blastic, lytic, or mixed) and spine alignment were classified using CT, and paraspinal extension, vertebral body collapse, and posterior involvement were evaluated with MRI.

VCF was defined as new VCF development (de novo) or fracture progression in a previously fractured vertebra after RT without evidence of tumor metastasis or progression. Fracture progression was defined as >20% reduction in vertebral body height [14]. VCF development was determined using follow-up MRI or CT, usually performed at 1–3-month intervals after RT or based on a physician's judgment.

2.4. Statistical analysis

The VCF rates for all categorical variables were compared using Fisher's exact test or chi-square test. The cumulative incidence of VCF was estimated from the end date of RT to the date the VCF developed or the date of the last imaging study if no fracture was present, taking competing events such as deaths into consideration, and the differences were evaluated using Gray's test [15]. Multivariate analysis was performed by comparing the cumulative incidence of VCF using Fine and Gray regression analysis. Statistical significance was set at a p-value of <0.05. Statistical analyses were performed using R version 4.2.1 (R Development Core Team).

3. Results

3.1. Patient characteristics

The median follow up was 10 months (range, 6–110 months). The median patient age was 59 years (range, 35–87 years), with a predominance of males (81%). Most patients had well-compensated liver function (Child-Pugh class A, 70 patients, 83%) and 69 patients (82%) had controlled primary HCC. Most patients had good performance status (ECOG 0 or 1, 69 patients, 82%). Sixty-two patients (74%) received systemic therapy with either sorafenib (55 patients, 66%) or chemotherapy (7 patients, 8%). No patient treated with systemic therapy and SABR concurrently, and interruption of systemic therapy was as short as 1 week and as long as 2 weeks.

Spinal segment characteristics are summarized in Table 1. A total of 63 patients with 110 spinal segment (76%) underwent spinal MRI at diagnosis. Among 84 patients, 13 had multiple metastatic segments. There were 7 patients with 2 metastatic segments, 4 patients with 3, and 2 patients with 4, with a total of 34 segments for multiple metastatic segments. Details of treatments are summarized in Table 2. The total and fractional doses were 48 Gy (range, 18–75 Gy) and 6.75 Gy (range, 5–15.0 Gy), respectively. The most common dose prescription was 48 Gy in 8 fractions (55%) followed by 60 Gy in 4 fractions (29%), 48 Gy in 4 fractions (8%) and 42 Gy in 5 fractions (8%). The median BED was 76.8

Table 1
Baseline characteristics in spinal segments (n = 144).

Variables	n	% or range
Spine level		
Cervical	25	17%
Thoracic	55	38%
Lumbar	47	33%
Sacral	17	12%
Solitary lesion	110	76%
Multiple lesions	34	24%
Pre-existing VCF		
No	118	82%
Yes	26	18%
BMI, kg/M^2		
<25	117	81%
≥25	27	19%
Soft tissue extension		
No	54	37%
Yes	90	63%
SINS class		
I	38	27%
II	94	65%
III	12	8%

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV/HCV; HCC, hepatocellular carcinoma; VCFs, vertebral compression fractures; BMI, body mass index; SINS, spinal instability neoplastic score.

Table 2
Details of treatments.

Details of treatment	n	% or range
Total RT dose (median in Gy)	48.0	18.0–75.0
Fractional RT dose (median in Gy)	6.75	5.0–15.0
48 Gy in 8 fx	80	55%
42 Gy in 5 fx	11	8%
48 Gy in 4 fx	11	8%
60 Gy in 4 fx	42	29%
BED in Gy_{10}		
Median	76.8	
Range	30–150	
$BED_{\alpha/\beta=10}$, Gy		
≤76.8	92	64%
>76.8	52	36%
Systemic therapy		
No	36	25%
Chemotherapy	13	9%
Sorafenib	95	66%

RT, radiotherapy; BED, biologically effective dose;

Gy (range, 30–150 Gy). Of 144 spinal segments, 26 (18%) had a pre-existing VCF and 90 (63%) had bone metastasis with soft tissue extension. The proportions of SINS classes I, II, and III were 27% (n = 38), 65% (n = 94), and 8% (n = 12), respectively.

3.2. VCF and predictive variables

Among the 144 spinal segments, 14 (12%) out of 118 segments that had no pre-existing VCF were new VCF, and 20 out of 26 segments that had pre-existing VCF were fractured progressions. In total, 34 VCFs (24%) were identified. The median time to the VCF development was 6 months (range, 1–12 months).

The 12-month cumulative incidence of VCF was 24% (Fig. 1). The cumulative incidence of VCF at 12 months with SINS class I, II and III was 0%, 26% and 83%, respectively ($p < 0.001$, Fig. 2). In univariate analysis, pre-existing VCF, soft tissue extension, high BED, and SINS class were significant factors for the VCF development. In multivariate analysis, pre-existing VCF was significantly associated with the VCF development (Table 3). VCF were not identified in SINS class I, only SINS class II and III were included in analysis.

The VCF rates according to the SINS criteria are listed in Table 4.

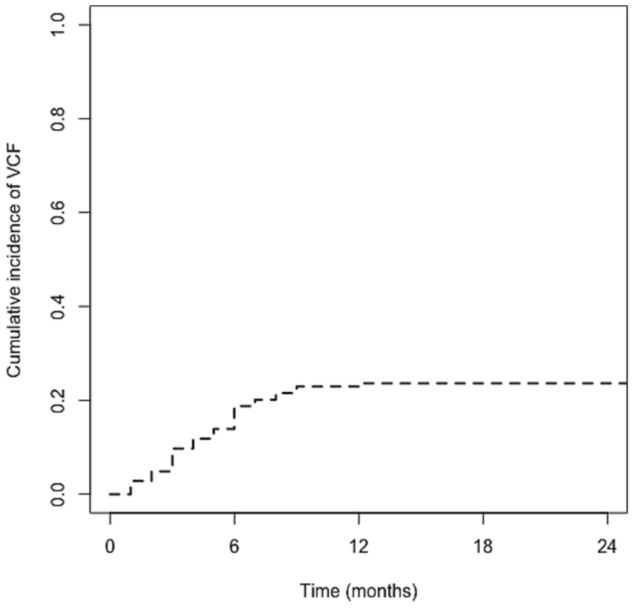

Fig. 1. Cumulative incidence of vertebral compression fracture in the spinal segments (Gray's test).

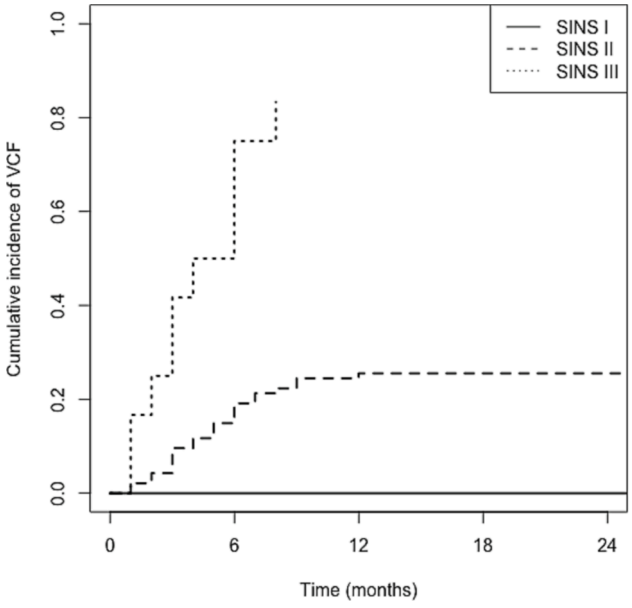

Fig. 2. Cumulative incidence of vertebral compression fracture stratified by the spinal instability neoplastic score class (Gray's test).

Among the six SINS criteria, the intensity of pain ($p = 0.014$), type of bone lesion ($p = 0.003$), spine alignment ($p = 0.001$), vertebral body collapse status ($p < 0.001$), and posterolateral involvement ($p = 0.008$) were risk factors for the VCF development, whereas the location of the lesion ($p = 0.444$) was not.

Nineteen patients (23%) experienced grade 2 pain related to VCF and 12 patients (14%) experienced grade 3 pain related to VCF. Among 12 patients who experienced grade 3 pain, 6 patients were referred for anesthesiology and neurosurgery department for surgical treatment consultation. Twenty-four patients experienced grade 1 fatigue, 19 patients experienced grade 2 nausea/vomiting, respectively.

Table 3
Univariate and multivariate analyses of incidence of VCFs.

Variable	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (<60 vs. ≥ 60)	1.501	0.775–2.905	0.230			
Sex (Male vs. female)	1.166	0.488–2.789	0.730			
BMI (<25 vs. ≥ 25)	1.152	0.508–2.614	0.730			
Pre-existing VCF (No vs. Yes)	10.415	5.397–20.098	<0.001	5.635	2.598–12.223	<0.001
Soft tissue extension (No vs. Yes)	2.488	1.085–5.705	0.031	0.930	0.376–2.299	0.880
$BED_{\alpha/\beta=10}$ (≤76.8 vs. >76.8)	2.233	1.154–4.321	0.017	1.918	0.945–3.893	0.071
Fraction dose (<10 vs. >10)	1.074	0.894–1.288	0.440			
SINS class (II vs. III)	5.337	2.709–10.515	<0.001	1.764	0.820–3.797	0.150

BMI, body mass index; BED, biologically effective dose; SINS, spinal instability neoplastic score.

Table 4
Vertebral compression fracture according to the SINS criteria.

Variables	No. of VCFs (-)	No. of VCFs (+)	VCF rate (%)	*P*-value
SINS criteria				
Location				0.444
Rigid (S2–5)	6	0	0.0	
Semirigid (T3–10)	23	10	30.3	
Mobile spine (C3-6, L2–4)	33	8	19.5	
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	48	16	25.0	
Pain				0.014
Pain free	19	0		
Occasional and nonmechanical	40	13	24.5	
Mechanical	51	21	29.2	
Type of bone lesion				0.003
Blastic	10	1	9.1	
Mixed	20	0	0.0	
Lytic	80	33	29.2	
Spine alignment				0.001
Normal	106	26	19.7	
Kyphosis/scoliosis	1	1	50.0	
Subluxation/translation	3	7	70.0	
Vertebral body collapse				<0.001
None of the below	55	5	8.3	
No collapse but > 50% of body involved by tumor	49	9	15.5	
<50%	6	13	68.4	
≥50%	0	7	100.0	
Posterolateral involvement				0.008
Not involved	44	6	12.0	
Unilateral	51	16	23.9	
Bilateral	15	12	44.4	
SINS class				<0.001
I	38	0	0.0	
II	70	13	25.5	
III	2	10	83.3	

VCFs, vertebral compression fractures; SINS, spinal instability neoplastic score; C, cervical; T, thoracic; L, lumbar, S, sacral.

4. Discussion

In the current study, we examined VCF incidence and identified its predictive factors after SABR for oligometastatic bone lesions from HCC. Patients with pre-existing baseline VCF and SINS class II/III should be carefully followed up after SABR.

VCF occurrence has been reported in 11%–39% of patients after SABR for spinal metastases [16,17]. This study showed a similar rate of new VCF occurrence after SABR for bone metastasis from HCC. He et al. [18] reported that purely osteolytic lesions were present in only 2.4% of patients, and most lesions were a combination of osteolytic and osteoblastic components in patients with bone metastasis from HCC. Several studies have reported that spinal metastasis with lytic features is a significant risk factor for VCF after SABR [19,20]. In our study, 79% of the lesions were osteolytic, which might have contributed to the VCF occurrence.

The effect of VCF after SABR for spinal metastases from various tumors has been well established; however, the relationship between VCF rate and the clinical features of HCC has not been fully explored. We carefully selected potential risk factors, such as sex, age, body mass index, presence of baseline VCF, soft tissue extension, RT dose, and SINS criteria, which enabled predicting the risk of VCF development. A unique characteristic of bone metastasis from HCC was soft tissue extension that lyses the bone framework [21,22]. In our study, 63% of the spinal segments were accompanied by soft tissue extension, which is less common in other bone metastases from less aggressive cancers. Bone metastases with soft tissue extension require high RT doses and have a high failure rate because of the probability of residual tumors [18]. We prescribed a relatively high RT dose, with a median BED of 76.8 Gy, which corresponds to 48 Gy in 8 fractions, to control bone metastasis with soft tissue extension. Although not statistically significant in multivariate analysis, soft tissue extension and high RT dose were significant factors for the VCF development in univariate analysis. In addition, the risk of VCF was significantly increased in patients with a pre-existing baseline VCF and SINS class II/III. Overall, we confirmed that the SINS criteria are a powerful predictor for VCF risk analysis in metastatic vertebral segments. Our study suggests that patients at high risk of VCF need careful optimization of an RT dose.

This study has several limitations owing to its retrospective nature. First, limited clinical information was available; limited patients underwent spinal MRI at diagnosis (76%) and/or follow-up visits (42%), although MRI is more accurate in determining metastatic status or spine fracture than other imaging techniques. In case for patients who did not undergo spinal MRI, target volume definition was performed with simulation CT fused with PET. Moreover, due to the data from three different institutions, there was heterogeneity in RT protocol, systemic treatment, and different follow-up measures, despite our best efforts to reduce bias related to patient and treatment characteristics. Therefore, future prospective studies are warranted. Finally, our study had a short follow-up period to assess delayed toxicity; therefore, a longer follow-up period may be required to detect more VCF cases.

In conclusion, SABR to oligometastatic vertebral bone lesions from HCC resulted in substantial rate of new VCF development and pre-existing VCF progression. Pre-existing VCF and SINS class II/III were significant factors for VCF development, which require special attention in patient care. Patients with SINS class III should be considered surgical treatment rather than upfront SABR.

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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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