

Bone Fracture in Breast Cancer Patients with Isolated Bone Metastasis*

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Rezumat

Fracturi osoase la bolnavii de cancer mamar cu metastaze osoase izolate

Scop: Să analizăm incidența fracturilor osoase la pacientele cu cancer mamar cu metastaze osoase izolate și efectele acestora asupra supraviețuirii. Am încercat să găsim un răspuns la întrebarea: "Putem prezice dezvoltarea fracturilor osoase?"

Metode: Între 1993-2006, 139 de paciente cu neoplazie mamară cu metastaze osoase izolate au fost examinate. Pacientele au fost distribuite în două grupuri în funcție de dezvoltarea de fracturi osoase pe os patologic.

Rezultate: 41 de paciente (29.5%) au dezvoltat fracturi în până la 41 de luni de urmărire. Localizările fracturilor pe os patologic au fost: vertebrale la 26 de paciente (63.4%), femurale la 11 paciente (26.8%), și fractură de șold la 4 paciente (9.8%). Frecvența fracturilor la paciente hormon sensibile și hormon rezistente a fost de 31.2%, respectiv 14.3%. Rata fracturilor la 13 paciente triplu negative și non-triplu negative a fost de 7.7%, respectiv 31.4%, ($p=0.07$). Valori crescute ale CA 15-3 la momentul apariției metastazelor la pacientele cu și fără fracturi au apărut în proporții de 68.4%, respectiv 61.1%. Riscul de fractură a fost de asemenea mai crescut la pacientele Her2-neu pozitive (38.7% vs. 26.5%). În timp ce incidența fracturilor în asociere cu unul din factorii menționați mai sus a

fost de 22.2%, aceasta a crescut la 36.1% în prezența a doi sau 3 factori ($p=0.13$). Supraviețuirea medie a pacienților cu și fără fracturi a fost de 48, respectiv 39 de luni ($p=0.65$).

Concluzie: Sensibilitatea hormonală, nivelul crescut de CA 15-3 și statusul Her2-neu pozitiv sunt factori de risc slab pentru apariția fracturilor osoase. Supraviețuirea nu a fost diferită la pacientele cu fracturi osoase față de cele fără.

Cuvinte cheie: cancer mamar, fractură osoasă, metastaze osoase, evenimente scheletale, supraviețuire

Abstract

Aim: To analyse the incidence of bone fracture of breast cancer patients with isolated bone metastasis and its effect on survival. We tried to find an answer to the question of "Can the development of bone fracture be predicted?"

Methods: Between 1993-2006, 139 breast cancer patients with isolated bone metastasis were examined. Patients were divided into two groups depending on the development of pathologic bone fracture.

Results: Fractures were developed in 41 patients (29.5%) within 41 months of follow-up. The locations of pathologic bone fracture were vertebral fracture in 26 patients (63.4%), femur fracture in 11 patients (26.8%), and hip fracture in four patients (9.8%). Fracture rates in hormone sensitive and resistant patients were 31.2% and 14.3%, respectively. The fracture rates in 13 triple negative and non triple negative patients were 7.7% and 31.4%, respectively ($p=0.07$). High CA 15-3 levels at the time of metastasis in patients with and without fractures were 68.4% and 61.1%, respectively. The risk for fracture was also high in Her2-neu positive patients

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(38.7% vs. 26.5%). While the incidence of fracture with the presence of one factor mentioned above was 22.2%, it was increased to 36.1% in the presence of two or three factors ($p=0.13$). Median survivals of the patients with and without fractures were 48 and 39 months, respectively ($p=0.65$).

Conclusion: Hormone sensitivity, high CA 15-3 levels and positive Her2-neu status are slight risk factors for bone fractures. Survival was not different in patients with or without bone fractures.

Key words: breast carcinoma, bone fracture, bone metastases, skeletal related events, survival

Introduction

Breast cancer is the most common cancer of women. Globally, it accounted for 1.15 million incident cases in 2002, while 2.7 million new cases are projected for 2030 (1). At the time of diagnosis of breast cancer approximately, 5-6% of women present with distant spread to bone representing the most common site of metastatic lesions (2,3). In the advanced stage of breast cancer, 65-75% of patients eventually develop bone metastases (4,5).

Breast cancer cells arriving at bone tissues mount supportive microenvironment by recruiting and modulating activity of several host tissue cell types including specialized bone cells: osteoblasts and osteoclasts. Pathologically activated osteoclasts produce osteolytic lesions (6). Breast carcinoma with metastases confined to the bone is generally regarded as an indolent disease, bone secondaries usually present with bone pain and may be complicated with skeletal related events (SREs) such as pathological fractures, cord compression, bone marrow infiltration, or hypercalcemia of malignancy (7). Patients with bone metastasis experience an average of 3-4 SREs every year in the absence of bisphosphonate therapy (8). However, the risk of experiencing subsequent SREs increases approximately 2-fold after the first incident; therefore, SREs usually occur in clusters and become more frequent as the disease progresses (4). Skeletal morbidity also undermines patients' quality of life and their ability to function in daily living, and fractures have been associated with significantly reduced survival (9).

The aim of the present study was to analyse the incidence of bone fracture in breast cancer patients with isolated bone metastasis and its effect on survival. We tried to find the answer to the question of "Can the development of bone fracture be predicted?"

Patients and Methods

Study Design

Between January 1993 and December 2006, 139 consecutive female breast cancer patients with isolated bone metastases treated and followed from the development of bone metastases

until the death, or until March 2013, whichever happened first, at Ankara Oncology Education and Research Hospital, were reviewed. Medical records and imaging procedures were reviewed and the tumor characteristics, treatment of the primary tumor or metastatic disease, and survival were analysed. Unilateral breast cancer patients without any synchronous second primary cancer were included in the study. Forty-four patients with skeletal metastasis at the time of diagnosis and 95 patients (68.3%) with the metastasis developed during the follow-up period were selected. Bone metastases were diagnosed by imaging studies. Histopathological bone examination was only obtained from the patients who underwent surgery for patho-logical bone fractures. Patients were divided into two groups depending on the development of pathologic bone fracture. Patients irradiated with the suspicion of compression fractures were not defined as bone fracture. The groups were compared with respect to age, menopausal status, the time for the bone metastasis, histologic type, serum cancer antigen 15-3 (CA 15-3) levels, the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her-2/neu) expression. Additionally, the time from the diagnosis of bone metastases to death in deceased patients and follow-up period in living patients were also compared. The effect of bone fracture on overall survival was also evaluated. The data were collected retrospectively and the study was approved by our institutional ethical committee.

Definition of risk factors for skeletal morbidity

Histological classification of breast tumor was performed according to the WHO classification. The values for tumor marker (serum CA 15-3) when osseous metastasis was diagnosed were classified as: below, within or above the reference value. The reference value for the upper limit was 35 U/ml. The status of ER, PR and HER-2/neu proteins were examined by immunohistochemistry. Estrogen and progesterone receptor status were categorized as positive when $\geq 10\%$ of tumor cells expressed staining. HER-2/neu protein expression was evaluated on staining pattern (0, 1+, 2+, and 3+) and 3+ values were accepted as positive. Furthermore, for cases with 2+ HER-2/neu expression, 2+ was accepted as positive if fluorescence in situ hybridization or silver enhanced in situ hybridization was positive.

Systemic treatment after the diagnosis of isolated bone metastases

Systemic hormonal and/or cytotoxic therapies were given to the patients. Hormonal therapy was used alone in 22 (53.6%) patients with fracture and 57 (58.2%) patients without fracture. Tamoxifen for premenopausal patients and tamoxifen or aromatase inhibitors for postmenopausal patients were preferred. Chemotherapy alone was used in five (12.2%) patients in the fracture group and 13 (13.3%) patients in the non-fracture group. The remaining 42 patients received both chemotherapy and hormonal therapy (36.6% and 27.6% in fracture and non-fracture groups, respectively). Antracycline, and/or taxane-

containing regimens were preferred. First-line trastuzumab was used only in two HER-2/neu overexpressed patients. All patients received systemic bisphosphonates. Zoledronate (4 mg, intravenous, per month) was given to 104 patients and the remainder were given 1600 mg oral clodronate. One hundred and eight patients required palliative radiotherapy at a time during the course of the disease.

Follow-up

Bone scanning was used for the diagnosis of skeletal metastasis; it was initially performed before the surgery for staging purposes. The follow-up protocol after the diagnosis of skeletal event was as follows: the patients visited at hospital and performed a physical examination and laboratory tests, including CA 15-3, liver function test, complete blood count every three to six months and chest radiography, abdominal ultrasonography and mammography annually. Patients who were given adjuvant therapy were followed up more frequently. Bone scans were repeated if the physicians suspected the presence of new skeletal metastasis or wanted to evaluate the response to treatment. In the presence of positive or equivocal bone scans, other imaging techniques including X-ray, computed tomography and magnetic resonance imaging were also used to confirm the diagnosis.

Statistical analyses

Chi-square or Fisher's exact tests were used to compare the distribution of demographic and tumor-related characteristics between the groups. The difference in age between two groups was tested by using student-t test. Survival was defined either as the time from the diagnosis of isolated bone metastases until death or last follow-up. Kaplan-Meier curves for overall survival was estimated by the development of fracture and compared by using the log rank test. These analyses were used to calculate the hazard ratios and 95% confidence intervals. P values < .05 were considered as statistically significant. All analyses were performed by using SPSS software (version 16.0; SPSS Inc, Chicago, IL).

Results

The distribution of histologies reported was as follows; invasive ductal carcinoma in 120 patients (86.3%), invasive lobular carcinoma in 15 patients (10.8%), invasive ductal and lobular carcinoma in 3 patients (2.2%) and mucinous carcinoma in one patient (0.7%). Synchronous bone metastasis at the time of diagnosis was detected in 31.7% of patients. Metachronous bone metastases developed at a median of 35 months (range, 9-204 months) after surgery for the primary tumor in 95 patients. Median age at the time of diagnosis of bone metastases was 50 years (range, 23-81 years). Fractures were developed by 41 out of 139 patients (29.5%) within a median follow-up of 41 months (range, 8-152 months). Median ages of the patients with and without fracture were 54 and 49, respectively ($p=0.67$). The distributions of pathologic bone fracture were as

follows: vertebra in 26 patients (63.4%), femur in 11 patients (26.8%), and hip in four patients (9.8%). The median period needed for the development of bone fracture from the diagnosis of skeletal metastasis was 12 months (0-72 months). Breast cancer was diagnosed as the primary site in 9 patients by using histological specimens obtained from metastatic sites (4 vertebra, 3 femur and 2 hip fractures).

The results of the comparison in breast cancer patients with bone metastasis with respect to the development of bone fracture are shown in Table 1. High serum CA 15-3 levels detected at the diagnosis of metastasis in patients with and without fractures were 68.4% and 61.1%, respectively. Fracture rates in hormone sensitive and resistant patients were 31.2% and 14.3%, respectively. The fracture rates in 13 triple negative and non triple negative patients were 7.7% and 31.4%, respectively ($p=0.07$). Fracture risk was also higher in Her2-neu positive patients (38.7% vs. 26.5%). While the incidence of fracture in the presence of one of the factors mentioned above was 22.2%, it was increased to 36.1% in the presence of two or three factors ($p=0.13$).

Figure 1 shows Kaplan Meier curves for overall survival in patients with and without pathologic fracture. Median survival of the patients with and without fractures was 48 and 39 months, respectively ($p=0.65$). For dead patients ($n=119$), the median time from the diagnosis of bone metastases to death was 48 and 40 months ($p=0.42$) with respect to the presence or absence of fracture. At the end of the study period, 20 patients were still alive (14 patients without fracture and 6 patients with fracture, $p=0.95$).

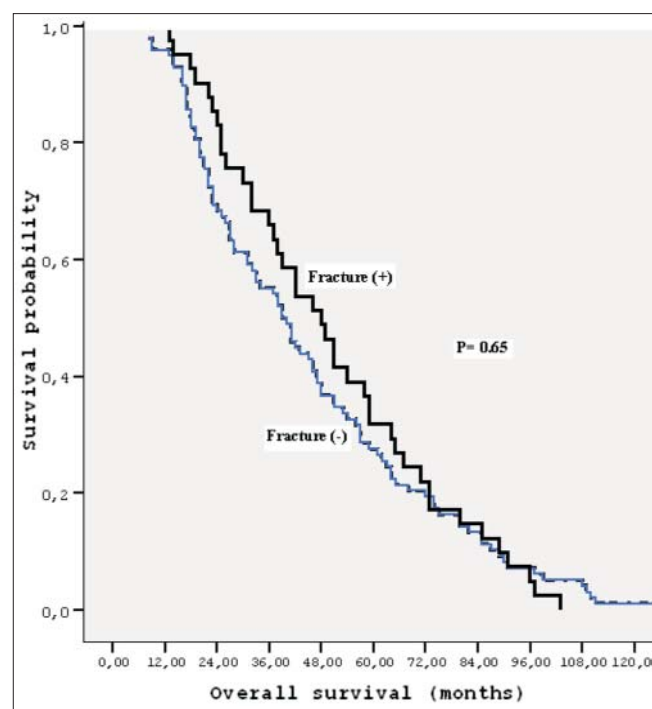


Figure 1. Kaplan-Meier curves for overall survival in patients with and without pathologic fracture

Table 1. The comparison of results for breast cancer patients with bone metastasis according to development of bone fracture

		Fracture (+) group no=41 pts	Fracture (-) group no=98 pts	P
Age at diagnosis of bone metastases	Median years (min-max)	54(23-74)	49(26-81)	0.67
Menopausal status	Premenopausal	15(36.6%)	41(41.8%)	0.56
	Postmenopausal	26(63.4%)	57(58.2%)	
Bone metastasis development time	Synchronous	14(34.1%)	30(30.6%)	0.68
	Metachronous	27(65.9%)	68(69.4%)	
Ca15-3	Normal	12(29.3%)	35(35.7%)	0.72
	High	26(63.4%)	55(56.1%)	
	Unknown	3(7.3%)	8(8.2%)	
Estrogen receptor	Negative	5(12.2%)	20(20.4%)	0.50
	Positive	34(82.9%)	73(74.5%)	
	Unknown	2(4.9%)	5(5.1%)	
Progesterone receptor	Negative	11(26.8%)	29(29.6%)	0.93
	Positive	24(58.6%)	54(55.1%)	
	Unknown	6(14.6%)	15(15.3%)	
Hormone sensitivity	No	2(4.9%)	12(12.2%)	0.18
	Yes	39(95.1%)	86(87.8%)	
Her-2/neu status	Negative	22(53.7%)	61(62.2%)	0.43
	Positive	12(29.3%)	19(19.4%)	
	Unknown	7(17.1%)	18(18.4%)	

Discussion

The most frequent skeletal related events which occur in patients with advanced breast cancer are radiation to the bone, pathological fractures, bone surgery related to bone metastasis, and spinal cord compression. The increased expression of receptor activator of nuclear factor in the proximity of the tumor leads to the proliferation of osteoclasts and promotes their survival, and results in osteolytic lesions (10). In a study with 35,912 breast cancer patients SREs were developed in 46.4% patients within median 0.7 years of follow up. The incidence of bone metastases was highest in the first year after the primary breast cancer diagnosis, particularly in patients with advanced breast cancer at diagnosis. Similarly, the incidence of the first SRE was highest in the first year after the diagnosis of bone metastasis (11). In another study, the cumulative incidence of SREs was 38.5% at 1 year and 51.7% at 5 years. In follow-up data over 24 months, the incidence of any skeletal complication in patients treated with pamidronate was 64%; of radiation to bone, 43%; of pathologic fracture, 52%; of surgery to bone, 11%; of spinal cord compression, 3%; and of hypercalcemia, 13% (12). This retrospective study showed that breast cancer patients with a history of previous skeletal complication had a higher risk of subsequent SREs: the risk of subsequent events was twice as high (68%) in patients who had suffered at least one SRE before inclusion in the study compared to patients with no previous SRE (13). In our series, fractures developed in 29.5% patients and palliative radiotherapy to control bone pain was needed in 77.7% patients within median 41 months of follow-up. The median time from the diagnosis of skeletal metastasis to the bone fracture was 12 months.

The prognostic indicators for disease progression in patients with metastatic bone disease are currently available. The history of osteoporosis and the presence of bone-only

metastases increase the risk of SRE (14). Multivariate analyses from a phase III study identified that age over 60 years, pain score greater than 3 on the Brief Pain Inventory, history of a SRE before study entry, and predominantly osteolytic lesions are the base-line predictors of the first SRE (15). Elevated baseline levels of C-telopeptides and N-terminal telopeptide of type I collagen-a marker of bone resorption- and the number of bone lesions have also been found to influence the rate of skeletal complications (16,17).

Breast cancer is divided into two distinctive molecular patterns according to their transcriptional profile. Cancers with relatively good-prognosis show a gene expression reminiscent of a luminal or normal-like breast pattern, including positive expression of estrogen receptor. More aggressive cancers usually demonstrate a basal-like phenotype or one that is characterized by the expression of human epidermal growth factor receptor 2 (18,19). Smid et al. (20) have shown that around two-thirds of bone relapses occurred in luminal (ER+) cases while only 7% belonged to basal tumors. In a study from Canada, the pattern of metastatic disease in 180 patients with triple-negative (i.e., estrogen receptor-negative, progesterone receptor-negative and HER2/neu-negative) breast cancer compared to other subgroups of breast cancer. The risk of bone metastases within 10 years of diagnosis was 7%-9% for all subgroups (21). In their study, the fracture rate was 31.2% and 14.3% in patients with hormone sensitivity and resistance, respectively. In our series, the fracture rates in 13 triple negative and non-triple negative patients were 7.7% and 31.4%, respectively ($p=0.07$). Similarly, it was stated that bone (including bone marrow) is the most common site of metastasis in advanced breast cancer for all subtypes except basal-like cancers (22). However, no validated algorithm to predict SRE risk in a patient with bone metastases is still available (23).

The most common metastatic sites affected in decreasing order of frequency were the spine, pelvis, skull, ribs and femur

(24). In some other series, the most common locations of bone metastases were the spine and the proximal femur, humerus, pelvis and ribs (25). In general, the proximal parts of the long bones are the most frequently involved sites (26) and the proximal femur is the most common metastatic site requiring surgical intervention. In our series, the most frequent locations of pathologic bone fractures were the vertebrae (63.4%), femur (26.8%), and hip (9.8%). Although the location of skeletal lesions affected the cumulative mean incidence of SREs, it did not appear to affect the survival (27).

After the initial diagnosis of bone metastasis, the median survival for breast cancer patients is approximately 18 to 26 months (28). Age and the type of orthopedic surgery had no impact on survival in multivariate analysis (25). Positive progesterone-receptor, pain score and prior radiotherapy were described as the variables correlated significantly with overall survival (27). In our series, the median survival of the patients with and without fractures was 48 and 39 months, respectively ($p = 0.65$). In another series, the median survival of the patients without fractures in comparison to patients with fractures was significantly longer (25 months vs. 10 months), which should encourage to perform orthopedic surgery in an earlier stage of disease to prevent fractures (25). With this approach, overall treatment success has become excellent: 89% of patients survive at least 5 years from the initial diagnosis (29).

Can SERs induced by bone metastases be prevented and can the progression free and overall survivals be increased? The questions above should be answered in this group of patients. Improved therapeutical measures can prolong the survival. Different therapeutic options are available to treat symptomatic bone metastases, such as analgesics and systemic chemotherapy for pain relief as well as radiotherapy and prophylactic stabilization for long term prevention of fractures (30). Bisphosphonates (pamidronate, zoledronate, ibandronate) induce apoptotic processes in the osteoclasts and reduce the risk of SREs by 17%. Bisphosphonates neither appear to reduce the incidence of SREs in women without bone metastases, nor improve disease-free survival or overall survival (31). Denosumab is the first antibody approved to use for prevention of skeletal complications in patients with bone metastases caused by solid tumors. Percutaneous image-guided radiofrequency ablation and stereotactic radio surgery are other new treatment modalities, but their exact role is still investigated.

Conclusion

The survival of patients with bone metastasis is increasing day by day. Despite the progress in treatment modalities, SREs can be seen in the first year of metastasis. Hormone sensitivity, high CA 15-3 levels and positive Her2-neu status are the risk factors for bone fractures. Both the bone metastasis and pathological fractures are seen less in triple negative patients. The answer to the question of "Can the development of bone fracture and fractures be prevented?" will be possible to obtain with the definition of the pathophysiology of metastasis and molecular patterns in triple negative and non-triple negative breast

cancer patients. Survival is not different in patients with or without bone fractures.

Conflict of interest statement

All authors have declared no conflict of interest.

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