Local control after palliative external beam radiotherapy for bone metastases in patients with favorable prognosis

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Abstract. Advancement in systemic therapy has increased the importance of local control (LC) of bone metastatic sites treated with radiotherapy in intermediate-term survivors (surviving ≥1 year). To establish individualized radiotherapy for bone metastases, factors affecting LC of bone metastases treated with traditional fractionated moderate dose palliative radiotherapy (FMRT) in intermediate-term survivors were evaluated. Between January 2010 and December 2019, 317 lesions in 240 patients treated with FMRT for bone metastases surviving for at least 1 year and followed-up with CT for at least 6 months were reviewed retrospectively. The median survival and radiographic follow-up times were 24 months (range, 12-123 months) and 20 months (range, 1-119 months), respectively. The median FMRT dose [biologically effective dose (BED)10] was 39.0 Gy (range, 28.0-71.7 Gy). Multivariate analysis revealed that age (≥70 years), non-vertebral bone metastasis, bone metastasis from moderate and unfavorable primary tumor sites (esophageal, colorectal, hepatobiliary/pancreatic, kidney/ureter and sarcoma/melanoma cancers), and no administration of post-FMRT bone-modifying agents (BMAs) were unfavorable factors for LC of bone metastasis. The 2-year LC rates for FMRT doses (BED10) ≤39.0 Gy and >39.0 Gy were 90 and 87%, respectively. The 2-year LC rates of patients administered and not administered post-FMRT antineoplastic agents (ATs) were 91 and 78%, respectively. The sites of bone metastasis and primary tumors, and post-FMRT BMAs were factors associated with LC of bone metastasis in long-term survivors. However, a FMRT dose (BED10) ≥39.0 Gy and post-FMRT ATs were not significant factors.

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Abbreviations: FMRT, fractionated moderate-dose palliative radiotherapy; SBRT, stereotactic body radiotherapy; LC, local control; BED, biological effective dose; OS, overall survival; HRs, hazard ratios; CIs, confidence intervals; BMAs, bone-modifying agents; ATs, antineoplastic agents

Key words: bone metastasis, local control, fractionated moderate-dose palliative radiotherapy , individualized radiotherapy

Introduction

In patients with advanced cancer, distant metastasis commonly occurs in bone. A recent study estimated the incidence rate of bone metastasis within 10 years of an advanced cancer diagnosis to be 8.4% (1). Radiotherapy is a well-established treatment modality to relieve pain from bone metastasis. Many guidelines for the management of bone metastasis recommend 8 Gy of single-fraction radiotherapy as palliative treatment as this regimen provides pain relief comparable to fractionated moderate-dose palliative radiotherapy (FMRT) (2,3). However, the need for multiple rounds of treatment was higher for patients receiving single-fraction radiotherapy than for those receiving FMRT (4). Therefore, the FMRT regimen of 10x3 Gy (biologically effective dose (BED) calculated using an α/β of 10 Gy (BED10), 39.0 Gy) remains the most widely used for bone metastasis (5). Furthermore, some facilities use stereotactic body radiotherapy (SBRT) for the local control (LC) of bone metastasis in patients expected to have long-term survival (6,7).

Recently, significant progress in systemic and supportive therapies has improved the prognosis of patients with various advanced cancers (8,9). Patients with bone metastases are also expected to have prolonged prognoses. Therefore, although many guidelines have recommended 8 Gy single-fraction radiotherapy as palliative treatment for bone metastases for patients with expected short-term survival, FMRT may be an appropriate treatment for bone metastases for some patients expected to have comparatively good prognosis. Thus, in this study, to examine the usefulness of FMRT for bone metastases in intermediate-term survivors, LC of bone metastases treated with FMRT in patients surviving for ≥1 year (intermediate-term survivors) was investigated.

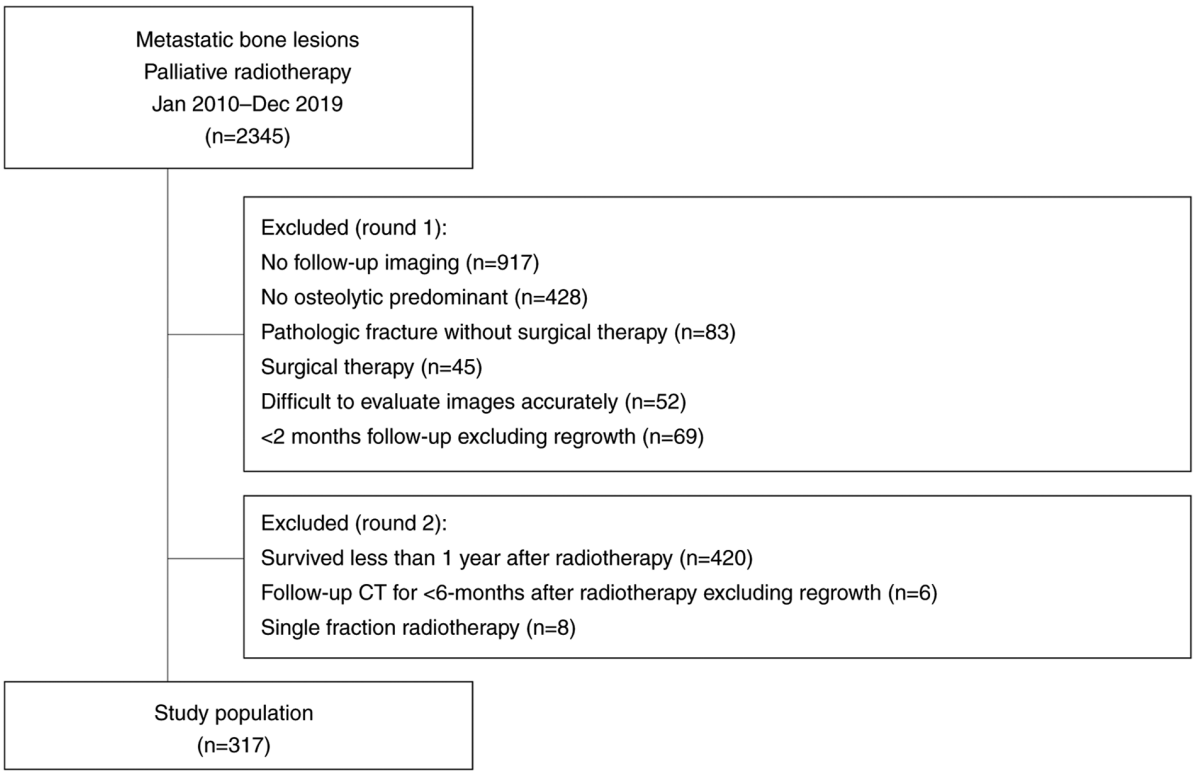


Figure 1. Study flow diagram.

Materials and methods

Study protocol and lesions. Majority of the eligibility criteria used in this study have been reported previously (10). Briefly, from January 2010 to December 2019, a total of 2,345 metastatic bone lesions in 1,750 patients were treated with palliative radiotherapy using three-dimensional conformal radiotherapy in three institutions: a cancer center (n=1514), a university hospital (n=594), and a community hospital (n=237). The exclusion criteria were as follows: absence of follow-up imaging data (n=917), predominantly not osteolytic cancer (n=428), pathologic fracture without surgical therapy (n=83), surgical therapy (n=45), lack of accurate evaluation of images (n=52), and follow-up time of <2 months excluding regrowth (n=69). Thus, 751 predominantly osteolytic metastatic bone lesions in 536 patients were followed-up using computed tomography (CT).

In addition, patients who survived for <1 year after radiotherapy (n=420), had follow-up CT for <6 months after radiotherapy excluding regrowth (n=6), and had single fraction radiotherapy of 8 Gy (n=8) were excluded. Finally, we retrospectively evaluated LC of 317 lesions in 240 patients with bone metastasis treated with FMRT (Fig. 1). This retrospective study was approved by the appropriate institutional review boards of Ehime University Hospital (1912010), Shikoku Cancer Center (RIN2019-79), and Saiseikai Imabari Hospital (I2-1-2), and we applied the opt-out method to obtain consent for this study.

Effectiveness assessment. For the purpose of the present study, local failure was defined as enlargement of lytic change or extraosseous mass at the FMRT sites of bone metastases based on the size of osteolytic change before FMRT as a reference. Two observers (a radiologist and a radiation oncologist) were blinded to the follow-up information and outcomes during the evaluation of the images.

Radiotherapy. The doses of FMRT were determined at the discretion of each physician and institution. The most common dose administered was 30 Gy in 10 fractions. To compare the various fractionated schedules, BED was calculated. The BED10 (BED calculated using an α/β of 10 Gy) was calculated using the equation: $n \times d\ (1 + d/(\alpha/\beta))$, where d is the fraction dose, n is the number of fractions, and α/β is 10 Gy.

Statistical analysis. The time of survival and LC of the FMRT sites was calculated from the beginning of FMRT. The Kaplan-Meier method was used to generate the LC curves. Cox proportional hazards models were used to determine hazard ratios (HRs), including 95% confidence intervals (CIs), and P-values. Univariate and multivariate analyses were used to assess the predictive factors associated with LC rates of FMRT sites. Statistical significance was defined as a two-sided P-value <0.05. Statistical analyses were performed using JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics. Data from 240 patients (male/female=113/127; median age [range]: 66 (34-90) years) with 317 lesions were included in the analysis. The median follow-up and radiographic follow-up times were 24 (range, 12-123) and 20 (range, 1-119) months, respectively. The characteristics of the lesions are presented in Table I. The

Table I. Characteristics of lesions.

Characteristic	No. of lesions (%)
Age, years	
<70	213 (67.2)
≥70	104 (32.8)
Sex	
Male	147 (46.4)
Female	170 (53.6)
Primary tumor sites	
Lung	93 (29.3)
Breast	103 (32.5)
Head and neck	27 (8.5)
Esophagus	3 (0.1)
Hepatobiliary/pancreatic	19 (6.0)
Kidney/ureter	30 (9.5)
Colorectal	10 (3.2)
Gynecological	9 (2.8)
Sarcoma/melanoma/mesothelioma	8 (2.5)
Others	15 (4.7)
FMRT sites	
Vertebral	201 (63.4)
Pelvis	72 (22.7)
Rib	24 (7.6)
Others	20 (6.3)
Bone cortex destruction	
Yes	225 (71.0)
No	92 (29.0)
FMRT dose (BED10)	
<39.0	18 (5.7)
39	176 (55.5)
>39.0	123 (38.8)
Post-FMRT BMAs	
Yes	223 (70.3)
No	94 (29.7)
Pre-FMRT ATs	
Yes	180 (56.8)
No	137 (43.2)
Post-FMRT ATs	
Yes	252 (79.5)
No	65 (20.5)

FMRT, fractionated moderate-dose palliative radiotherapy; BMAs, bone modifying agents; ATs, antineoplastic agents; BED, biologically effective dose.

median FMRT dose was BED10=39.0 Gy (30 Gy in 10 fractions). The other fraction schedules, in sequential order, were as follows: 28.0 Gy (5x4 Gy), 31.2 Gy (10x2.5 Gy), 46.9-50.0 Gy (15-16x2.5 Gy), 46.8-58.5 Gy (12-15x3 Gy), 60.0 Gy (25x2 Gy), 39.7 Gy (5x4 Gy + 3x3 Gy), and 71.7 Gy (3x3 Gy + 25x2 Gy).

The 2- and 3-year LC rates of the FMRT sites were 88 and 84%, respectively (Fig. 2A). Local recurrence was observed in 12.9% (41 of 317 lesions) of the lesions, and the median time to recurrence was 10 (range, 1-106) months.

LC according to primary tumor sites. The primary tumor sites were classified into three groups based on reported radiosensitivity and the results of the 1- and 3-year LC rates (unfavorable group, 1-year LC of <50%; moderately unfavorable group, 3-year LC of <50%; favorable group, 3-year LC of ≥50%) in our previous study (10,11). Esophageal, colorectal, and hepatobiliary/pancreatic cancers were classified in the unfavorable group (n=32), kidney/ureter cancer and non-epithelial cancers were classified in the moderately unfavorable group (n=38), and the remaining cancers (i.e., lung cancer, breast cancer, head and neck cancer, gastric cancer, genitourinary cancer, and skin cancers other than melanoma) were classified in the favorable group (n=247).

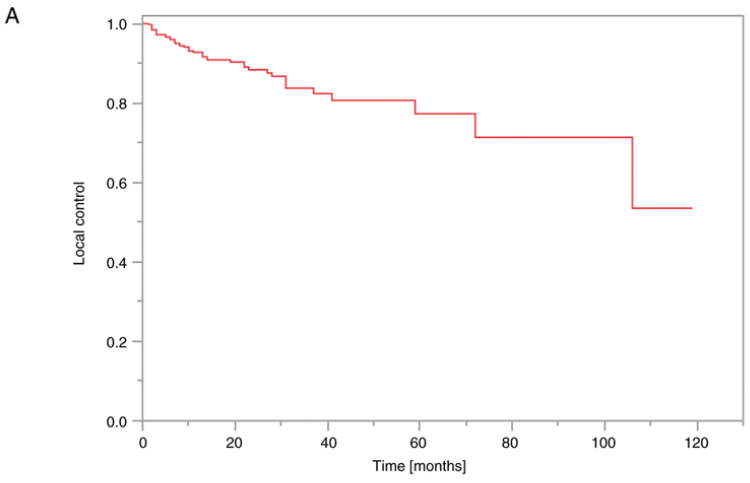
The number of recurrent bone metastatic sites was 18/247 (7.3%) in the favorable group, 10/38 (26.3%) in the moderately unfavorable group, and 13/32 (40.5%) in the unfavorable group. The 2- and 3-year LC rates were 60 and 45% for the unfavorable group, 84 and 63% for the moderately unfavorable group, and 93 and 92% for the favorable group, respectively (Fig. 2B). In univariate analysis, LC rates were significantly lower in the unfavorable group than in the moderately unfavorable group (HR 2.47, 95% CI 1.06-5.76, P=0.036) and significantly higher in the favorable group than in the moderately unfavorable group (HR 0.11, 95% CI 0.05-0.23, P<0.001, Table II).

LC according to FMRT dose (BED10). The 2- and 3-year LC rates were 90 and 83% for bone metastasis with a FMRT dose (BED10) of ≤39.0 Gy and 87 and 85% for a dose >39.0 Gy, respectively (Fig. 2C). In univariate analysis, LC rates were not significantly lower in the FMRT dose (BED10) of ≤39.0 Gy than in a dose >39.0 Gy (HR 1.19, 95% CI 0.64-2.22, P=0.580, Table II).

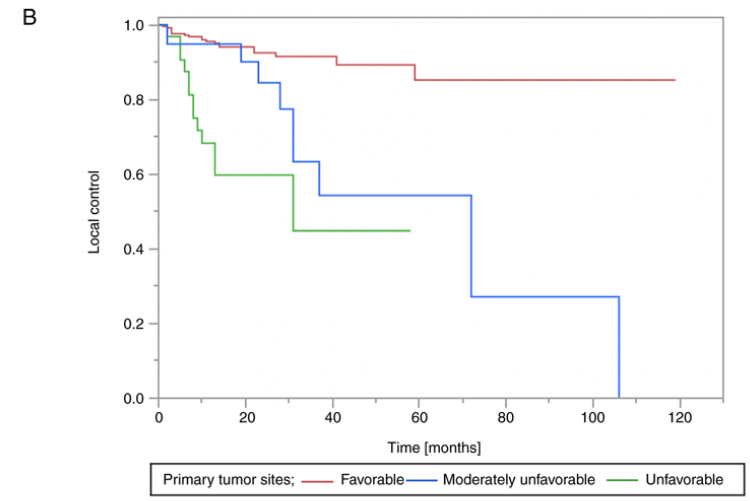
In the favorable group, the 2-year LC rates of patients treated with a FMRT dose (BED10) ≤39.0 Gy (n=159) and >39.0 Gy (n=88) were 95 and 91%, respectively (P=0.507, log-rank). In the unfavorable and moderately unfavorable groups, the 2-year LC rates of patients treated with a FMRT dose (BED10) ≤39.0 Gy (n=35) and >39.0 Gy (n=35) were 67 and 73%, respectively (P=0.990, log-rank).

LC according to FMRT sites. The 2-year and 3-year LC rates were 92 and 89% for vertebral bones, and 82 and 75% for non-vertebral bones (pelvic bone, 87 and 77%; other bone, 75 and 75%), respectively (Fig. 2D). In univariate analysis, LC rates were significantly lower in non-vertebral bones than in vertebral bones (HR 3.14, 95% CI 1.66-5.94, P<0.001, Table II).

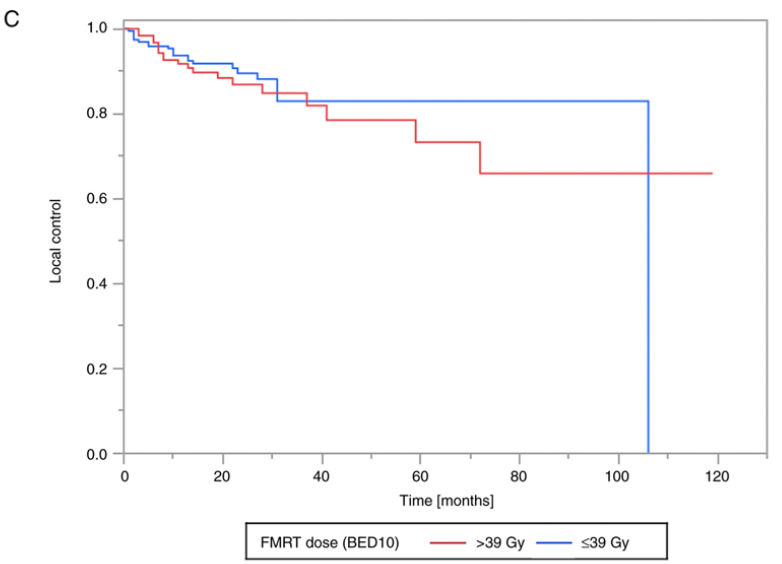
LC according to other factors. Older age (≥70 years) and non-administration of post-FMRT bone-modifying agents (BMAs) and/or antineoplastic agents (ATs) were statistically significant unfavorable factors for LC of bone metastasis in the univariate analysis (Table II). Furthermore, bone cortex destruction and sex were significantly associated with LC (Table II). In addition, LC rates were not significantly low in non-administration of pre-FMRT ATs than in administration of pre-FMRT ATs (Table II).



All bone metastases	317	160	51	24	10	5	–



Favorable	247	134	44	22	9	4	–
Moderately unfavorable	38	18	7	3	2	1	–
Unfavorable	32	9	3	–	–	–	–



>39 Gy	123	67	25	15	9	4	–
≤39 Gy	194	93	26	9	3	2	–

Figure 2. Continued.

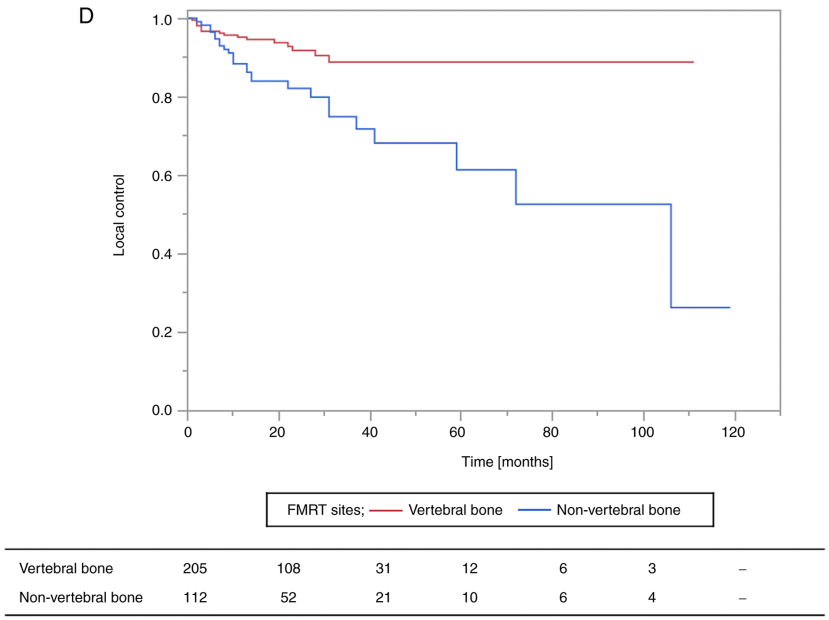


Figure 2. Local control of bone metastases. (A) Local control of all bone metastatic lesions. (B) Primary tumor sites (favorable group vs. moderate group vs. unfavorable group; favorable group, head and neck, lung/mediastinal, breast, gastric, gynecologic, prostate, bladder and skin cancer; moderate group, kidney/ureter and non-epithelial cancer; unfavorable group, esophageal, colorectal and hepatobiliary/pancreatic cancer). (C) FMRT dose (BED10) (≤39.0 vs. >39.0). (D) FMRT sites (vertebral bone vs. non-vertebral bone). BED, biological effective dose; FMRT, fractionated moderate-dose palliative radiotherapy.

Multivariate Cox regression analysis. On multivariate analysis, older age (≥70 years), non-vertebral bone metastasis, bone metastasis from unfavorable and moderately unfavorable primary tumor sites, and no administration of post-FMRT BMAs were significantly unfavorable factors for LC of bone metastasis in long-term survivors (Table II).

Discussion

This study showed that age, primary tumor sites, FMRT sites, and administration of post-FMRT BMAs were significant factors for LC of bone metastasis after FMRT in intermediate-term survivors (surviving for ≥1 year). However, higher FMRT doses (BED10 >39.0 Gy [10x3 Gy]) and the administration of pre- and post-FMRT ATs were not significant factors for LC of bone metastasis.

In our present study, LC did not differ according to the FMRT dose in intermediate-term survivors, in contrast to the results of our previous study (10). The selection bias of including only patients who survived for >1 year in this study could have resulted in the relatively high number of patients with indolent tumors and a good response to systemic therapy. Although the palliative radiotherapy for bone metastases does not contribute to prolonged prognosis (12), SBRT was associated with an improvement in overall survival in patients with oligometastatic paradigm (13). In the cases of non-oligometastatic bone metastases, FMRT was an acceptable option in terms of the LC of FMRT sites even when intermediate-term survival was expected.

Although all patients in the unfavorable group survived for >1 year, only 68% of them experienced LC in 1-year (data not shown). Moreover, LC of bone metastasis from unfavorable primary tumor sites is insufficient even when SBRT, a more aggressive treatment than FMRT, is used (14,15). However, although moderate-dose escalation did not improve LC of bone metastasis, an extremely high radiation dose may have the potential to control bone metastasis from these tumors (16,17). When bone metastases from unfavorable primary tumor sites are treated using radiotherapy and intermediate- and long-term survival is desired, extremely high radiation doses using intensity-modulated radiotherapy or heavy ion radiotherapy may be warranted. On the contrary, some studies have shown that SBRT resulted in good LC of bone metastases from moderately unfavorable primary tumor sites (18-20). Thus, SBRT, rather than FMRT, should be aggressively utilized for bone metastases from moderately unfavorable primary tumor sites for patients expected to have intermediate- and long-term survival.

In addition, the sites of the bone metastases seemed to influence the LC. Non-vertebral bone metastases had unfavorable LC in our study. Although the reasons were unclear, one of the possible explanations is that vertebral bone metastases often occur via Batson's vertebral venous plexus (21); these may have occurred early as compared to the non-vertebral bone metastases. Therefore, non-vertebral bone metastases may represent a more aggressive tumor compared to vertebral bone metastases.

In contrast to the results of our previous study, the administration of post-FMRT ATs did not improve the LC of FMRT sites (10), perhaps due to the indolent nature of the tumors in intermediate-term survivors without post-FMRT ATs. Furthermore, Ahmed *et al* (22) showed that the radiation sensitivity of each metastatic site was different according to the anatomical location of metastases, even if each metastasis occurred from the same primary tumor site. In addition, the development and progression of bone metastases are influenced by osteoclasts and osteoblasts, which are different from the microenvironment of other metastases (23,24). Even when a comparatively low FMRT dose (≤39.0 Gy) and no post-FMRT ATs are used to treat bone metastasis, local regrowth may be restricted by the damage to osteoclasts and osteoblasts.

Table II. LC rates after FMRT and results of univariate and multivariate analyses.

			Univariate analysis		Multivariate analysis	
Characteristics	2-year LC, %	3-year LC, %	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (<70 years vs. ≥70 years)	92 vs. 80	87 vs. 77	2.45 (1.31-4.58)	0.006	3.53 (1.62-7.67)	0.002
Sex (female vs. male)	91 vs. 85	86 vs. 80	1.88 (1.01-3.51)	0.047	1.39 (0.70-2.77)	0.344
Primary tumor sites						
Moderately unfavorable vs. favorable	84 vs. 93	63 vs. 92	0.11 (0.05-0.23)	<0.001	0.23 (0.10-0.54)	0.001
Moderately unfavorable vs. unfavorable	84 vs. 60	63 vs. 45	2.47 (1.06-5.76)	0.036	2.70 (1.08-6.74)	0.033
FMRT sites (vertebral bone vs. non-vertebral bone)	92 vs. 82	89 vs. 75	3.14 (1.66-5.94)	<0.001	2.25 (1.17-4.31)	0.015
FMRT dose (BED10) (≤39.0 Gy vs. >39.0 Gy)	90 vs. 87	83 vs. 85	1.19 (0.64-2.22)	0.580	-	-
Post-FMRT BMAs (yes vs. no)	95 vs. 72	90 vs. 68	4.69 (2.47-8.89)	<0.001	3.54 (1.85-6.78)	<0.001
Post-FMRT ATs (yes vs. no)	91 vs. 78	85 vs. 78	2.63 (1.36-5.07)	0.004	1.04 (0.49-2.19)	0.924
Bone cortex destruction (yes vs. no)	85 vs. 90	78 vs. 86	0.54 (0.29-1.02)	0.057	0.59 (0.30-1.16)	0.128
Pre-FMRT ATs (yes vs. no)	89 vs. 87	81 vs. 87	0.99 (0.53-1.84)	0.972	-	-

LC, local control; FMRT, fractionated moderate-dose palliative radiotherapy; BMAs, bone modifying agents; ATs, antineoplastic agents; BED, biologically effective dose; HR, hazard ratio; CI, confidence interval.

This study had some limitations due to its retrospective nature. First, overall survival could not be evaluated because only patients surviving ≥1 year were included in this study. Second, although some studies examined the prognostic factors in patients with bone metastases (25,26), our study could not investigate the relationship between prognosis and LC of FMRT sites because the large number of missing values (general condition, the severity of spinal cord palsy, the number of bone metastases, and metastases to the major internal organs) limited the detailed evaluation. Third, in this study, although the tumor aggressiveness is relatively homogeneous because only cases that survived >1 year were evaluated, the influence of tumor aggressiveness could not be completely excluded. Therefore, careful interpretation of the results is necessary. Furthermore, tumor aggressiveness may depend on the unfavorable group (primary tumor sites) and systemic control. However, because some patients in the unfavorable group survived for ≥1 year and had local failure within a few months, increased intensity treatment may be necessary for these cases. Finally, this study was substantially affected by the small number of recurrences that occurred compared with our previous study (10); thus, future studies are required to verify these results. In addition, this study aimed to investigate LC in patients surviving for ≥1 year, in contrast to our previous study (10). In patients with a short prognosis, pain relief with a single-fraction radiotherapy is optimal. In cases with a long prognosis (especially oligometastatic bone lesion), SBRT may be preferable. However, in cases with intermediate prognosis, it is often difficult to select an appropriate irradiation dose in clinical practice. Based on the results of the previous study alone, it was difficult to consider cases in which FMRT is truly preferable. Therefore, this study focusing on LC of bone metastases with palliative radiotherapy could help in determining the appropriate radiation dose in cases with intermediate prognosis.

In conclusion, the sites of bone metastasis and primary tumors, as well as the administration of post-FMRT BMAs were significant factors associated with LC of bone metastasis in intermediate-term survivors. However, an FMRT dose (BED10) >39.0 Gy and the administration of post-FMRT ATs were not significantly useful for the LC of bone metastasis. Although further study of LC of bone metastasis from various cancer sites is warranted, these results should be considered for the individualized radiotherapy for bone metastasis.

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Availability of data and materials

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

Authors' contributions

KM and YH designed the study concepts and confirm the authenticity of all the raw data. KM and YH prepared the manuscript and MK and HK edited the manuscript. KM, YH, HK, MK, SY, KN, HI, NT, ST, KU and TK collected patient

data, were involved in the data analysis, drafted the article and collaborated in the discussion. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study was approved by Ethics Committee of Ehime University Hospital (Toon, Ehime, Japan; approval reference no. 1912010), Ethics Committee of Shikoku Cancer Center (Matsuyama, Ehime, Japan; approval reference no. RIN2019-79) and Ethics Committee of Saiseikai Imabari Hospital (Imabari, Ehime, Japan; approval reference no. I2-1-2). Patients consented in writing to the use of their anonymous data for research at the time of treatment and consented to this research via the opt-out method.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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