Surgical outcomes of metastatic bone tumors in the extremities (Surgical outcomes of bone metastases)

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ABSTRACT

Background: Skeletal related events due to metastatic bone tumors markedly affect the activities of daily living (ADL) and quality of life (QOL) in cancer patients. We focused on multidisciplinary therapy for metastatic bone tumors. This study aimed to evaluate the outcomes of surgical treatment for metastatic bone tumors in the extremities.

Methods: We retrospectively reviewed 114 patients who underwent surgical treatment for metastatic bone tumors of the extremities between 2008 and 2019 and 69 patients were reassessed for more than 6 months after surgery. The most common primary tumor was renal, followed by lung, thyroid, and breast cancers. We assessed 69 patients' performance status (PS), Barthel Index (BI) for ADL, EuroQol 5 Dimensions (EQ-5D) for QOL, and numerical rating scale (NRS) for pain and analyzed these postoperative values relative to preoperative values using Friedman's test. The postoperative overall survival and the prognostic factors were evaluated using the Kaplan-Meier method, the log-rank test and Cox proportional hazards analysis.

Results: The 1-year overall survival rate was 59%, and the median survival time after surgery was 20 months. Primary tumor, visceral metastasis, and surgical procedure were risk factors correlated with overall survival. PS, BI, EQ-5D, and NRS improved at 3 months after surgery and these improvements were maintained for 6 months after surgery regardless of the surgical procedure.

Conclusions: The significant factors affecting survival after surgical treatment for bone metastases included the primary tumor, presence of visceral metastases, and internal fixation without tumor resection or curettage. Surgical treatment for metastatic bone tumors effectively reduced pain and improved PS, ADL, and QOL postoperatively after 3 months.

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1. Introduction

Approximately 18 million people are newly diagnosed with cancer every year in the world [1]. We have entered a "cancer era," in which one out of every two Japanese people will suffer from cancer at some point in their lives. Bone is one of the most common sites of metastatic disease [2,3]. The prolonged survival of cancer patients and improvements in diagnostic imaging equipment may result in increase of cancer patients with bone metastasis. Skeletal related events (SREs) due to bone metastases greatly affect activities of daily living (ADL) and quality of life (QOL) in cancer patients. In particular, SREs such pathological fractures of the long bones, paralysis due to spinal cord compression, or hypercalcemia

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require urgent treatment [4]. Bone metastasis in the extremities often requires surgical treatment to reduce pain and structurally support the bone structure [5]. Surgical treatment for bone metastasis aims to improve or maintain a patient's performance status (PS), ADL, and QOL. The improvement of PS may enable the patients to continue the treatment for primary cancer subsequently and lead to prolonged survival. Palliative surgery may also benefit near-terminal cancer patients. However, there are no standard guidelines regarding surgical indications and the surgical procedures for bone metastasis. A multidisciplinary approach involving a team of specialists in oncology, palliative care, radiotherapy, orthopedics, nuclear medicine, and rehabilitation is essential for the effective management of patients with bone metastases. Although the level of evidence is not high, there have been some reports suggesting the usefulness of such approaches [6,7]. In our hospital, the management of bone metastases by such a multidisciplinary approach through a cancer board is performed. The aim of this study was to examine the postoperative outcomes of patients with surgically treated bone metastasis in the extremities and to evaluate the influence of cancer board.

2. Patients and methods

2.1. Patient population

This study included 114 patients (61 men, 53 women; median age, 66 [range, 22–87] years) who underwent surgery for limb and acetabular bone metastases between 2008 and 2019 in our institution. To determine if the bone metastatic lesion had spread, X-rays, computed tomography (CT) and/or magnetic resonance images (MRI) were obtained from all patients. Distant metastases were assessed using enhanced CT/MRI, bone scan, and positron emission tomography with 18F-fluoro-2-deoxy-D-glucose (FDG-PET) if necessary. The patients were registered at operation and followed until December 2019 or death. The median duration of follow-up was 12 (range, 0–130) months. There was surgical indication for bone metastasis with severe pain and high risk of pathological fracture. In some cases, the bone metastasis was radically resected. We defined the patient's general condition needed to be

tolerable for surgery, whose expectable prognosis needed at least one month. We needed to discuss the risk of surgery and the benefits for each patient in multidisciplinary approach, so we established the bone metastasis board (BMB), the cancer board for bone metastasis, in our institution in 2013, and then the surgical indication and the surgical procedure were decided in the BMB.

2.2. Surgical procedures

The patients were classified into three groups based on surgical procedures (1) the fixation group (59 cases), in which only internal fixation was performed without tumor curettage or resection; (2) the curettage group (27 cases), in which internal fixation was performed in addition to bone cement filling after intra-tumoral resection (tumor curettage); and (3) the resection group (28 cases), in which en-bloc tumor resection was followed by reconstruction using an implant.

We selected the surgical procedure in consideration of the invasiveness and curability of the surgery. We made the algorithm (Fig. 1) of the surgical treatment for limb and acetabular bone metastases.

2.3. Statistical analyses

To control for other factors affecting patient prognosis, we evaluated age, sex, presence of pathological fracture, type of primary tumor, presence of visceral metastases, presence of multiple bone metastases, history of chemotherapy, history of radiation therapy to surgical sites, surgical procedures for bone metastases, and the use of bone-modifying agents (BMA). Primary tumors were classified as three subgroups according to Katagiri score [8] (Table 1). The Kaplan-Meier plot and log-rank test were used to compare overall survival for each factor. A Cox proportional hazards model was used to calculate the adjusted hazard ratios with 95% confidence intervals. A chi-square test of independence was calculated comparing the frequency of pathological fracture in presence or absence of preoperative administration of BMA. As for 69 out of 114 cases that could be followed up for more than 6 months after surgery, we evaluated PS, ADL, QOL, and pain at 3 and 6 months
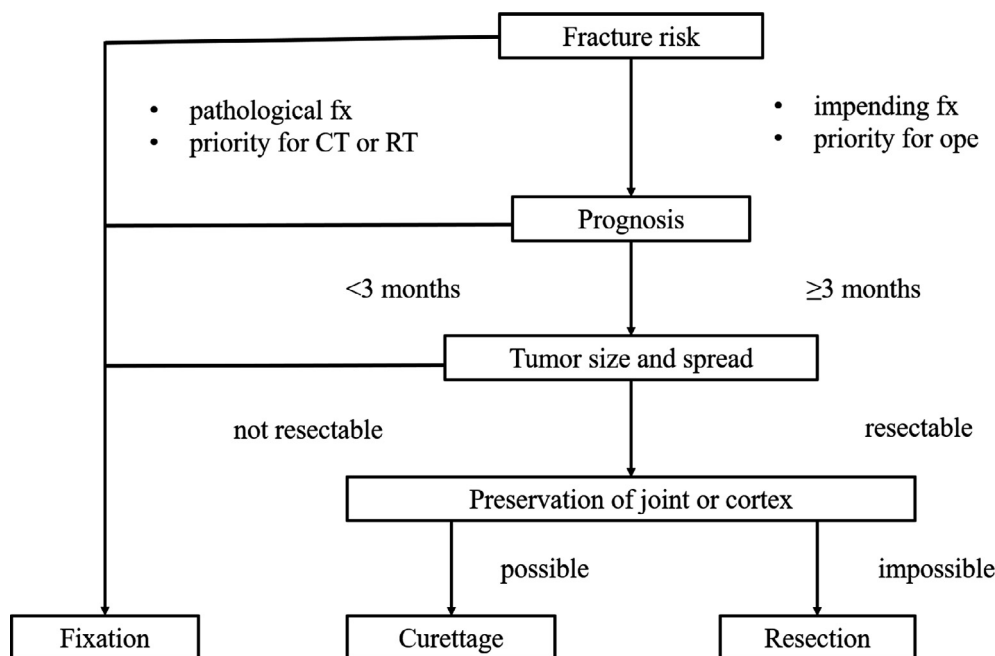

Fig. 1. Algorithm for the selection of a surgical procedure for bone metastasis in the limb or acetabular.

Table 1
Subgroups of primary tumors by site.

Primary site	
Slow growth	Hormone-dependent breast and prostate cancer
	Thyroid cancer
	Multiple myeloma
	Malignant lymphoma
Moderate growth	Lung cancer treated with molecularly targeted drugs
	Hormone-independent breast and prostate cancer
	Renal cell carcinoma
	Endometrial and ovarian cancer
	Sarcoma
	Others
Rapid growth	Lung cancer treated without molecularly targeted drugs
	Colorectal cancer
	Gastric cancer
	Pancreatic cancer
	Head and neck cancer
	Esophageal cancer
	Other urological cancers
	Melanoma
	Hepatocellular carcinoma
	Gall bladder cancer
	Cervical cancer
	Cancers of unknown origin

Table 2
Primary tumors of patients who underwent surgery for bone metastases.

Primary tumor	N (%)
Renal	31 (27)
Lung	17 (15)
Thyroid	14 (12)
Breast	12 (11)
*HR+	9 (8)
HR-	3 (3)
Blood	7 (6)
Prostate	7 (6)
Liver	6 (5)
Sarcoma	6 (5)
Head & Neck	4 (4)
Bladder	2 (2)
Cervical	2 (2)
Bile duct	2 (2)
Others	4 (4)

*HR: hormone receptor.

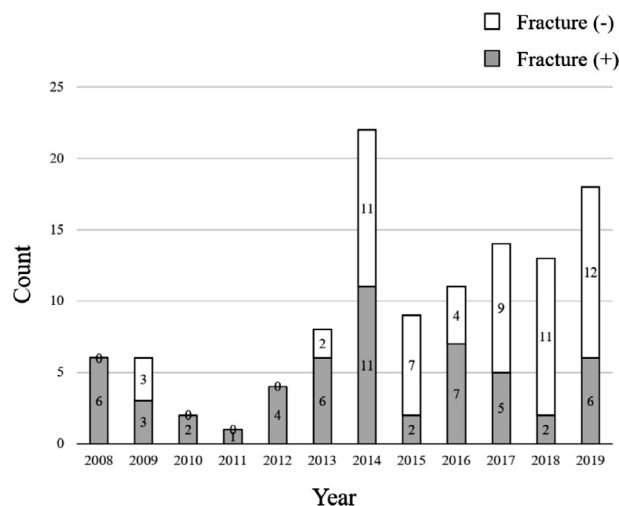**Fig. 2.** Annual number of surgeries performed for bone metastases of the extremities and the incidence of pathological fractures.

postoperative relative to these preoperative values. PS was evaluated using the Eastern Cooperative Oncology Group (Zubrod, World Health Organization) performance scale. ADL, QOL, and pain were assessed using the Barthel Index (BI), EuroQoL 5 Dimensions (EQ-5D), and Numerical Rating Scale (NRS), respectively. Friedman's test was used for the statistical analysis, and values $p < 0.05$ were considered statistically significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [9]. This study was approved by the Ethics Review Boards of our institution (B200070) and subjects were provided with information using opt-out methods.

3. Results

3.1. Surgeries for bone metastasis

The most common type of primary tumor was renal cancer, followed by lung cancer, thyroid cancer, and breast cancer (Table 2). The surgical sites of bone metastasis were 33 upper limbs, 51 peritrochanteric, 30 non-peritrochanteric lower limbs (5 acetabulums and 25 the others). Fig. 2 shows the number of surgeries and the incidence of pathological fractures annually in our institution. The bone metastasis board (BMB), the cancer board for bone metastasis, was established in our institution in 2013. Since then, our multidisciplinary team has been providing bone metastasis management, and the number of preventive surgeries without pathological fractures has increased, resulting in an increased number of surgeries.

3.2. Outcomes

Fig. 3 shows the Kaplan-Meier curve of overall survival time for our subjects. The 1-year survival rate was 58.6%, median survival time was 20 months, and median follow-up time was 12 (range, 0–130) months. Table 3 shows a comparative analysis of each factor's effect on survival time. We confirmed in advances that three subgroups of primary tumor according to Katagiri score had a sig-
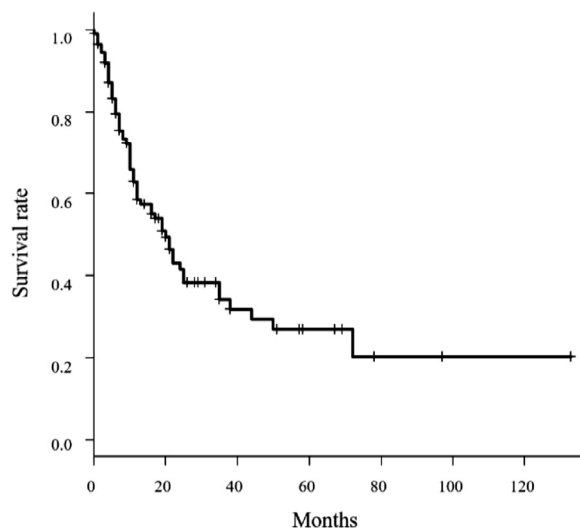

Fig. 3. Kaplan-Meier curve of overall survival time for of the 114 patients.

Table 3
Univariate analysis of prognostic factors affecting overall survival.

Factor	n	Survival rate (95% CI)	Median survival (M)	p-value
age				0.0525
≥65	65	0.658 (0.515–0.767)	22	
<65	49	0.498 (0.346–0.633)	12	
sex				0.852
f	53	0.540 (0.384–0.672)	20	
m	61	0.624 (0.483–0.737)	19	
pathological fracture				**0.0292**
–	59	0.711 (0.565–0.815)	22	
+	55	0.451 (0.308–0.584)	11	
Katagiri score (primary tumor)				**0.000925**
slow growth	32	0.702 (0.490–0.839)	35	
moderate growth	56	0.643 (0.493–0.759)	21	
rapid growth	26	0.326 (0.151–0.515)	7	
visceral metastasis				**0.00763**
–	43	0.694 (0.524–0.814)	44	
+	71	0.518 (0.386–0.635)	13	
multiple bone metastasis				0.557
–	31	0.626 (0.426–0.774)	21	
+	83	0.569 (0.445–0.675)	19	
preoperative chemotherapy				0.16
–	53	0.639 (0.483–0.759)	22	
+	61	0.539 (0.397–0.661)	17	
postoperative chemotherapy				0.0753
–	38	0.466 (0.291–0.624)	10	
+	76	0.643 (0.516–0.745)	21	
preoperative radiotherapy				0.481
–	84	0.608 (0.486–0.710)	20	
+	30	0.529 (0.330–0.695)	16	
postoperative radiotherapy				0.284
–	56	0.637 (0.487–0.754)	24	
+	58	0.540 (0.395–0.665)	16	
surgical procedure				**0.00000742**
fixation	59	0.378 (0.247–0.508)	10	
curettage	27	0.836 (0.619–0.935)	44	
resection	28	0.784 (0.556–0.904)	35	
bone modifying agent				0.346
–	40	0.549 (0.377–0.692)	20	
+	74	0.607 (0.475–0.716)	21	

nificant difference in survival rate for our subjects. Pathological fracture, type of primary tumor, visceral metastasis, and surgical procedure negatively affected patient prognosis. Furthermore, multivariate analysis revealed that type of primary tumor, visceral metastasis, and surgical procedure were independent prognostic factors (Table 4). Specifically, patients in the "rapid growth" Katagiri subgroup, those with visceral metastasis, and those who received only internal fixation had poor prognoses relative to other patients (Fig. 4).

In the 69 patients who completed the longer than 6 months of postoperative follow-up, PS, ADL (BI), QOL (EQ-5D), and pain (NRS) improved 3 months and 6 months after surgery relative to these preoperative values. There were no significant differences between 3 months and 6 months after surgery (Figs. 5 and 6).

Table 4
Prognostic factors by multivariate analysis hazard rate, cumulative interval, and p values.

Prognostic factor	HR	95% CI	p-value
Katagiri score (primary tumor)	1.49	1.15–1.93	0.0025
visceral metastasis	2.19	1.24–3.86	0.0067
surgical procedure	2.04	1.40–2.96	0.00019

Thirty-one patients out of 119 patients were received BMA preoperatively. There was no significant difference between preoperative BMA administration and pathological fracture.

3.3. Complications

Postoperative complications occurred in 7/114 patients (6.1%), including two cases of deep surgical site infection, one case of dislocation after modular endoprosthetic replacement, one case of implant loosening, and three cases of fracture. Of these, only three patients (2.6%) required reoperation. The first patient required reoperation due to infection after endoprosthetic replacement. The patient suffered bone metastasis of the distal femur from renal cancer, and had undergone irradiation (45 Gy) before the endoprosthetic replacement. The patient was unable to undergo revision arthroplasty due to an uncontrolled infection and died of the primary cancer. The second patient required reoperation due to dislocation after modular endoprosthetic replacement of the proximal femur. The patient suffered bone metastasis from breast cancer, and had undergone irradiation (30 Gy) before the endoprosthetic replacement. The patient was treated by open reduction of the bipolar head and repair of the posterior soft tissue as the secondary operation. The third patient required reoperation due to periprosthetic infection after endoprosthetic replacement of the proximal femur. Surgical debridement, implant retention, and
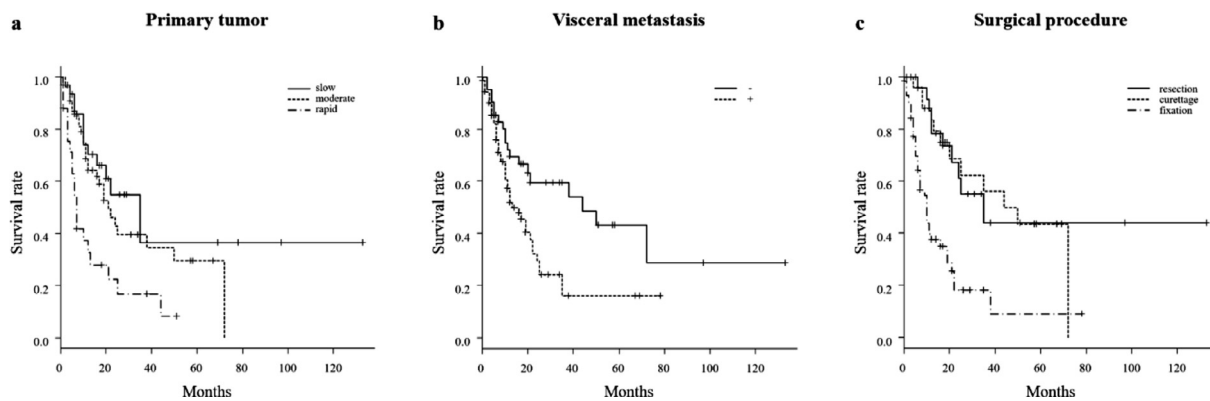
Fig. 4. Kaplan-Meier curves of independent prognostic factors affecting overall survival. a The rapid growth group of the primary tumor classified by the Katagiri scoring system was significantly lower than those of the other two groups. b The patients with in the visceral metastasis had were a lower survival rate than patients those without visceral metastasis. c The fixation group had was a significantly lower survival rate than the resection and the curettage groups.
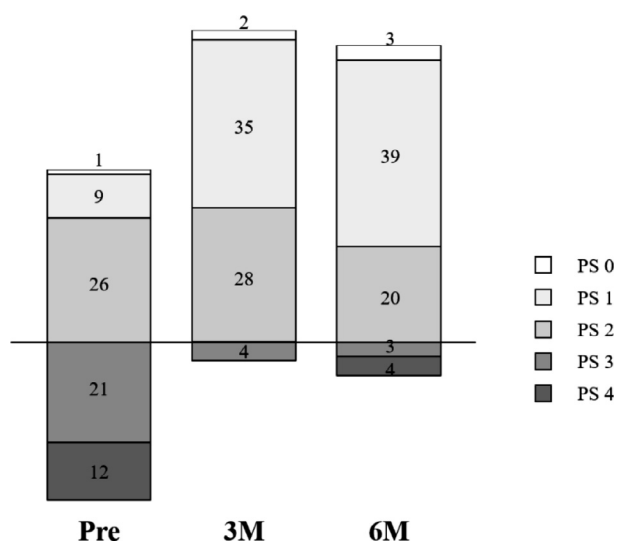

Fig. 5. Trends in performance status (PS) following surgery for the 69 patients.

antibiotic therapy were effective. One case of implant loosening was observed conservatively. All three cases of fracture were located around the bone cement and observed appropriately. Local tumor recurrence (regrowth) was detected in 10/114 cases on postoperative imaging analysis. The local progression-free survival rate was favorable at 92.6% at 1 year postoperative. Local recurrence (regrowth) occurred in 6/59 cases (10.2%) in the fixation group, 3/27 cases (11.1%) in the curettage group, and in 1/28 cases (3.6%) in the en-bloc resection group. There was no statistically significant difference in local progression-free survival rates among the groups, but of course, en-bloc resection is superior in controlling tumors locally. No patient required surgical treatment for local tumor recurrence (regrowth). In one case of the fixation group, subcutaneous tumor recurrence due to dissemination was observed after intramedullary fixation and postoperative radiation therapy (30 Gy) for renal cancer bone metastasis of the humerus. This case involved effective re-irradiation (30 Gy) for local control.

4. Discussion

Previously, conventional treatments for bone metastasis in cancer patients focused on palliative therapies such as radiation therapy, administration of opioids for pain, and emergency orthopedic surgery for pathological fracture or spinal cord compression. However, with advances in cancer treatment, the goal of bone metastasis treatment has significantly changed. SREs due to bone metastases negatively affect the ADL and QOL of cancer patients and may also influence on the choice of treatment for the primary lesion. Bone metastasis management should provide appropriate treatment for cancer patient to avoid being bedridden or to ambulate independently if possible. Therefore, preventing from the pathological fracture of metastatic bone is important to avoid reduction in the ADL and QOL of cancer patient and in emergency
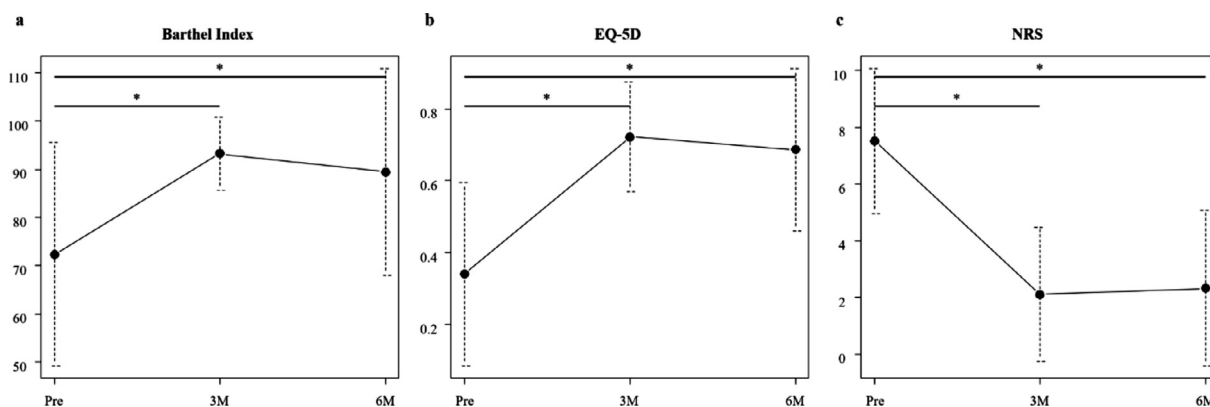

Fig. 6. Improvement in a BI (Barthel Index), b EuroQoL 5 Dimensions (EQ-5D), and c Numerical Rating Scale (NRS) scores at pre-operation, 3 months, and 6 months for the 69 patients. The mean scores are plotted. Error The error bars represent standard deviations. *Values of Significant at p < 0.05 are considered statistically significant.

hospitalization and surgery. A cancer board comprising a multidisciplinary team is essential for bone metastasis management, although there is not sufficient evidence yet to prove a significant usefulness of cancer board [7,10,11]. We established a BMB in our institution in 2013 and have since been providing multidisciplinary bone metastasis management. Prior to the establishment of the BMB, we performed surgeries mostly for pathological fractures due to bone metastases in the limbs and acetabulum. Since the establishment of the BMB, the number of preventive surgeries has increased.

In our study, the 1-year survival rate after surgery for bone metastasis in the limbs and acetabulum was 59%. The reported prognosis in previous studies was poorer with 1-year survival rates of 39% [12] and 41% [13]. The differences in survival rate may depend on primary tumor type, treatment advances, and surgical indication. In our study, the primary tumor was one of the independent factors affecting prognosis. The patients with primary tumors in the "rapid growth" Katagiri subgroup [8] showed poor prognosis relative to patients in other subgroups. Ratasvuori et al. [13] also reported that primary cancer type affected patient prognosis. Hansen et al. [12] reported that lung cancer was associated with poor prognosis in 2004. However, advances in drug therapy have enabled some patients with lung cancer to survive longer, therefore, Katagiri et al. [6] considered the presence or absence of molecularly targeted therapy for lung cancer when categorizing the primary tumor groups (Table 2). It should be noted that the second independent poor prognosis factor, visceral metastasis, is also a factor that lowers ADL and QOL in cancer patients. The results of this study also showed that patients in the fixation group, who underwent internal fixation without tumor curettage or resection, had poor prognosis compared to the other groups. This result may have been subjected to bias by surgical procedure selection in which a patient with a poor prognosis tended to undergo surgery with low invasiveness. We speculate that this result indicated that a minimally invasive surgical procedure was selected for patients with a poor prognosis and that our management for bone metastasis was appropriate. Prophylactic surgery for patients at high risk of fracture can contribute to improving the QOL of patients with bone metastases. We believe that BMB plays a major role in screening such cases. However, the analysis including the non-surgery group was not performed in this study, so the effect of preventive surgery on the QOL of patients with bone metastases could not be investigated. There are no standard guidelines regarding surgical indication or selection of surgical procedures for bone metastasis. We therefore have determined the surgical indication and procedure on a case-by-case basis in patient prognosis as well as bone metastasis site, number and extent of metastatic lesions, and type of bone metastatic lesion. From the results of this study, it should be considered that the type of primary tumor and the presence of visceral metastasis can affect the prognosis. It is also necessary to consider a patient's medical history and future treatment options for a primary tumor in addition to a patient's social background, activity level, and needs for life support in a multidisciplinary meeting.

To examine the patients' postoperative courses, we compared PS, ADL, QOL, and pain score before and after the surgery for bone metastasis. We found that PS, ADL, QOL, and pain score had improved at three months after surgery and these improvements had been maintained until six months after surgery. In the fixation group, who underwent a minimally invasive procedure, all outcomes were improved at one month after surgery relative to preoperative. Although the data not shown in the data, these outcomes gradually worsened at over nine months after surgery and there was no longer a significant difference in these outcomes relative to their preoperative values. This result suggests that systemic status of the patients with bone metastasis may primarily affect PS, ADL, QOL, and pain score in the terminal stage even after surgical treatment for bone metastasis. We propose the following algorithm (Fig. 1): For patients with pathological fractures, who require chemoradiotherapy, or who have a survival prognosis of one month to less than three months, internal fixation alone could be provided. For patients with a survival prognosis of longer than three months in whom surgery can be prioritized, tumor resection or curettage could be considered based on tumor size and progression. If the tumor is unresectable because of skipping or spreading lesions, internal fixation could be performed. In cases in which the cortical bone and joint around the metastatic bone lesion can be preserved, combined tumor curettage and internal fixation or cementing could be considered. If such preservation is not possible, combined tumor resection and reconstruction could be performed. Patients in the fixation and curettage groups could undergo adjuvant radiation therapy before or after surgery.

The incidence of postoperative complications in our study was 6.1%. Previous studies reported an incidence of postoperative complications for limb bone metastasis of 5.8% [14] and 12.9% [13]. In some studies, the postoperative incidence of complication was higher than 20% for vertebra bone metastasis [15,16]. Reconstruction surgery using a tumor prosthesis reportedly resulted in a higher complication rate than internal fixation [14]. On the other hand, according to many reports, the reoperation rate due to local mechanical failure is higher in patients who undergo internal fixation than in patients who undergo reconstruction surgery using an endoprosthesis [17]. In our study, three patients required reoperation due to complications after tumor prosthetic reconstruction, no case with mechanical failure was observed but two patients of them had received radiotherapy before surgery. There were no significant differences in the relapse-free survival rates among the surgical procedures. However, it was reasonable that the local recurrence rate was low in the resection group, while many patients in the fixation group experienced recurrence early after surgery. We believe that local mechanical failure can be avoided by appropriately choosing the surgical procedure. Therefore, it is necessary to select an appropriate surgical procedure for bone metastasis based on patient prognosis, local tumor control, and the likelihood of postoperative complications.

There were some limitations in our study. First, it was a retrospective and single arm study and had its limitations. The exact indications for surgical treatment varied during the study period and there could be patient and treatment selection biases. Second, the patients included in our study had different type of primary tumor. The further analysis for each primary tumor is required.

In summary, significant factors affecting survival after surgical treatment for bone metastases included the primary tumor, presence of visceral metastases, and internal fixation without tumor resection or curettage. PS, ADL, QOL, and pain improved at 3 months and these improvements were maintained until 6 months after surgery regardless of surgical procedure. It is important that the most appropriate surgical treatment, based on several factors including patient prognosis, local tumor control, and the likelihood of postoperative complications, should be provided for patients with bone metastases. We think that surgery using a tumor prosthesis after irradiation should be aware for postoperative complications. We recommend that the management of bone metastases be decided by a multidisciplinary team.

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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