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Similar Prognosis of Patients with Bone-only Metastatic Breast Cancer and Visceral Metastasis

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ABSTRACT

Background: Bone-only metastatic breast cancer is believed to be non-life-threatening, and mild therapy is frequently selected to avoid adverse events of drug therapy. However, the prognoses of such patients are not well studied.

Methods: Patients who received drug therapies for metastatic breast cancer between 2004 and 2016 at our institution were divided into the "Bone-only metastasis", "non-visceral", and "visceral" groups based on the mode of the first metastasis, and the efficacy of the first-line therapy and survival of these patients were compared.

Results: There were 131 eligible patients, and the bone-only metastasis, non-visceral, and visceral groups included 26, 25, and 80 patients, respectively. The median survival time (MST) of the overall survival (OS) in each group was 35.1, 34.9, and 37.4 months, respectively (p=0.71). The clinical benefit rates of first-line therapy in the bone-only metastasis, non-visceral, and visceral groups were 66.7%, 45%, and 69.3%, respectively, and the MST of the time to treatment failure (TTF) in each group was 6.3, 5.5, and 5.8 months, respectively, showing that the efficacy of first-line therapy did not significantly differ among the groups. In the bone-only metastasis group, patients with <5 metastases tended to have a good prognosis, and those with a low nuclear grade and long first-line therapy duration had a significantly better prognosis than others.

Conclusion: The patients with bone-only metastasis had a similar prognosis and treatment response to those with other modes of metastasis, and the patients with a good response to the first-line therapy had a good prognosis.

Introduction

Although metastatic breast cancer (MBC) is unlikely to be cured,[1] the survival of patients with MBC has been improved by the development of drug therapies, such as chemotherapy and hormone therapy.[2] According to the guidelines for MBC, such as Hortobagyi's algorithm and the National Comprehensive Cancer Network (NCCN) guidelines, hormone therapy should be introduced in cases of hormone-receptor (HR)-positive MBC prior to chemotherapy if the metastatic tumor is not life-threatening, as the adverse effect of hormone therapy is mild.[3-4]

Bone metastases are often treated with hormone therapy because most cases are HR-positive, and bone metastasis is believed to be non-life-threatening.[5] Indeed, some patients with bone-only metastasis have a very long survival time.[6] However, almost all patients with bone metastasis ultimately develop life-threatening visceral metastases and die due to their MBC, like other modes of metastasis. To

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our knowledge, the prognoses of the patients with bone-only metastasis have not been well studied, and whether or not bone-only metastasis can be treated with mild therapy, such as hormone therapy alone, is unclear.

In the present study, we retrospectively compared the prognoses of patients with bone-only metastasis as the first site of MBC with those of patients with other modes of metastases to elucidate how best to manage bone metastasis.

Methods

This was a retrospective study where the clinical records of breast cancer patients who received drug therapy for advanced or metastatic breast cancer at Gifu University Hospital between 2004 and 2016 were reviewed. The patients were divided into three groups based on the mode of the first metastasis as follows: "Bone-only metastasis" for patients who developed only bone metastasis as the first recurrence, "Non-visceral" for patients with local recurrence or lymph node metastasis with/without bone metastasis as the first recurrence, and "Visceral" for patients with visceral metastasis with/without bone metastasis and/or non-visceral metastasis as the first recurrence.

The efficacy of the first-line drug therapy in each case was evaluated from the perspective of the objective response assessed by the investigators based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and time to treatment failure (TTF).[1] The objective response was divided into three categories: complete response (CR; all lesions disappeared), non-complete response/non-progressive disease (non-CR/non-PD; lesions were unchanged or diminished), and progressive disease (PD; lesions apparently increased). The clinical benefit rate (CBR) was then calculated as CR + non-CR / non-PD. The TTF was defined as the time from the start of the therapy to the end of the therapy.

Ethical approval

This study was approved by the Institutional Ethics Committee of Gifu University, Graduate School of Medicine (Approval number: 29-108) and informed consent was obtained via the opt-out method on the website.

Statistical analyses

The TTF and survival of the patients were analyzed using Kaplan-Meier curves and compared by log-rank test. The median survival time (MST) was then calculated. The CBR was analyzed using the chi-squared test. All statistical analyses were conducted using the software EZR software program (version 3.4.1 with R commander 2.4-0).

Results

Patient characteristics

A total of 139 patients received drug therapy for locally advanced or metastatic breast cancer and eight patients were excluded because of a lack of detailed records. Therefore, 131 patients were included. The patients were a median 61 years of age. Most of the primary tumors were 2-5 cm in size (T2). A total of 94 (74%) patients had N(+) status, 87 (66%) had estrogen-receptor (ER)-positive tumors, and 25

Table 1. Patients' characteristics

	Bone-only metastasis	Non-visceral	Visceral
	26	25	80
Age (N)			
<50	5	1	17
50-59	11	12	17
>59	10	12	46
Menopausal status			
Premenopausal	5	1	17
Postmenopausal	21	24	63
T factor			
T1	3	2	10
T2	12	11	29
T3	3	0	6
T4	3	4	22
Unknown	5	8	13
Nodal status			
N(-)	4	4	13
N(+)	17	17	60
Unknown	5	4	7
Subtype			
Luminal A/B	22	13	42
Luminal HER2	1	2	7
HER2	1	5	14
Triple negative	2	5	16
First-line therapy			
Hormone therapy	21	13	36
Chemotherapy	5	12	44

T factor was defined based on Union for International Cancer Control (UICC) 7th

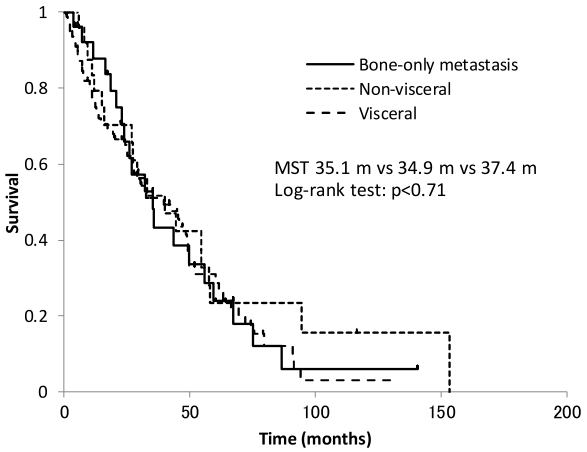

Figure 1. The overall survival of the patients with bone-only metastasis, non-visceral metastasis, and visceral metastasis. Bone-only metastasis means only bone metastasis was detected at first recurrence. Non-visceral metastasis includes local recurrence and lymph node metastasis with/without bone metastasis. Visceral metastasis means visceral metastasis with/without bone metastasis.

(19%) had HER2-positive tumors. The bone-only metastasis, non-visceral, and visceral groups included 26, 25, and 80 patients, respectively. There were significantly more HR-positive cases in the bone-only metastasis group than in the other groups (vs. non-visceral group: p=0.017, vs. visceral group: p=0.012). Seventy (53%) patients received hormone therapy, and 21 (81%) patients in the bone-only metastasis group received hormone therapy as the first-line therapy. The details are shown in Table 1.

The survival of the bone-only metastasis group versus other groups

Kaplan-Meier curves for the overall survival (OS) in each group are shown in Figure 1. The MST values in the bone-only metastasis, non-visceral, and visceral groups were 35.1, 34.9, and 37.4 months, respectively. There were no significant differences in the OS among groups (log-rank test: p=0.71). These results indicated that the survival time of the patients with bone-only metastasis were not necessarily better than in other groups.

The efficacy of the first-line therapy in the bone-only metastasis group vs. other groups

We compared the efficacy of the first-line therapy in each group based on the objective response and TTF. The CBR values in the bone-only metastasis, non-visceral, and visceral groups were 67%, 45%, and 69.3%, respectively. There were no significant differences in the CBR among the groups (bone-only metastasis group vs. non-visceral group: p=0.20, bone-only metastasis vs. visceral group: p=0.85; Figure 2a). The MST values of the TTF in the bone-only metastasis, non-visceral, and visceral groups were 6.3, 5.5, and 5.8 months, respectively. There were no significant differences in the TTF among the groups (bone-only metastasis group vs. non-visceral

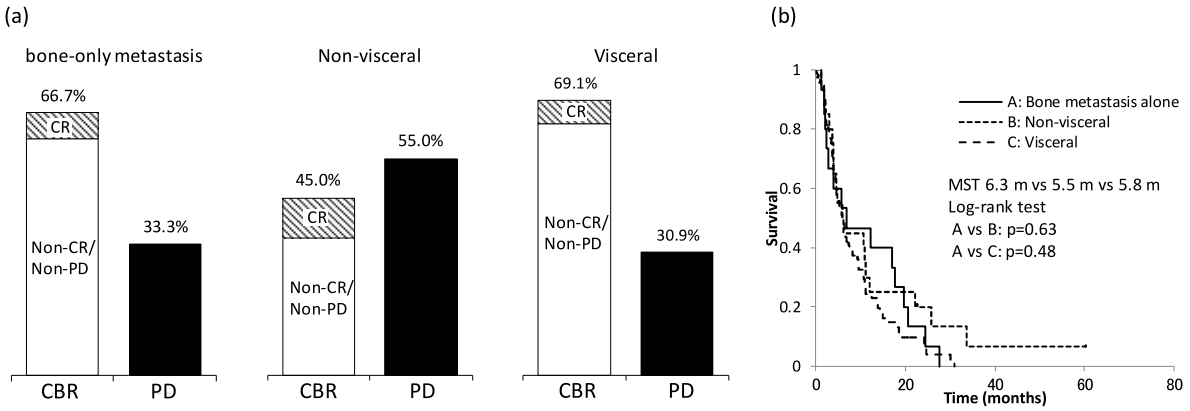

Figure 2. The efficacy of the first-line therapy. (a) The clinical benefit rate (CBR) and progressive disease (PD) of the patients with bone-only metastasis, with non-visceral metastasis, and with visceral metastasis. (b) The time to treatment failure of the first-line therapy among the patients with bone-only metastasis, with non-visceral metastasis, and with visceral metastasis.

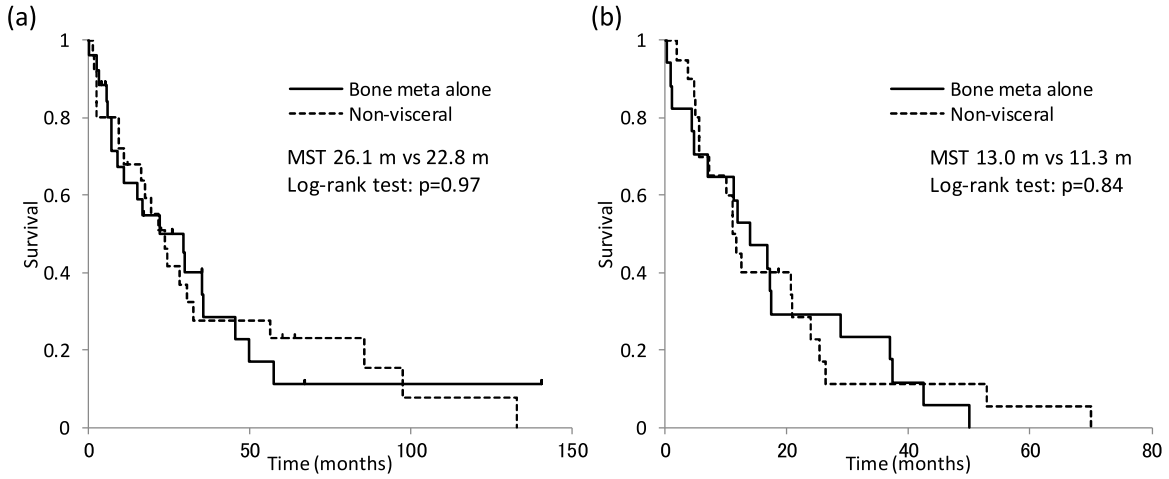

Figure 3. A comparison of the prognoses between the patients with bone-only metastasis and with non-visceral metastasis. (a) The time to the development of visceral metastasis. (b) The survival time after the development of visceral metastasis.

group: p=0.63, bone-only metastasis vs. visceral group: p=0.48; Figure 2b).

These results suggested that the efficacy of the first-line therapy in the patients with bone-only metastasis was similar to that in other groups

Rate of developing visceral metastasis in the bone-only metastasis group vs. non-visceral group

The development of visceral metastasis is considered to be associated with death from cancer. Therefore, we compared the rate of developing visceral metastasis in the bone-only metastasis group with that in the non-visceral group.

The MST values of the time to the development of visceral metastasis in the bone-only metastasis and non-visceral groups were 26.1 and 22.8 months, respectively, with no significant difference (Figure 3a). Furthermore, the MST values of the survival after the development of visceral metastasis in the bone-only metastasis and non-visceral metastasis groups were 13.0 and 11.3 months, respectively, with no significant difference (Figure 3b).

These results suggested that the patients with bone-only metastasis did not have a better outcome than those with non-visceral metastasis.

.Prognostic factors among the patients with bone-only metastasis.

As described above, we found that the prognosis of the patients with bone-only metastasis was not better than that of the patients with other modes of metastasis. However, some patients with bone-only metastasis still had a very good survival. Therefore, we investigated the prognostic factors among the patients with bone-only metastasis.

The survival of patients with <5 metastases tended to be long but not significantly as compared with that of the patients with ≥5 metastases (MST: 35.3 vs. 22.2 months, p=0.42; Figure 4a). "Nuclear grade" refers to the tumor grading system used in Japan, which consists of a nuclear atypia score and mitotic count score[2], and the survival of the patients with a low nuclear grade (nuclear grade 1 or 2) was good compared with that of the patients with a high nuclear grade (nuclear grade 3) (MST: 35.1 vs. 16.1 months, p<0.01; Figure 4b). The patients who received first-line therapy for ≥9.6 months, which was the median duration of first-line therapy, had a good survival compared to those with <9.6 months of first-line therapy (MST: 47.4 vs. 19.8 months, p<0.01; Figure 4c)

These results suggested that the tumor biology

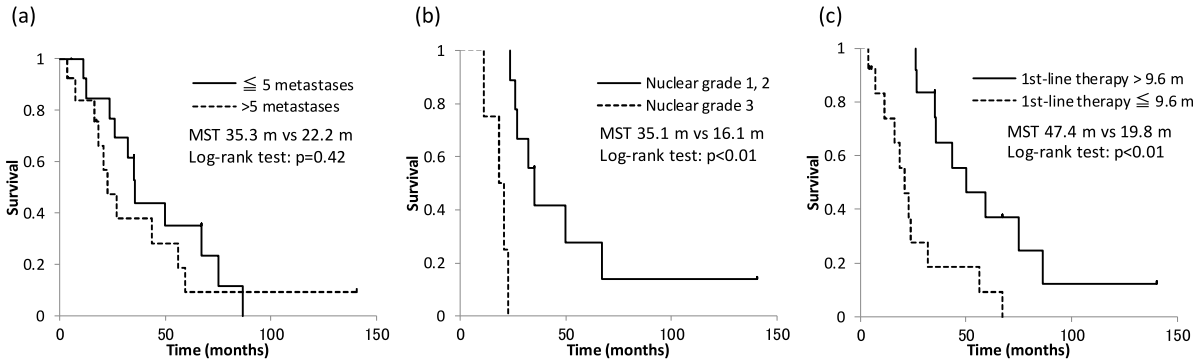

Figure 4. An analysis of the prognostic factors among the patients with bone-only metastasis. The overall survival of the patients with (a) ≤5 metastases or >5 metastases, (b) nuclear grade 1/2 or nuclear grade 3, and (c) a short duration (≤9.6 months) of first-line therapy or long duration (>9.6 month) of the first-line therapy. A duration of 9.6 months is the median duration of first-line therapy.

and treatment efficacy were important to consider when predicting patients' prognoses.

Discussion

We investigated the prognosis of the patients with bone-only metastasis and found that the survival of such patients was similar to that of the patients with other modes of metastasis. In addition, we found that the nuclear grade and duration of the first-line therapy was more influential than the number of metastases on the prognosis of the patients with bone-only metastasis.

Although there was a study comparing the prognoses of the patients with bone-only metastasis and that with non-bone-only metastasis,[9] to our knowledge, no other study has compared the prognosis of patients with bone-only metastasis with that of patients with non-visceral metastasis or with visceral metastasis. Most physicians believe that patients with bone-only metastases have a good prognosis because bone metastasis is not life-threatening and mild therapy is frequently selected. Therefore, our finding that patients with bone-only metastasis have a good prognosis is not necessarily good is modest and innovative.

Meanwhile, there have been some studies investigating the prognostic factors among patients with bone metastasis. Niikura et al. investigated the prognostic factors for patients with bone-only metastases using the patient records from The University of Texas MD Anderson Cancer Center and reported that a performance status of 0-1, a single metastasis, and asymptomatic bone disease were related to a longer OS.[10] Kai et al. investigated the clinical course of bone-only metastasis in inflammatory breast cancer and non-inflammatory breast cancer and found that the OS did not differ significantly between the two groups.[11] Ahn et al. also investigated the prognostic factors of the patients with bone-only metastasis using the patient records at Gangnam Severance Hospital and found that bisphosphonate treatment, estrogen receptor positivity, and solitary bone metastasis were significantly associated with a longer OS.[12] Taken together, these previous reports indicate that there are two types of prognostic factor: the tumor burden of metastasis and the tumor biology of the primary site. Our results were largely consistent with those of these reports, although the tumor biology—such as a low nuclear grade and long continuation of first-line therapy—was found to be more important than the tumor burden.

The result of the present study that we emphasize particularly was that the patients with bone-only metastasis did not have a better survival than those with other modes of metastasis, even though many physicians believe that bone metastasis is not life-threatening. This result suggested that treatment for patients with bone-only metastasis should not be weakened, although some patients with bone-only metastasis have a very good survival.

The limitations of this study are the small population and retrospective nature of our study. However, we believe that our results provide important evidence for clinical practice and that these findings may help prolong the survival of patients with metastatic breast cancer. A larger prospective study investigating how to manage bone metastasis will be required in the future.

In conclusion, we found that patients with bone-only metastasis had a similar prognosis to those with other modes of metastasis. Therefore, treatment for such patients should be selected as for patients with other modes of metastasis.

Conflict of Interests

The authors declare that there is no conflict of interest.

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