

EXTERNAL BEAM RADIOTHERAPY FOR PAINFUL BONE METASTASES FROM HEPATOCELLULAR CARCINOMA: MULTIPLE FRACTIONS COMPARED WITH AN 8-GY SINGLE FRACTION

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ABSTRACT

External beam radiotherapy (EBRT) for hepatocellular carcinoma (HCC) bone metastases has not been popular in palliative therapy, and optimum dose schedules have not been decided because of limited published reports. We here evaluated the palliative effect of EBRT for HCC bone metastases and compared the dose–response relationship between multiple fractions (MFs) and an 8-Gy single fraction (SF). Twenty-eight patients (42 sites) with painful bone metastases who received EBRT and were analyzed retrospectively. Eight patients (12 sites) received SF. Of the remaining 20 patients (30 sites), 10 received MFs at moderate doses (20–30 Gy; 17 sites) and 10 received MFs at high doses (36–52 Gy; 13 sites). Overall response was achieved at 83% (35) of all sites; 75% (9) and 87% (26) for the SF and MF patients (88%, moderate dose; 85%, high dose), respectively. No significant differences in overall response were observed between each fraction schedule. Response duration was significantly longer for the high-dose MF patients than for the SF patients and moderate-dose MF patients ($P < 0.05$). SF was as effective as MF radiotherapy in terms of pain relief, but high-dose MF delivery relieved pain for a significantly longer duration.

Key Words: Hepatocellular carcinoma, Bone metastases, Palliative therapy, Radiotherapy, Dose–response relationship

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and has the highest incidence in Asia.¹⁾ The most frequent site of extrahepatic metastases is the lung, followed by the lymph nodes, bone, and adrenal glands.²⁾ In the past, the incidence of bone metastases has been comparatively low. However, it has increased recently³⁾ and been reported to be 25.4–38.5%.^{2,4,5)} The typical radiographic features of bone metastases from HCC are osteolytic, destructive, and expansible lesions with large, bulky, soft-tissue masses.⁶⁾ These masses are unique to bone metastases from HCC, and almost 40% patients have an accompanying hypervascular soft-tissue mass.⁷⁾ Patients with bony lesions often suffer from pain, which has a severe adverse effect on the quality of life. External beam radiotherapy (EBRT) is effective at relieving bone pain from bone metastasis. A wide variety of dose schedules has been used, varying from a

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single fraction (SF) of 8 Gy to multiple fractions (MFs). In two previous studies, no significant differences between SF and MFs were observed for overall and complete response (OR and CR, respectively) rates, and no dose–response relationship could be detected.^{8,9)} However, in all of the studies described above, the main primary tumors were breast, lung, and prostate cancer. In bone metastases from HCC, radiotherapy is also effective and pain relief has been achieved in 73–99.5% patients.^{7,10–12)} Various dose/fraction regimens has been reported to be effective. For pain relief, some clinical reports have showed that a dose–response relationship could be found^{10,11)} but others have not.^{7,12)} In all of these studies on bone metastasis from HCC, radiation schedules used MFs, there have been no previous reports on the schedules using SF. We here retrospectively analyzed the palliative effect of radiotherapy including SF and MF dosing schedules for painful bone metastases from HCC.

MATERIALS AND METHODS

Patients

From January 2000 to December 2011, 28 patients (42 sites) who had painful bone metastases from HCC received EBRT. Diagnoses of bone metastases were established on the basis of clinical courses, presence of symptoms, and radiological imaging studies. We excluded patients with clinical or radiographic evidence of spinal cord or nerve root compression, neuropathic pain due to a soft-tissue mass, previous radiotherapy at the same site and the use of bisphosphonates, systemic radionuclides, or targeted molecular therapy. No patient was treated with systemic chemotherapy for 6 weeks before and after EBRT. The Institutional Medical Ethics Committee approved the treatment and all patients gave their informed consent to the study.

Radiotherapy

EBRT was performed using 4, 6 or 10MV x-rays from a linear accelerator. A CT simulator and 3D radiotherapy planning system (FOCUS Release 2.5–3.21; CMS/ELEKTA, Stockholm, Sweden or ECLIPSE, Version 6.5; Varian Medical Systems, CA, USA) were used to perform planning for all patients. Radiation volume involved gross tumor volume plus 1- to 1.5-cm margins. In case of vertebral bone metastasis, radiation fields included one additional vertebra above and below the metastatic segments. Decisions regarding the dose and number of fractions were left to the discretion of the treating radiation oncologists and patients' preference. The total radiation dose ranged from 8 Gy to 52 Gy. Various fraction sizes were used. All patients were treated within normal tissue tolerance doses. Fourteen patients who had 2 painful sites were treated simultaneously using the same fraction sizes and total doses. No patient had more than 2 sites treated.

Eight patients (12 sites) received 8 Gy in SF. Twenty patients (30 sites) received MFs according to the following schedules: 20 Gy in 5 fractions or 30 Gy in 10 fractions in 10 patients (17 sites), and 36 Gy in 13 fractions or 40–52 Gy of 2 Gy/fraction in 10 patients (13 sites). In this study, we classified the patients who received MFs into two groups: the moderate-dose MF (20–30 Gy) group and the high-dose MF (36–52 Gy) group.

Evaluation of pain response

Assessment of pain was on a scale from 0 to 10, with boundaries of 0 representing no pain and 10 representing maximal pain.^{13,14)} Analgesics for pain relief were given according to WHO recommendations that identify three-step analgesic ladders in cancer pain: non-narcotic, weak narcotic, and narcotic. Assessments were performed at follow-up clinical visits. The evaluation method of Arnalot *et al.*,¹⁵⁾ with some modifications, was used to calculate the response. CR was

defined as the absence of pain without the need for increasing analgesics, and partial response (PR) was defined as an improvement of ≥ 2 on the pain scale without the need for increasing analgesia or a change in analgesics from a higher level to a lower level. Responses for each irradiated site were evaluated within 1 month after EBRT. Patients with the same or worse condition within a month were considered to have no response. Pain progression was defined as an increase in pain with return to the initial pain score or higher without analgesic increase or as an increase in analgesics from a lower level to a higher level. Response duration was calculated from the day of the first evaluation to relapse, or in absence of relapse, to the day of the last evaluation or death.

Statistical analysis

The following statistical tests were applied: Student's t-test to compare continuous quantitative variables, Mann–Whitney *U* to compare ordinal quantitative variables, and chi-square test with Fisher's exact test to compare qualitative variables. The Kaplan–Meier method was used to calculate survival and response duration, and the log rank test was used to make group comparisons. A *P* value of <0.05 was considered significant.

RESULTS

Patient characteristics

Table 1 summarizes the pretreatment characteristics of the 28 patients according to whether they received EBRT in SF or MFs. Performance status in the MF was significantly better than that in the SF group ($P = 0.03$). No other significant differences were observed between the SF and MF groups. Table 2 summarizes the pretreatment characteristics of the 20 patients according to the moderate- and high-dose MF status. The moderate-dose MF group had more multiple bone metastases ($P = 0.02$). No other significant differences were observed between the two groups.

Pain response

Of the 42 sites of bone metastases, CR was achieved at 7 (17%), PR at 28 (67%), and OR at 35 sites (83%). Of the sites of bone metastases in the SF group, CR was achieved at the 17% (2 sites), PR at 58% (7 sites) and OR 75% sites (9 sites). Of the sites of bone metastases in the MF group, CR was achieved at 17% (5 sites), PR at 70% (21 sites), and OR at 87% sites (26 sites). No significant differences were observed between the SF and MF groups (Table 3).

Of the sites of bone metastases in the moderate-dose MF group, CR was achieved at 12% (2 sites), PR at 76% (13 sites), and OR at 88% sites (15 sites). Of the sites in the high-dose MF group, CR was achieved at 23% (3 sites), PR at 62% (8 sites), and OR at 85% (11 sites). No significant differences were observed between the moderate- and high-dose MF groups (Table 3).

Of the sites in which OR was achieved, the median response duration was 1.8 months for the SF group and 3.8 months for the MF group. The response duration was significantly longer for the MF group than for the SF group ($P = 0.004$) (Fig. 1a). In the MF group, the median response duration was 3.0 months for the moderate-dose MF group and 5.0 months for the high-dose MF group. The Response duration was significantly longer for the high-dose MF group than for the SF and moderate-dose MF groups ($p = 0.019$). No significant differences were observed between the SF and moderate-dose MF groups (Fig. 1a).

Table 1 Pretreatment characteristics of patients according to the SF and MF status

	Total (n = 28) 42 sites	SF (n = 8) 12 sites	MF (n = 20) 30 sites	P value
Dose		8 Gy	20–30 Gy (n = 10) 17 sites 36–52 Gy (n = 10) 13 sites	
Age				
Mean ± SD (range)	66 ± 8.1 years (48–79)	68 ± 8.8 years (54–79)	65 ± 7.9 years (48–78)	0.47
Gender				
Female	5	1	4	0.64
Male	23	7	16	
Performance status (ECOG)				
0/1/2/3/4	0/13/12/3/0	0/1/5/2/0	0/12/7/1/0	0.03
Intrahepatic tumor				
Uncontrolled	19	6	13	0.67
Well controlled	9	2	7	
No. of bone metastases				
Solitary	12	2	10	0.22
Multiple	16	6	10	
Bone site				
Spine	20	6	14	0.73
Pelvis	13	3	10	
Rib	5	1	4	
Long bones	4	2	2	

SF: single fraction; MF: multiple fraction; ECOG: Eastern Cooperative Oncology Group.

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Table 2 Pretreatment characteristics of patients according to the moderate- and high-dose MF status

	Moderate-dose MF (n = 10) 17 sites	High-dose MF (n = 10) 13 sites	<i>P</i> value
Age			
Mean \pm SD (range)	66 \pm 8.5 years (48–75)	65 \pm 7.8years (55–78)	0.71
Gender			
Female	2	2	n.s.
Male	8	8	
Performance status (ECOG)			
0/1/2/3/4	0/5/4/1/0	0/7/3/0/0	0.38
Intrahepatic tumor			
Uncontrolled	7	6	0.64
Well controlled	3	4	
No. of bone metastases			
Solitary	3	7	0.02
Multiple	7	3	
Bone site			
Spine	9	5	0.29
Pelvis	5	5	
Rib	1	3	
Long bones	2	0	

SF: single fraction; MF: multiple fraction; ECOG: Eastern Cooperative Oncology Group; ns: no significant difference.

Table 3 Response to radiotherapy according to the SF and MF status

	Total (n = 42) n (%)	SF (n = 12) n (%)	MF (n = 30) n (%)	P value
CR	7 (17)	2 (17)	5 (17)	0.99
PR	28 (67)	7 (58)	21 (70)	0.47
Overall (CR+PR)	35 (83)	9 (75)	26 (87)	0.34

	Moderate-dose MF (n = 17) n (%)	High-dose MF (n = 13) n (%)	P value
CR	2 (12)	3 (23)	0.68
PR	13 (76)	8 (62)	0.78
Overall (CR+PR)	15 (88)	11 (85)	0.77

SF: single fraction; MF: multiple fraction; CR: complete response; PR: partial response.

Toxicity and adverse events

Treatment was well tolerated by patients: there were no grade 3 and 4 toxicity (Common Terminology Criteria for Adverse Events (CTCAE) version 4.0). The most common acute toxicity (grade 2) was nausea. It was observed in 17.9% (5 patients) of all patients (2 patients in the SF group and 3 patients in the MF group). Diarrhea (grade 2) was reported in one patient in the moderate-dose MF group. Dermatitis or radiation pneumonitis (grade 2) was seen in each one high-dose MF patient. There were no major late complications such as radiation-induced myelopathy and respiratory dysfunction induced by radiation fibrosis.

Survival

Survival results from the completion of EBRT for bone metastasis are shown in Figure 1b. The median survival time was 7.0 months. The overall survival rates at 1 and 2 years were 13.8% and 6.9%, respectively.

DISCUSSION

Radiotherapy is generally effective for painful bone metastases, and the role of palliative EBRT is well established.⁹⁾ However, in previous reports, the main primary sites have been the lung, breast, and prostate.^{9, 15–17)} There have been a few reports concerning the pain relief provided by EBRT of bone metastasis from HCC. Some reports have stated that 72.7–99.5% patients obtained overall pain improvement, and complete pain relief was noted in 32–50% patients.^{7, 10–12)} Our results are similar to those of these earlier reports, and the OR rate was 83%. Although the complete pain relief rate was 17%, a rate of 23% was observed in the high-dose MF group (36–52 Gy).

A wide variety of dose/fractions schedules has been used for palliating bone pain. Recent studies and a meta-analysis reported that although retreatment is needed for SF radiotherapy, SF was as effective as

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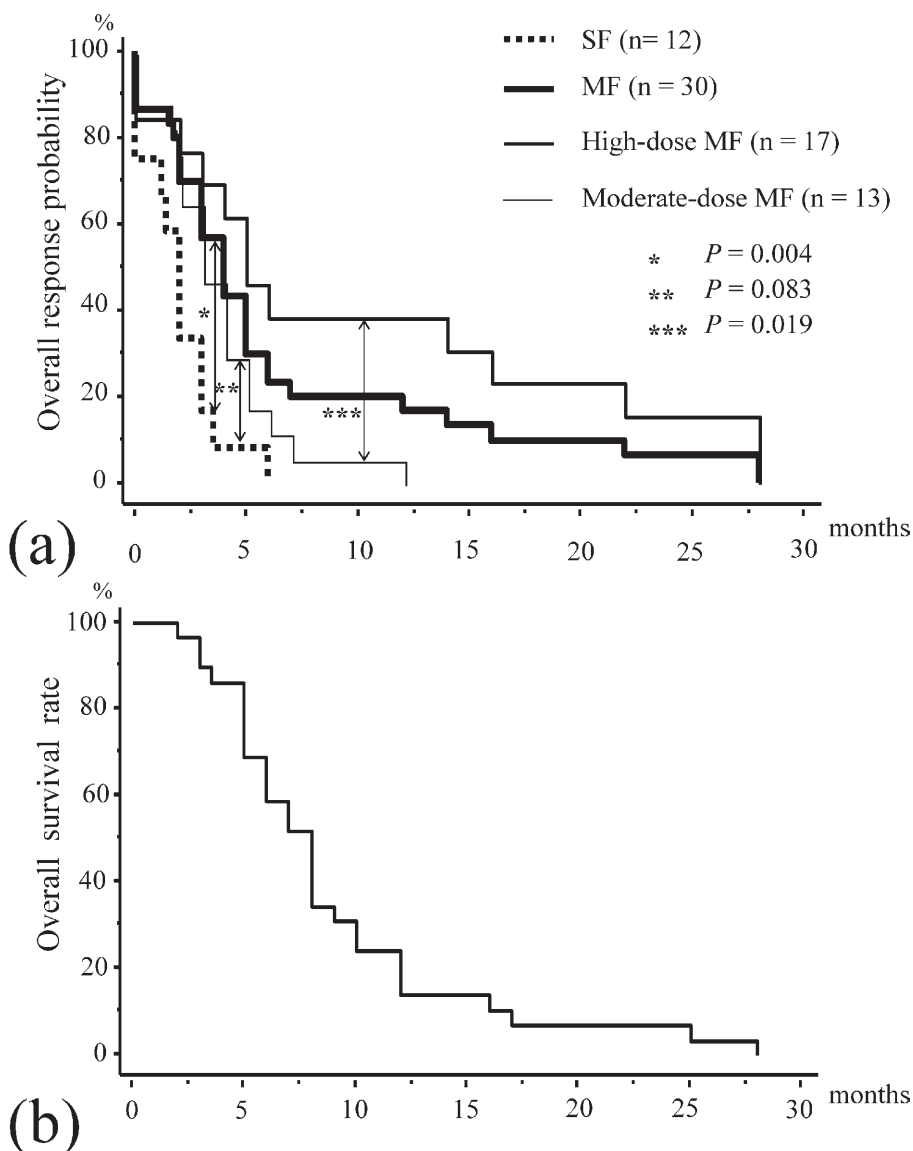


Fig. 1 (a) The actuarial curve of the overall response probability between the SF (single fraction), MF (multiple fraction), moderate-dose MF, and high-dose MF patients.
 (b) Overall survival curve for 28 patients after external beam radiotherapy for bone metastasis.

MF.^{9,15,16,18}) In all past published reports on HCC, the radiation schedules used MF dosing, and there have been no previous studies on the schedules using SF dosing. In our study, OR was 75% for the SF patients and 87% for the MF patients. The CR and PR rates were 17% and 58% for the SF patients and 17% and 70% for the MF patients, respectively. No significant differences were observed between the two schedules. Furthermore, no differences were observed between the moderate- and high-dose MF patients. No dose-response relationship could be found. He *et al.*⁷) and Matsuura *et al.*¹²) reported that no dose relationship was apparent for pain relief.

In contrast, Seong *et al.*¹¹⁾ reported that the symptomatic response rate was 70% at biological effective dose (BED) of 43 Gy and 96% at BED of >43 Gy, which was a significant difference. However, 25% of their analyzed patients had neurological symptoms in addition to bone pain, and radiotherapy achieved pain relief as well as tumor shrinkage, which relived pressure on surrounding structures. The patients with neuropathic pain due to masses were excluded from our study. Therefore, it is difficult to compare these previous results with ours.

Response duration was significantly longer in the MF patients than in the SF patients. However, no differences were observed between the SF and moderate-dose MF patients (20–30 Gy). This result was similar to the results of other series for other primary cancers.^{15,19,20)} In the study of Arnalot *et al.*,¹⁵⁾ the mean response duration was 23 weeks for the MF (30 Gy /10 fr) schedule and 23 weeks for the SF (8 Gy) schedule, but the difference was not significant. No significant differences were observed in the response in the study by van der Linden *et al.* (8 Gy vs. 24 Gy/4 fr)¹⁹⁾ and by Gaze *et al.* (10 Gy vs. 22.5 Gy/5 fr).²⁰⁾ Furthermore, our results showed the response duration was significantly longer in the high-dose MF patients (36–52 Gy) than in the SF and moderate-dose MF patients. In the study on HCC by Kaizu *et al.*,¹⁰⁾ the patients treated with a time, dose and fractionation value of ≥ 77 (almost equal to 48 Gy/24 fr, 39 Gy/13 fr) responded better, and the therapeutic effects persisted until the patient's death.

The median survival time and overall survival rates at 1 year from the start of EBRT or the occurrence of bone metastasis have been reported to be 5–7.4 months and 15–32.4%, respectively.^{7,10–12)} These results were similar to our results; the prognosis of patients with bone metastasis from HCC is generally poor. Some prognostic factors have been reported, such as solitary bone metastasis, metastasis to other organs, tumor stage within the liver, extent of vascular invasion, Karnofsky performance status, tumor markers, controlled intrahepatic tumor, and hepatic reserve (Child–Pugh classification).^{2,5,7, 10–12)} In the present study, we did not examine prognostic factors for survival; however, 2 patients with better performance status (PS 1) and controlled intrahepatic tumors survived >2 years. These 2 patients received high-dose MF EBRT for painful bone metastases and achieved CR with pain relief that persisted until the patients' death.

In conclusion, this study showed that EBRT was effective at palliating painful bone metastases from HCC and that 8Gy in SF was as effective as MFs for pain relief. High-dose MF schedules may provide longer pain relief. However, this study had a small number of patients. Therefore, prospective studies with a larger number of patients are needed to address the issue of optimum radiotherapy in terms of dose and fractions.

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CONFLICT OF INTEREST

The authors declare that no actual or potential conflicts of interest exist regarding this article.

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