



# Clinical analysis of the patients with osseous metastatic breast cancer

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The incidence of osseous metastatic breast cancer is on the rise. However, there are few systematic studies, particularly in patients with osseous metastatic breast cancer after orthopedic surgery. We performed a medical record review of 34 patients who underwent orthopedic surgery for osseous metastasis from breast cancer during 2012. 1–2015. 1. The average age was 48.5 (27–74). A total of 49 orthopedic surgeries were done. The femur was the most common site for orthopedic surgery for osseous metastasis (17 cases, 34.6%). And the most common surgery was curettage, bone cementing and intramedullary nailing (23 cases, 46.9%). Estrogen receptor positive was the most common case with 25 cases (73.5%), triple negative was 3 cases (8.8%). Mean survival time and median survival time were 15.5 months (4–36) and 10 months each after orthopedic surgery. Orthopedic surgery should be considered depending on the condition, after careful evaluation of the patients with osseous metastasis due to breast cancer.

**Keywords:** Incidence; Bone neoplasms; Orthopedics; Survival rate

## INTRODUCTION

Cancer is the main cause of death worldwide. In 2012, about 14 million individuals were diagnosed with cancer and 8.2 million cancer-related deaths were reported [1]. The incidence of cancer in Korea, including breast cancer, has increased due to population aging and westernization of lifestyle in recent year [2]. According to the cancer registration report issued by the Ministry of Health and Welfare, breast cancer ranked as the third most common cancer in women before 1998, became the most common cancer in 2017, and accounted for about 20.3% of all cancer in Korean women in 2017 [2-4]. Moreover, the incidence of breast cancer has continued to rise in the last several decades [4].

Fortunately, due to recent advances in systemic therapy, the survival rate of breast cancer patients is increasing regardless of whether or not bone metastasis is present [5]. As a consequence, the prevalence of patients with a history of breast cancer is increasing as the rate of survival improves, making breast cancer in many aspects a chronic condition [6].

Recently, studied on the hormonal receptor mutation status for breast cancer have been actively conducted, leading to the development of the chemotherapy or targeted therapies. Although somewhat controversial, the metastasis pattern of breast cancer varies by hormone receptor status. It is known that metastasis of other organs including the brain is fast and the overall treatment effect is also poor in case of triple negative, namely estrogen receptor (ER) negative, pro-

gesterone receptor (PR) negative, human epidermal growth factor receptor2 (HER2) negative. Long-term survival rates are relatively higher in patients with ER positive, but bone metastasis is reported to be more frequent [7].

Breast cancer frequently metastasizes to the bone, and around 70% of patients with recurrent breast cancer have bone metastasis, a common cause of morbidity and mortality [8]. So that, when breast cancer metastasis to other organs, bone metastasis is almost always present, and such bone related events such as pain, pathological fracture, and hypercalcemia are not rare clinical complications [9].

Despite the trend of bone metastasis in breast cancer, there are few research results related to the patients with osseous metastatic breast cancer. In this study, so we performed a retrospective study to evaluate the clinical features, hormone receptor status, orthopedic treatment and its results in patients of breast cancer with long bone metastasis.

## MATERIALS AND METHODS

The study was based on a consecutive series of breast cancer patients operated for osseous metastasis during 2012. 1-2015. 1 at Bone and Soft tissue sarcoma Clinic at the Yonsei University College of Medicine, Seoul, Korea. The study was conducted in agreement with the guidelines and approved by the Ethics Committee of the Chosun University Hospital (CHOSUN 2020-06-001). The breast cancer was diagnosed based on histologic analysis of biopsy and open surgical specimen. Osseous metastasis and other organ metastasis were confirmed via positive bone scan. This included patients who were operated for osseous metastatic breast cancer irrespective of whether spine is involved. Indication for orthopedic operation of the limbs was complete or impending skeletal fractures. We excluded patients with other primary cancers, patients without orthopedic surgery, and patients who were dropped out during follow-up. Duration from diagnosis to final follow-up, age at diagnosis of primary cancer, outcome of primary cancer pathology, size, whether it is menopause at diagnosis, hormonal receptor mutation status of primary cancer, other organ metastasis sites, location of the osseous metastasis of the limbs, type of orthopedic surgery and the results were collected and analyzed.

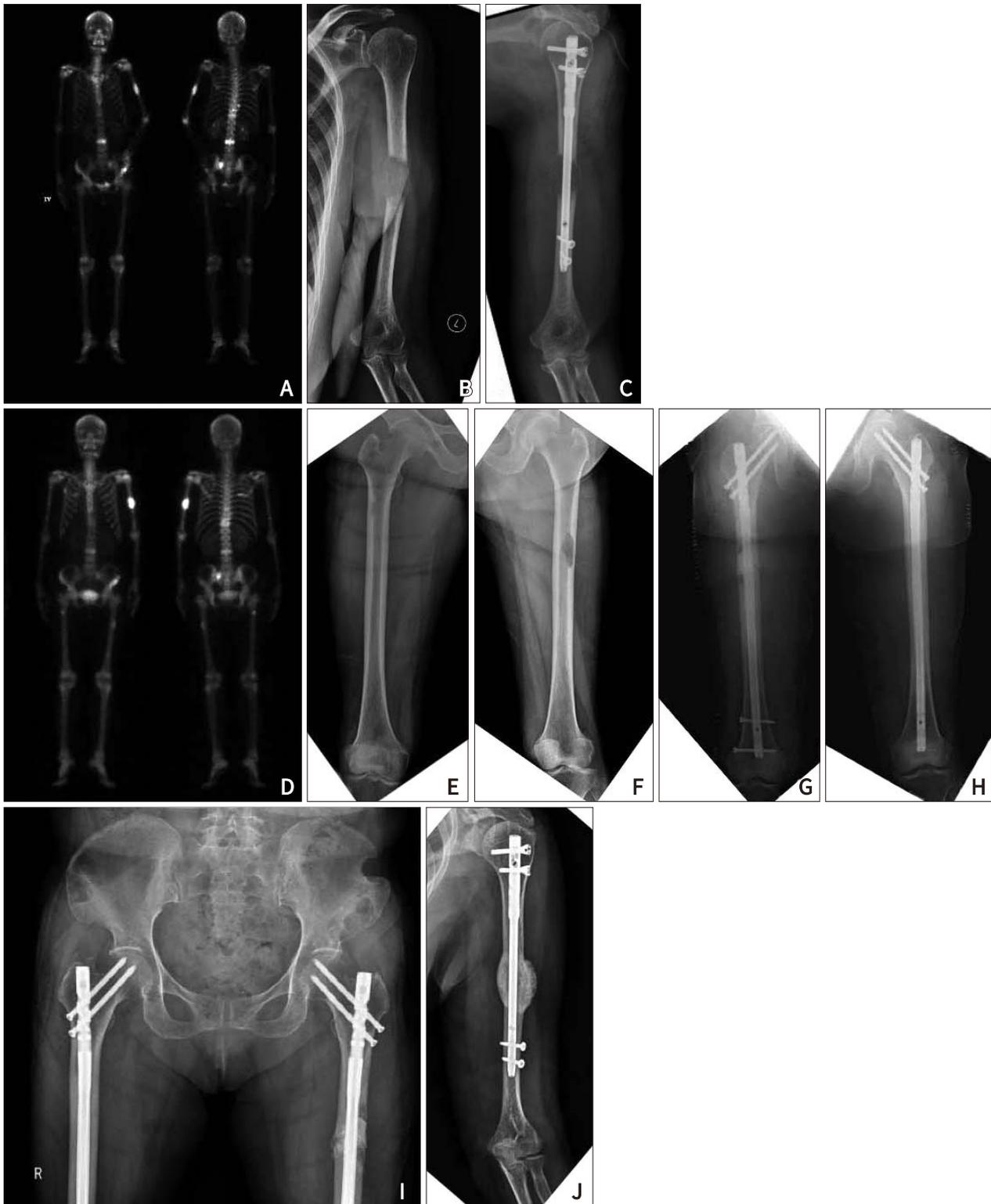
## RESULTS

Osseous metastasis occurred in 34 cases, all cases were female, and the average age was 48.5 years (27-74) (Table 1). 20 (58.8%) underwent one surgery, 13 (38.2%) underwent two surgeries, and one (2.9%) underwent three surgeries (Fig. 1). A total of 49 operations were performed. The most common surgery for osseous metastasis was curettage with bone cementing and intramedullary nailing, performed in 23 cases (46.9%), 12 cases for femur trochanter and shaft, 10 cases for humerus, and one case for tibia. There were 13 cases arthroplasty surgeries. There were 10, two, one cases of hip joint, shoulder joint and knee joint, respectively. There were five cases of curettage with plate fixation on the femur shaft. The curettage with bone cementing was performed in five cases in the pelvis. The excision was performed in three cases at the supraclavicular area. The most common surgical sites were femur in 17 cases (34.6%), hip joint and humerus in 10 cases, and pelvis in five cases (Table 2). Complication related to surgery was not observed, and case of fixation failure before death was not found, either.

At the time of diagnosis of primary breast cancer, there were 21 cases (61.8%) of lymph node metastasis and 18 cases (52.9%) of menopause (Table 1). According to the pathological results of primary breast cancer surgery, the histological grade was I in 10 cases (29.4%), II in 12 cases (35.3%), and III in 12 cases (35.3%). Lobular carcinoma was found in two patients (5.9%), mucous adenocarcinoma in one patient (2.9%), and invasive ductal carcinoma in 31 patients (91.2%). The size of the primary lesion was less than 2 cm in 12 cases (35.3%), 2 to 5 cm in 19 cases (55.9%), and more than 5

**Table 1.** Baseline characteristics of 34 breast cancer patients

Variables	Value
Patients	
Female	34 (100%)
Male	0 (0%)
Age	48.5 (27-74)
Menopause at diagnosis	
Yes	18 (52.9%)
No	16 (47.1%)
Regional lymph node involvement	
Yes	21 (61.8%)
No	13 (38.2%)



**Fig. 1.** A case of 63 years old female patient who underwent 3 surgeries. (A) A whole body bone scan shows increased uptake on left humerus, (B and C) a plain radiography of preoperative and postoperative of the left humerus, curettage with bone cementing and intramedullary nailing was done, (D) a whole body bone scan after 6 months from the surgery of the left humerus shows increased uptake on both femur shaft, (E, F and G, H) a plain radiography of preoperative and postoperative of the both femur, curettage with bone cementing and intramedullary nailing was done, (I and J) a plain radiography after 12 months from the femur surgery. She was able to walk independently with one cane support.

**Table 2.** Orthopedic operation for osseous metastasis

Variables	Value
A number of operation	
1 operation	20
2 operations	13
3 operations	1
Location	
Supraclavicular area	3
Shoulder	2
Humerus	10
Pelvis	5
Hip	10
Femur trochanter and shaft	17
Knee	1
Tibia	1
Operation	
Arthroplasty	13
Curettage with bone cementing, IM nailing	23
Curettage with bone cementing, plate fixation	5
Curettage and cementing	5
Excision	3

**Table 3.** Histopathologic characteristics

Variables	Value
Histologic grade	
I	10 (29.4%)
II	12 (35.3%)
III	12 (35.3%)
Pathology	
Infiltrating ductal carcinoma	31 (91.2%)
Lobular carcinoma	2 (5.9%)
Mucinous adenocarcinoma	1 (2.9%)
Size (cm)	
<2	12 (35.3%)
2-5	19 (55.9%)
5<	3 (8.8%)
Other organ metastasis at diagnosis	
Yes	13 (38.2%)
No	21 (61.8%)

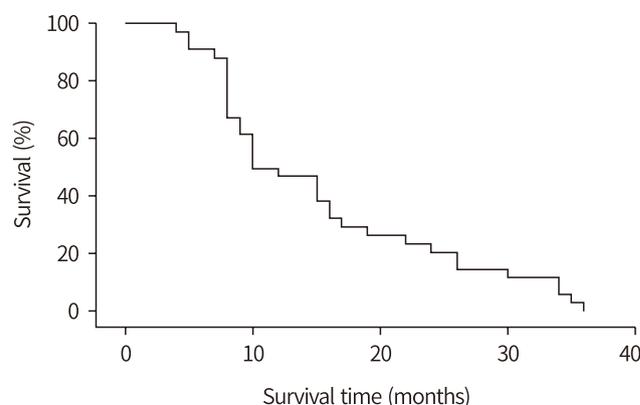
cm in three cases (8.8%). At the time of diagnosis, 13 cases (38.2%) metastasized to other organs and 21 cases (61.8%) metastasized to other organs during the follow-up period (Table 3). There were 14 liver metastasis (41.2%), 16 lung metastasis (47.1%), and five intracranial metastasis (14.7%) excluding osseous metastasis at the last follow-up.

Hormonal receptor mutation status of primary carcinoma

**Table 4.** The results of tissue microarrays

Variables	Value
ER receptor	
Positive	25 (73.5%)
Negative	9 (26.5%)
HER2 receptor	
Positive	10 (29.4%)
Negative	24 (70.6%)
PR receptor	
Positive	18 (52.9%)
Negative	16 (47.1%)
Triple negative	3 (8.8%)
ER negative and HER2 positive	3 (8.8%)

ER: estrogen, HER2: human epidermal growth factor 2, PR: progesterone.



**Fig. 2.** Kaplan-Meier survival analysis of breast cancer patients with osseous metastasis after surgery.

is 25 cases (73.5%) of ER positive, 10 cases of HER2 positive (29.4%), 3 cases of Triple negative (8.8%), ER was negative while HER2 was positive in 3 cases (8.8%). PR positive was 18 cases (52.9%) (Table 4). The average survival period of triple negative patients was 13 months (8-19). It took an average of 30 months (0-140) for osseous metastasis to be detected from the time of primary carcinoma diagnosis. Osseous metastasis was found at an average of 29 months in triple negative cases, while at 57 months in other cases. There was, however, no statistical significance due to the short follow-up period and few cases.

At the last follow-up, all patients died, and mean survival time was 15.5 months (4-36) and median survival time was 10 months after orthopedic surgery. The 1-year postoperative survival rate was 47.1%, and the 2-year postoperative survival rate was 20.6% (Fig. 2).

## DISCUSSION

The numbers of newly diagnosed cancer cases and cancer-related deaths in 2017, in the Korea were 232,255 and 78,863, respectively. Although overall cancer incidence and mortality have declined since 2011 and 2002, respectively, some cancers, such as breast and prostate cancer, demonstrate increasing trends with respect to both incidence and mortality [4]. The frequency of osseous metastasis is 5% at the time of primary diagnosis [10,11], however, osseous metastasis are found in one third of patients with recurrent disease [12].

According to Kelly et al. [13], 257 patients were enrolled in their study for metastatic disease of the long bones. Of the 257 patients, femoral metastasis was the highest as 182 cases. The revision rate for the operative intervention was 3%, however, in-hospital mortality was 14%. They insisted that the mortality rate does seem high, but the procedures were undertaken as palliative interventions and as part of a multipart of the patient's final care. They assumed that overall fixation methods appeared durable, so that, the high mortality rate may reflect delay in seeking orthopedic opinion.

Recently, there was a study to identify prognostic variables associated with survival in a large cohort of breast cancer patients after surgical treatment of osseous metastasis [5]. The study identified 301 individual patients who underwent 355 surgical procedures. The median age at the first surgical procedure was 61 (52-70) years. Approximately half of the patients had multiple skeletal metastases at surgery and most patients presented with complete pathological fractures. The femur was the most common site of surgery, accounting for 190 procedures (54%). The cumulative 1-, 2-, and 5-year survival rates after surgery were 45%, 27%, and 8%, respectively. At the end of the study, 90% of the patients had died (median follow-up time 1 year). The overall complication rate was 25%. The re-operation rate was 14%. The most common reason for re-operation was implant failure. They revealed an increased risk of death after surgery for over 60 years of age and low hemoglobin levels. According to the clinical analysis of patients with skeletal metastasis of lung cancer, also, patients who survived longer were less than 60 years old [14]. The older age was not seen by others [15,16], however, low hemoglobin has been shown in patients with other primary tumors [15,17].

As a result of studies on the clinical characteristics of breast cancer [7], it was known that other organ metastasis are found on average 30 months after breast cancer diagnosis, and within 5 years after diagnosis of primary cancer, 75.8% of other organ metastases are found. In the correlation analysis of hormonal receptor mutation status for breast cancer metastasis pattern, it was reported that median overall survival of patients with both ER and HER2 negative is significantly shorter than that of patients with ER negative and HER2 positive or ER positive, 27 and 52, 76 or 79, respectively. In recent study while the incidence of osseous metastasis was significantly higher in HR positive and HER2 positive than in patients with different subtypes [18], patients with a triple-negative subtype were, most likely to develop visceral metastases rather than osseous metastasis [18,19].

Some studies suggested that female breast cancer survival may be associated with different metastasis patterns [20-22]. Errani et al. reported that breast cancer patients with lungs, the first site of distant metastasis, had the highest survival rate (58.5 months) compared to bone (44.4 months), liver (36.7 months), or brain (7.35 months) with first metastasis confirmed [21]. The 5-year survival rate was, however, significantly increased in patients with bone metastases compared to other metastases in other studies [21]. Cleeland et al. have shown that patients with bone metastasis have the best prognosis and brain metastasis is the most aggressive subgroup in their study [19]. The clinical treatment of osseous metastasis from breast cancer is essentially aimed at palliating pain, maintaining function and preventing skeletal-related events [23-25]. Systemic therapies that block osteoclast activity, including bisphosphonates (zoledronic acid) and receptor activator for nuclear factor- $\kappa$ B ligand (RANKL) inhibitors (denosumab), can reduce the incidence of SREs [26,27]. The recent development of remarkable chemotherapy/immunotherapy and supportive therapies has caused the survival time in patients with breast cancer to dramatically increase, and interest in skeletal metastasis of breast cancer has increased [28]. In other words, breast cancer patients will survive longer and inhibited SREs by the use of bisphosphonates and RANKL inhibitors, advanced chemotherapy including immunotherapy.

The number of long bone metastasis is increasing in breast cancer patients, and mutation status of hormone

receptor plays a very important role in prognosis. It is often necessary, also, to perform surgery under general anesthesia multiple times on the other part of the same patient. Orthopedic surgery should be considered depending on the condition, after careful evaluation of the patients with osseous metastasis due to breast cancer.

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## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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