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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Improved oncologic outcomes by ablative radiotherapy in patients with bone metastasis from hepatocellular carcinoma

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Abstract

Purpose For bone metastasis from hepatocellular carcinoma (HCC), radiotherapy (RT) has been used a palliative treatment with little impact on survival. Currently, ablative RT is popularly used, and a more than palliative effect is expected. Herein, we investigated the clinical efficacy of ablative RT in patients with bone metastasis from HCC.

Methods In total, 530 patients with 887 lesions treated in 1992–2019 were reviewed. Oligometastasis was defined as the presence of < 5 lesions. Total doses were normalized to obtain biologically effective doses (BEDs). The cut-off threshold of the BED was determined via receiver operating characteristics curve analysis. The Kaplan–Meier method was used to calculate overall survival (OS); propensity score matching (PSM) was performed to balance the heterogeneity in cases while comparing BEDs of ≥ 60 and < 60 Gy.

Results The most common site of metastasis was the spine (59%); 59 patients (11%) presented with oligometastasis, and 76.2% of patients showed objective pain palliation after RT. Median OS was 5.1 months for all patients; patients with oligometastasis showed longer OS than those without (9.8 vs. 4.7 months). A Cox proportional hazards model showed that performance status, Child–Pugh class, extraosseous metastasis, primary HCC status, α-fetoprotein level, and radiation dose (BED) were significant prognostic factors. Post PSM, BED was the only treatment-related prognostic factor that remained significant; the median OS durations were 8.1 and 4.4 months when the BEDs were ≥ 60 and < 60 Gy, respectively.

Conclusion Ablative RT improved OS and pain palliation in patients with bone metastasis from HCC.

Keywords Bone metastasis · Radiotherapy · Overall survival · Oligometastasis · Ablative dose

Introduction

Recent advances in diagnostic and treatment methods have improved the survival outcomes of patients with hepatocellular carcinoma (HCC) (Kudo et al. 2018; Marrero et al. 2018; Uka et al. 2007). Consequently, the number of patients with metastatic HCC has increased, with bone metastasis observed in 5–25% of patients with HCC (Santini et al. 2014).

Radiotherapy (RT) has long been used as a palliative treatment, with little impact on the survival outcomes (Seong et al. 2005). RT can result in significant pain palliation in approximately 60–90% of patients; in fact, up to 33% of patients can achieve a complete pain response (CR) at the irradiated site (Chow et al. 2007). At our institution, researchers observed that RT results in effective palliation in patients with painful bone metastases from HCC during the substantial median survival time (Choi and Seong 2015).

With recent advancement in RT techniques, ablative RT—which delivers high doses in few fractions—is being popularly used, and more than palliative effect is expected (Zeng et al. 2019). According to the results of the SABR-COMET trials on various cancers other than HCC, some patients with < 5 metastatic lesions could achieve long-term survival, with ablative RT resulting in prolonged progression-free survival and overall survival (OS) (Palma et al.

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2020). However, the efficacy of ablative RT for bone metastases from HCC has not been evaluated despite the clinical need.

Therefore, in the current study, we evaluated the clinical efficacy of ablative RT administered using advanced techniques in patients with bone metastasis from HCC.

Methods

Patients

A list of patients with bone metastasis from HCC who were treated with RT between 1992 and 2019 was extracted from the institutional cancer registry. The clinical data of 530 patients who underwent RT for 887 bone metastasis lesions were reviewed. The pretreatment evaluation included medical history taking and physical examination, complete blood cell count, serum chemistry, liver function tests, serum α-fetoprotein (AFP) measurement, serum protein induced by vitamin K absence or antagonist-II (PIVKA-II) measurement, and diagnostic imaging studies. Liver function was evaluated using the Child–Pugh classification and scored according to serum bilirubin and albumin levels, prothrombin time prolongation, presence or absence of ascites, and encephalopathy. Controlled primary tumor was 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 computed tomography and/or magnetic resonance imaging. The procedures followed in the current retrospective study were in accordance with the Declaration of Helsinki in 1975, as revised in 2000, and the study was approved by our Institutional Review Board (IRB #4-2020-0756). All authors had access to the study data and reviewed and approved the final manuscript.

Diagnosis and evaluation of bone metastasis and pain

Bone metastases were diagnosed using imaging studies along with the measurement of serum AFP levels or biopsy and histological examination. Imaging studies for diagnosing bone metastases were as follows: computed tomography (CT, $n = 145$, 27%), magnetic resonance imaging (MRI, $n = 245$, 46%), whole body bone scan ($n = 221$, 42%), and positron emission tomography (PET, $n = 154$, 29%). A total of 209 patients (39%) were diagnosed using multiple imaging studies. Oligometastasis was defined as < 5 metastatic bone lesions. The subjective pain level was assessed using the Brief Pain Inventory. The numeric rating scale ranged from 0 to 10 (0, no pain; and 10, the worst imaginable pain).

Treatment and follow-up

Patients received systemic therapy consisting of either chemotherapeutic agents or a tyrosine kinase inhibitor. The most commonly used chemotherapy regimen included 5-fluorouracil and cisplatin (FP), whereas the most commonly used tyrosine kinase inhibitor was sorafenib.

RT was delivered using megavoltage photons (≥ 6 MV); previously, 2-dimensional (2D) RT was used. For 2D RT, radiation fields usually involved 1 normal vertebra above and below the metastatic lesion. After that, either 3-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) was used. The portion adjacent to the gross tumor volume (GTV) was included in the clinical target volume (CTV). Planning target volume modification (0–1 cm) was allowed if the CTV extended to critical organs. For IMRT, the simultaneously integrated boost technique was used. Most commonly used dose prescription in IMRT was 48 Gy in 8 fx for GTV and 32 Gy in 8 fx for CTV. Helical tomotherapy, an image-guided IMRT system using megavoltage CT that provides precise delivery, was used in IMRT. Volumetric-modulated arc therapy (VMAT) was also used for IMRT. Patients were immobilized using thermoplastic head-shoulder masks for the cervical spine, and 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 every day before each treatment for all patients for image guidance.

Total doses were re-calculated and normalized to obtain biologically effective doses (BEDs). The BED for the prescribed dose was calculated using the standard linear-quadratic model with an α/β of 10 Gy for HCC, a commonly used value. The actual total dose was converted to the BED as follows: $\mathrm{BED} = nd\,[1 + d/(\alpha/\beta)]$, where n is the number of fractions, and d is the dose per fraction. To assess the cut-off threshold of the BED, receiver operating characteristics curve analyses were performed, and the cut-off value was set based on the maximum Youden index.

Patients were interviewed by a physician before the start of RT, 2 weeks after RT, and every 3 months thereafter for 1 year. The pain response to treatment was defined according to the International Bone Metastases Consensus Working Party palliative RT endpoints. A CR was defined as a pain score of 0 at the treated site, with no concomitant increase in the daily intake of oral morphine-equivalent analgesics. A partial response (PR) was defined as a pain reduction of ≥ 2 points below the baseline at the treated site on a 0–10 scale without an increase in analgesic dose or an analgesic dose reduction of $\geq 25\%$ from the baseline without an increase in pain. Pain progression (PP)

was defined as an increase in pain of ≥ 2 points above the baseline at the treated site with stable analgesic use, a stable pain score, or a 1-point increase above the baseline with an increase of ≥ 25% in the daily intake of an oral morphine-equivalent analgesic. Patients who did not show a CR, PR, or PP were considered to have stable pain (SP). In addition to pain response, tumor response was assessed using imaging studies involving CT ($n = 197$, 37%), MRI ($n = 108$, 20%), whole body bone scan ($n = 80$, 15%), and PET ($n = 34$, 6%).

Treatment-related toxicities were monitored at least once a week and more often if clinically indicated. Treatment-related toxicities were graded according to the Common Toxicity Criteria for Adverse Events, version 4.0. Acute toxicities were defined as adverse events during RT and were assessed from patient records; the occurrence of radiation-induced myelopathy was defined as a late toxicity.

Statistical analysis

Statistical analyses were conducted using IBM SPSS, version 25.0 (IBM Corp., Armonk, NY). The OS was calculated from the date of the start of RT to the date of death or the last follow-up. The differences in characteristics and toxicities were compared using chi-square tests, and the Kaplan–Meier method was used to calculate the OS; the differences between the curves were analyzed using the log-rank test. A Cox proportional hazards model was used to assess the association of variables with survival and to calculate hazard ratios (HRs) as well as for multivariable analysis, which only included factors that showed statistical significance on univariable analysis. Statistical significance was defined with a p value < 0.05.

To minimize the difference between groups considering the selection bias and effects of potential confounders, patients were matched according to their propensity scores. Propensity score matching (PSM) analysis was performed using SPSS version 25 (SPSS, Chicago, IL, USA). Patients with the exact same scores were matched, and non-matched patients were eliminated.

Results

Patient characteristics

The patient, tumor, and treatment characteristics are summarized in Table 1. With a predominance of male patients (86%), the median patient age was 59 years (range 20–88 years). The most common etiology of HCC was chronic hepatitis B or C virus infection (82%). Most patients had well-compensated liver function (Child–Pugh class A,

Table 1 Baseline characteristics ($n = 530$)

Variables	*n*	% or range
Patient characteristics		
Age (median, in years)	59	20–88
Sex		
Male	454	86%
Female	76	14%
Performance status		
ECOG PS 0/1	386	73%
ECOG PS 2–4	139	27%
Etiology		
HBV	397	75%
HCV	44	8%
NBNC	89	17%
Child–Pugh class		
A	403	77%
B	108	21%
C	12	2%
Extraosseous metastases		
No	272	51%
Yes	258	49%
Primary HCC		
Controlled	273	52%
Uncontrolled	257	48%
Tumor characteristics		
AFP (median, in ng/mL)	197.3	0.3–37,767
PIVKA-II (median, in mAU/mL)	1382.0	5.0–120,000
Site of metastasis		
Total	887	100%
Spine	520	59%
Pelvis	221	25%
Rib	89	10%
Extremities	74	8%
Others	62	7%
Number of metastasis		
≤ 5 lesions	59	11%
> 5 lesions	471	89%
Details of treatment		
Systemic therapy		
No	262	49%
Chemotherapy	74	14%
Sorafenib	194	37%
Total RT dose (median, in Gy)	48.0	12.0–60.0
Fractional RT dose (median, in Gy)	3.0	1.5–15.0
RT modality		
IMRT	115	22%
3D-CRT/2D RT	415	78%
BED in Gy_{10}		
≥ 60	150	28%
< 60	380	72%

ECOG PS Eastern Cooperative Oncology Group Performance Status, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NBNC* non-HBV/HCV, *HCC* hepatocellular carcinoma, *AFP* alpha-fetoprotein, *PIVKA-II* proteins induced by vitamin K absence or antagonist-II, *RT* radiotherapy, *IMRT* intensity-modulated radiotherapy, *3D-CRT* 3-dimensional conformal radiotherapy, *2D RT* 2-dimensional radiotherapy, *BED* bio-

Table 1 (continued)

logically effective dose

77%). Approximately half of the patients had extraosseous metastases (49%) and controlled primary HCC (52%).

The median AFP and PIVKA-II values were 197.3 ng/mL and 1382.0 mAU/mL, respectively. Among the 887 sites of metastasis, the most common site was the spine ($n=520$, 59%), with the cervical spine, thoracic spine, and lumbar spine being the sites in 93 (10%), 230 (26%), and 197 patients (22%), respectively. The second most common site of metastasis was the pelvis ($n=221$, 25%), followed by the ribs ($n=89$, 10%) and extremities ($n=74$, 8%). Approximately 15% of patients ($n=82$) were treated for multiple sites of bone metastasis. In total, 59 patients (11%) presented with oligometastasis.

Systemic therapy was administered to 268 patients (51%) either with sorafenib (194 patients, 37%) or chemotherapy (74 patients, 14%). In total, 115 patients (22%) were treated with IMRT and 415 (78%) were treated with 3D-CRT or 2D RT. The total dose and fractional dose were 48 Gy (range 12–60 Gy) and 3 Gy (range 1.5–15.0 Gy), respectively. With a cut-off BED value of 60 Gy, 150 patients (28%) were treated with a BED ≥ 60 Gy. Figure 1 shows the distribution of the dose fractionation regimens. The most commonly used fractionation regimen was 30 Gy in 10 fractions ($n=111$, 27%). For ablative RT, the most commonly used fractionation regimen was 48 Gy in 8 fractions ($n=52$, 13%), followed by 60 Gy in 4 fractions ($n=24$, 4.5%) and 48 Gy in 4 fractions ($n=12$, 2.3%). The fractionation regimens used in fewer than 10 patients are not shown in Fig. 1.

The number of patients treated with RT increased over time, from 17 patients between 1992 and 1994 to 168 patients between 2015 and 2019. In addition, the use of IMRT increased over time: 0% between 1992 and 2004, 22% between 2010 and 2014, and 51% between 2015 and 2019 (Online Resource 1).

Survival analysis and prognostic factors

The OS rates at 6 months and 1 year after RT were 42.3% and 22.3%, respectively, and the median OS was 5.1 months (Online Resource 2); patients with oligometastasis had a longer OS than those without (9.8 vs 4.7 months, Fig. 2). On univariate analysis, young age, good performance status, Child–Pugh class A disease, chronic hepatitis B or C virus infection, absence of extraosseous metastasis, controlled primary HCC, AFP levels < 200 ng/mL, treatment with 2D or 3D-CRT, use of sorafenib, and a BED > 60 Gy were significantly associated with better survival. On multivariate analysis, good performance status, Child–Pugh class A, the absence of extraosseous metastasis, controlled primary HCC, AFP levels < 200 ng/mL, and BED > 60 Gy were significant factors for prognosis (Table 2).

As the BED was the only treatment-related prognostic factor, patient characteristics were analyzed according to the BED (≥ 60 or < 60 Gy), as summarized in Table 3. Before PSM, there were significant differences in age, performance status, Child–Pugh class, primary HCC status, AFP levels,

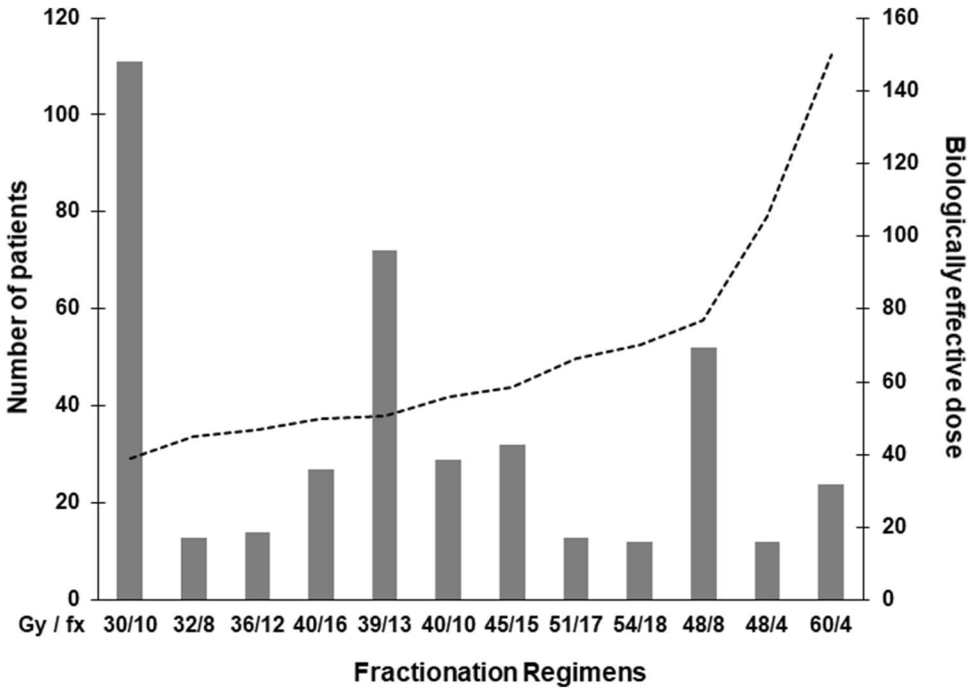

Fig. 1 Distribution of the dose fractionation regimens

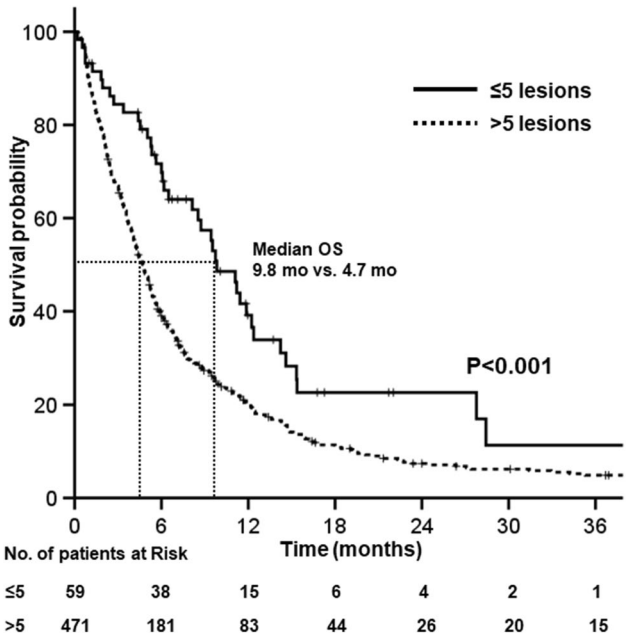

Fig. 2 Overall survival of patients with oligometastasis

and the use of systemic therapy, and a BED > 60 Gy was a significant prognostic factor for OS ($p < 0.001$, Fig. 3a). After PSM, all the characteristics were well balanced between the groups. A BED > 60 Gy remained a significant prognostic factor for OS ($p < 0.001$, Fig. 3b). The median OS durations were 8.1 and 5.3 months when the BEDs were ≥ 60 Gy and < 60 Gy, respectively.

Pain response

Of the 530 patients who were treated with RT, 113 (21.3%), 291 (54.9%), 57 (10.8%), and 69 (13.0%) showed CR, PR, SP, and PP, respectively. The overall pain response (CR + PR) was observed in 404 patients (76.2%). There was no significant correlation between the pain response and RT modality, and no significant correlation was observed between the pain response and RT dose (represented using the BED). Among patients treated with IMRT, overall pain response was observed in 82.4% of patients, while among patients treated with 3D-CRT or 2D RT, pain response was observed in 74.3% of patients ($p = 0.071$). Among patients treated with a BED of > 60 Gy, pain response was observed in 81.4% of patients; among patients treated with a BED of < 60 Gy, pain response was observed in 74.1% of patients ($p = 0.074$).

Toxicity

Overall, a total of 181 patients (34%) experienced grade 3 neutropenia or thrombocytopenia; no other severe (grade 3–4) acute toxicity was observed. One month after the initiation of RT, lymphopenia (grade 3) was observed in 43.2% of

Table 2 Prognostic factors for overall survival

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (continuous, year)	0.989	0.981–0.997	0.007	0.994	0.983–1.006	0.333
Sex (female vs. male)	1.118	0.864–1.448	0.396			
Performance (good vs. poor)	1.785	1.461–2.180	< 0.001	1.693	1.295–2.213	< 0.001
Child–Pugh class (A vs. B/C)	2.417	1.953–2.991	< 0.001	1.636	1.226–2.185	0.001
Etiology (HBV/HCV vs. NBNC)	0.724	0.526–0.995	0.047	0.804	0.573–1.128	0.206
Extraosseous metastases (no vs. yes)	2.237	1.852–2.702	< 0.001	2.231	1.721–2.893	< 0.001
Primary HCC (controlled vs. uncontrolled)	1.984	1.644–2.395	< 0.001	2.548	1.943–3.342	< 0.001
AFP (< 200 vs. ≥ 200)	1.563	1.302–1.876	< 0.001	1.599	1.259–2.032	< 0.001
Number of metastases (≤ 5 vs. > 5)	1.889	1.361–2.622	< 0.001	1.490	0.952–2.331	0.081
Treatment decade (1990s vs. 2000s)	1.095	0.813–1.476	0.549			
Treatment decade (1990s vs. 2010s)	0.758	0.562–1.022	0.069	0.985	0.740–1.311	0.919
Systemic therapy (no vs. chemotherapy)	0.828	0.633–1.083	0.169			
Systemic therapy (no vs. sorafenib)	0.709	0.581–0.866	0.001	0.954	0.718–1.267	0.744
RT modality (IMRT vs. 3D-CRT)	1.424	1.128–1.797	0.003	1.487	0.994–2.223	0.053
BED (≥ 60 vs. < 60)	1.667	1.352–2.056	< 0.001	1.524	1.073–2.165	0.019

HR hazard ratio, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NBNC* non-HBV/HCV, *HCC* hepatocellular carcinoma, *AFP* alpha-fetoprotein, *RT* radiotherapy, *BED* biologically effective dose (an α/β ratio of 10 was used for tumor control), *3D-CRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy

[a]The foreparts of the parentheses were set as the reference group in multivariable analysis

Table 3 Patient characteristics according to the dose group

Variables	Before PSM			After PSM		
	Palliative ($n=380$)	Ablative ($n=150$)	p value	Palliative ($n=150$)	Ablative ($n=150$)	p value
Age (years)			0.027			0.636
< 65	277 (73%)	94 (63%)		89 (59%)	94 (63%)	
≥ 65	103 (27%)	56 (36%)		61 (41%)	56 (37%)	
Sex			0.271			0.493
Male	321 (85%)	133 (89%)		128 (85%)	133 (89%)	
Female	59 (15%)	17 (11%)		22 (15%)	17 (11%)	
Performance status			0.003			0.882
ECOG 0/1	263 (69%)	123 (82%)		121 (81%)	123 (82%)	
ECOG 2–4	117 (31%)	27 (18%)		29 (19%)	27 (18%)	
Child–Pugh class			0.027			0.949
A	281 (74%)	127 (85%)		129 (86%)	127 (85%)	
B	89 (23%)	21 (14%)		19 (13%)	21 (14%)	
C	10 (3%)	2 (1%)		2 (1%)	2 (1%)	
Extraosseous metastases			0.442			0.166
No	191 (50%)	81 (46%)		68 (45%)	81 (54%)	
Yes	189 (50%)	69 (54%)		82 (55%)	69 (46%)	
Primary HCC			0.034			0.412
Controlled	207 (55%)	66 (44%)		58 (39%)	66 (44%)	
Uncontrolled	173 (45%)	84 (56%)		92 (61%)	84 (56%)	
AFP, ng/mL			0.012			0.203
< 200	168 (44%)	85 (57%)		73 (49%)	85 (57%)	
≥ 200	212 (56%)	65 (43%)		77 (51%)	65 (43%)	
Systemic therapy			< 0.001			0.869
No	219 (58%)	43 (29%)		41 (27%)	43 (29%)	
Chemotherapy	55 (14%)	19 (13%)		22 (15%)	19 (13%)	
Sorafenib	106 (28%)	88 (59%)		87 (58%)	88 (59%)	

PSM propensity score matching, *ECOG* Eastern Cooperative Oncology Group, *HCC* hepatocellular carcinoma, *AFP* alpha-fetoprotein

patients. Radiation-induced myelopathy was not observed in any patient during the follow-up period.

Discussion

In the current study, we identified that ablative RT with a BED of > 60 Gy was associated with improved OS after PSM; moreover, we analyzed the factors associated with survival. We found that there was no correlation between the pain response and RT dose or modality.

In the past, poor life expectancy was expected for patients with bone metastasis; therefore, palliative treatment using RT with dose of pain relief was usually performed. However, various prognostic factors affect the survival of patients with bone metastasis (Chang et al. 2014; Sohn et al. 2016). A meta-analysis of 26 patients performed by Goodwin et al. (2016) showed that patients who underwent surgery had a trend for prolonged survival. A graded prognostic assessment (GPA) scoring model that determines the factors affecting survival has been used for various cancers, and a GPA for HCC has been developed by Rim et al. (2017). Good performance status, controlled primary HCC, and extrahepatic metastases (other than bone metastases) were the factors included in the GPA for HCC bone metastasis. Similarly, the results of the current study showed performance status, Child–Pugh class, presence of extraosseous metastases, and status of primary HCC to be prognostic factors. As many studies have assessed these prognostic factors, the paradigm for treatment of bone metastasis has evolved. Aggressive and ablative local therapy, including surgery and ablative RT, should be considered for patients who are expected to show improved survival; this treatment regimen may also be effective for oligometastasis, an emerging concept.

Over the long study period, RT techniques have considerably evolved. IMRT was not used in any patient from 1992 to 2004 but was used in half of the patients from 2015 to 2019. A high dose (a BED of > 60 Gy) was used in only 1% of patients during the 1990s but was used in

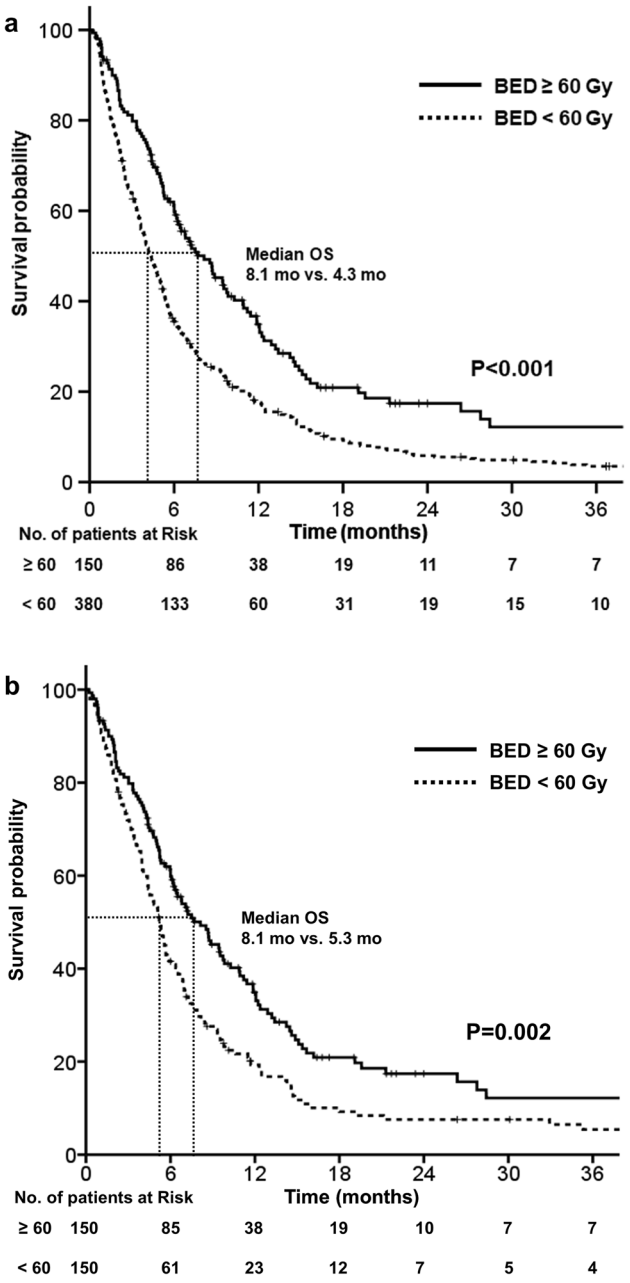

Fig. 3 Overall survival stratified by dose group. **a** Before propensity score matching, and **b** after propensity score matching

85% of patients during the 2010s. Moreover, with general improvements in medical care, the survival of HCC patients has improved over time. In our study, the median OS durations in the 1990s, 2000s, and 2010s were 4.2, 3.9, and 6.3 months, respectively. According to the multivariate analysis, treatment decade was not a significant factor for OS ($p = 0.919$). However, it is generally accepted that with advances in general medical care and treatment techniques, the survival of HCC patients has been improving since the 1990s.

Oligometastasis is defined as a limited metastatic burden that is amendable to aggressive local therapy to achieve long-term survival; the term was first described by Hellman and Weicheselbaum in 1995 (Guckenberger et al. 2020; Weichselbaum and Hellman 2011). According to the long-term results of the SABR-COMET trials, stereotactic ablative RT (SABR) for all metastatic lesions when there were < 5 lesions resulted in better survival than the standard of care, including palliative RT (Palma et al. 2020). Patients with different primary tumors were included: 20% of patients had breast cancer, 18% of patients had lung cancer, and 21% of patients had prostate cancer. The median OS in the SABR group was 50 months, and the 5-year OS rate was 42.3%. Similar results were observed in other studies. Treatment with SABR in patients with oligometastasis from prostate cancer resulted in improved progression-free survival in the ORIOLE trials (Phillips et al. 2020). In patients with oligometastatic lung cancer, SABR was beneficial, indicating that local consolidative therapy prolonged progression-free survival and OS compared to maintenance therapy or observation (Gomez et al. 2019; Iyengar et al. 2018). In the current study, 59 patients (11%) were diagnosed with oligometastasis, and the median OS of patients with oligometastasis from HCC was 9.8 months (Fig. 2); most of the patients ($n = 56$, 95%) were treated with ablative RT with a BED of > 60 Gy.

The dose fractionation of RT for bone metastasis is debatable, with some results indicating that a single fraction is as effective as multiple fractions ("8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party" 1999; Chow et al. 2017). In the current study, there was no significant correlation between the pain response and RT modality or dose, with 76% of the patients showing a good overall pain response (CR + PR). Therefore, a short course of RT with a palliative dose might be sufficient for pain palliation in patients with an expected poor prognosis; moreover, this will improve treatment compliance.

This study has several limitations, including its retrospective nature. As this study was performed over a long period between 1992 and 2018, there might have been many changes in the diagnostic tools, systemic agents, and RT techniques. Moreover, the study population was heterogeneous despite our best efforts to reduce bias related to patient characteristics. Therefore, future prospective studies should be performed to determine the efficacy of ablative RT in patients with bone metastasis from HCC.

In conclusion, ablative RT improved the OS as well as resulted in pain palliation in patients with bone metastasis from HCC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-021-03553-2.

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Author contributions This study was designed by THK and JS. SP, CHR, and CC contributed to the data collection and analysis. The manuscript was written by THK and JS, and commented on by all authors.

Data availability This study is original and is not text-recycling.

Code availability IBM SPSS, version 25.0 (IBM Corp., Armonk, NY).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate This study was approved by our Institutional Review Board (IRB #4-2020-0756).

Consent for publication All authors agreed to publication.

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