

A cross-sectional survey of the diagnosis and management of bone metastasis in breast cancer patients in Turkey

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Abstract

Purpose This study aimed to report the practice of managing breast cancer with bone metastasis in Turkey and to determine the adherence to the British Association of Surgical Oncology (BASO) guidelines.

Methods This multicenter, cross-sectional epidemiological survey was conducted in 38 centers across Turkey. Data from 1,026 breast cancer patients with bone metastases (mean age 54.0 ± 11.9 years) were analyzed.

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Results Over 30 % of patients had a diagnosis of metastatic breast cancer (stage IV) at the time of primary diagnosis. The imaging modalities used for diagnosing bone metastases were bone scintigraphy (57.8 %), radiography (22.8 %), and bone survey (4.4 %). Tumor markers were detected in 94.9 %, and markers of bone metabolism were measured in 90.4 % of patients. A total of 3.5 % of patients underwent surgery for bone metastasis, 26.4 % underwent palliative chemotherapy (most commonly docetaxel+capecitabine), and 56.5 % endured radiotherapy. Most patients (96 %) also received bisphosphonate. Radiography, bone scintigraphy, and CT were the main imaging tools used for postoperative follow-up of bone metastasis. Our results were >95 % in line with the BASO guidelines for the management of bone metastasis, except that interventional procedures, such as biopsy, were applied less frequently in our survey.

Conclusions The diagnosis and management practices of breast cancer with bone metastasis in Turkey were generally compatible with international guidelines. However, the awareness and knowledge of physicians on the current guidelines should be increased, and equipment for the appropriate interventional procedures should be provided in every clinic to obtain optimal and standard management of bone metastases.

Keywords Breast neoplasms · Neoplasm metastasis · Bones · Disease management · Epidemiology

Introduction

Breast cancer is the most common malignancy in females in Turkey and worldwide. According to the Turkish Ministry of Health statistics, the estimated incidence of breast cancer was 41.6 per 100,000 in 2008, which has increased gradually over the last 5 years [1]. 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 [2–4].

In spite of the recent advances in our understanding of the pathology of breast cancer and bone metastasis and in cancer therapy, the management of breast cancer patients with bone metastasis remains complex and challenging. However, the early diagnosis of metastatic breast cancer and optimization of systemic therapies in combination with optimal local treatment can increase patient survival [5–7]. Therefore, the presence and clinical implementation of the practical guidelines are crucial for the effective management of metastatic breast cancer. Although several international and national guidelines exist for early stage breast cancer [8–10], there are a limited number of international guidelines for metastatic breast cancer, particularly for the management of bone metastasis from

breast cancer. One example is the British Association of Surgical Oncology (BASO) guidelines [11, 12].

The current management practices for breast cancer patients with bone metastasis in Turkey have not been assessed in a comprehensive epidemiological study. Furthermore, there are no widely accepted standardized national guidelines that are followed. Data identifying the current clinical approach to these patients in daily practice and the rate of compliance to international guidelines would provide a basis for developing national guidelines and policies for the management of breast cancer patients with bone metastasis.

In this study, we aimed to report the current practice for the diagnosis and management of breast cancer patients with bone metastasis in Turkey and to determine the compatibility of these practices with the BASO guidelines for the management of metastatic bone disease in breast cancer [11].

Materials and methods

Study design and population

This was a multicenter, cross-sectional epidemiological survey performed in cancer patients with bone metastasis from 38 centers across Turkey between December 2010 and June 2011. Patients >18 years old with histologically diagnosed breast cancer, radiologically proven bone metastasis, and a life expectancy >6 months were enrolled in the study. Pregnant or nursing patients were excluded.

The study was approved by the İnönü University Medical Faculty Ethics Committee and was conducted in accordance with the Helsinki Declaration and local requirements. All patients provided informed consent before participation in the study.

Study procedures

Patients were evaluated for the practical approaches used for the diagnosis, treatment, and follow-up of bone metastasis in each center. The following information was recorded for evaluation: physical examination methods, radiological tools, interventional techniques, pathology and laboratory methods used for diagnosis, surgical approaches, chemotherapy, radiotherapy, bisphosphonates, supportive treatment, and other treatment regimens. Follow-up data were collected from three consecutive visits after the initial therapy. The duration of follow-up, the frequency of visits, the methods used for bone metastasis follow-up, and any changes (with reasons) to the treatment plan were recorded. We then determined the adherence to the BASO guidelines [11] separately for four aspects of care for metastatic bone disease: diagnosis, staging, treatment, and assessment of the response to treatment.

Statistical analysis

Sample size calculation was based on the hypothesis that the management practices of bone metastasis in breast cancer patients in Turkey showed 100 % adherence to the BASO guidelines. To determine this adherence rate with 0.2 % error, the sample size was calculated as 1,250 patients when the type 1 error was 0.05, type 2 error was 0.10 (power 90 %), and the dropout rate was 20 %.

Study data were summarized with descriptive statistics (such as frequency, percentage, mean, standard deviation, and range). Categorical variables were analyzed using chi-square and Fisher's exact tests, and ordinal variables were analyzed using the Mantel-Haenszel test. For continuous variables, the paired sample *t* test and Wilcoxon test were performed for normally and non-normally distributed data, respectively. The statistical level of significance was defined as $p < 0.05$.

Results

Study population

A total of 1,038 patients were enrolled in the study. Twelve patients were excluded from the analysis due to insufficient data ($n=10$) or not meeting the study selection criteria ($n=2$). Therefore, the final analysis was performed on data from 1,026 patients (mean age 54.0 ± 11.9 , range 22.4–87.2 years). Of these patients, 801 (78.1 %) were premenopausal, and 225 (21.9 %) were postmenopausal. The most common histological type of breast cancer was ductal carcinoma ($n=845$, 82.4 %).

Breast cancer history

The most common reasons for the referral of patients to the attending physician were masses detected on self-examination ($n=505$, 49.2 %), on physical examination ($n=215$, 21.0 %), and on radiological evaluation ($n=78$, 7.6 %), as well as bone pain ($n=61$, 6.9 %). At diagnosis, the primary breast tumor was >2 cm (\geq T2 stage) in 70.1 % of patients, had spread to at least one axillary lymph node or internal mammary lymph node (N1 stage and over) in 50.6 %, and metastasized to distant organs in 33.3 % of patients. All patients had bone metastasis that was diagnosed 1.3 ± 1.8 years before enrollment into the present survey (Table 1).

Diagnosis of bone metastasis

The most common imaging modality for diagnosing bone metastasis was bone scintigraphy, followed by direct radiography. Bone biopsy and fine-needle aspiration biopsy were

Table 1 Breast cancer diagnosis history of study patients ($n=1,026$)

		Mean \pm SD (range) or <i>n</i> (%)
Time since diagnosis of breast cancer (years)		4.1 \pm 4.0 (0.0–22.7)
Time since diagnosis of bone metastasis (years)		1.3 \pm 1.8 (0.0–13.7)
TNM staging at diagnosis		
T (primary tumor)	T0	1 (0.1 %)
	T1	140 (13.6 %)
	T2	457 (44.5 %)
	T3	147 (14.3 %)
	T4	116 (11.3 %)
N (lymph nodes)	N0	120 (11.7 %)
	N1	218 (21.2 %)
	N2	202 (19.7 %)
	N3	101 (9.8 %)
M (metastasis)	M0	612 (59.6 %)
	M1	342 (33.3 %)
Stage grouping at diagnosis		
	Stage I	44 (4.3 %)
	Stage II	267 (26 %)
	Stage III	331 (32.3 %)
	Stage IV	346 (33.7 %)

SD standard deviation

used as the diagnostic methods in only 46 patients (4.5 %). Tumor markers were detected in 974 patients (94.9 %), and bone metabolism markers (e.g., AP, Ca^{2+}) were measured in 927 (90.4 %). The use of diagnostic tests for bone metastasis is summarized in Table 2.

Treatment of bone metastasis

Of the 1,026 patients, 36 (3.5 %) underwent surgery, 26.4 % palliative chemotherapy, 56.5 % radiotherapy, and 10.4 % hormonal therapy for bone metastasis. Docetaxel+capecitabine was the most common regimen for palliative chemotherapy of bone metastasis. Most patients (96 %) received bisphosphonate, typically ibandronic acid and zoledronic acid (Table 3).

Follow-up after breast tumor surgery

The bone metastases were followed up postoperatively with radiological modalities and biochemical testing. The major imaging tools used were radiography, bone scintigraphy, and CT (Table 4).

Compatibility of survey results with the BASO guidelines

Our results were >95 % consistent with the BASO guidelines for the management of metastatic bone disease in breast cancer in the UK, for the use of radiological methods and laboratory tests for the diagnosis and staging of bone

Table 2 Tests for diagnosis and staging evaluation of bone metastasis

	Number (%)
Imaging modalities for diagnosis	
Bone scintigraphy	896 (87.3)
Radiography	453 (44.2)
MRI	380 (37.0)
CT	338 (32.9)
Bone survey ^a	124 (12.1)
Others	172 (16.8)
Interventional procedures for diagnosis	
Bone biopsy	36 (3.5)
Fine-needle aspiration biopsy	10 (1.0)
Others	53 (5.2)
None	932 (90.8)
Biochemical tests for diagnosis	
Tumor markers (CEA, Ca15.3)	974 (94.9)
Markers of bone metabolism	927 (90.4)
Markers of bone resorption	158 (15.4)
Markers of bone remodeling	134 (13.1)
Others	22 (2.1)
Imaging modalities for staging	
Bone scintigraphy	868 (84.6)
CT	685 (66.8)
Abdominal US	553 (53.9)
Radiography	493 (48.1)
MRI	362 (35.3)
Others	145 (14.1)
Biochemical tests for staging	
Liver function tests	1,009 (98.3)
Renal function tests	994 (96.9)
Complete blood count	980 (95.5)
Markers of bone metabolism	921 (89.8)
Others	33 (3.2)

^a Bone survey is a series of X-ray of the major bones (axial or cortical bones) in the body

metastasis, and for the use of chemotherapy and hormonal therapy for bone metastasis. In contrast, interventional procedures, such as biopsy, for diagnosing bone metastasis and surgical treatment were applied to a much lesser extent in our survey than recommended by the BASO guidelines (Table 5).

Discussion

In this large, cross-sectional, epidemiological survey, we analyzed the current clinical practice for the diagnosis and management of breast cancer patients with bone metastasis in Turkey. Our study population included breast cancer patients with bone metastasis; ~30 % had bone metastasis at initial

Table 3 Management of bone metastasis

Treatment of bone metastasis	Number (%)
Surgery	
Stabilization and reconstruction of pathologic fractures	20 (55.6)
Prophylactic fixation of metastatic region with fracture risk	9 (25.0)
Decompression of vertebral fractures	2 (5.6)
Others	5 (13.9)
Palliative chemotherapy	
Docetaxel+capecitabine	36 (13.3)
Docetaxel+trastuzumab	29 (10.7)
Docetaxel	25 (9.2)
Others	181 (66.7)
Radiotherapy	
Hormonal therapy	107 (10.4)
Letrozole	36 (33.6)
Anastrozole	21 (19.6)
Exemestane	14 (13.1)
Fulvestrant	7 (6.5)
Tamoxifen	7 (6.5)
Goserelin acetate	2 (1.9)
Combination regimens	20 (18.7)
Other treatment (bisphosphonate)	
Ibandronic acid	567 (57.6)
Zoledronic acid	266 (27.0)
Zoledronic acid+ibandronic acid	111 (11.3)
Others	41 (4.2)

Table 4 Follow-up modalities for bone metastasis after breast tumor surgery

	Visit 2 n (%)	Visit 3 n (%)	Visit 4 n (%)
Radiology			
Radiography	109 (37.2)	79 (31.5)	95 (35.3)
Bone scintigraphy	114 (38.9)	84 (33.5)	85 (31.6)
CT	84 (28.7)	92 (36.7)	96 (35.7)
MRI	34 (11.6)	41 (16.3)	40 (14.9)
Bone survey ^a	13 (4.4)	11 (4.4)	12 (4.5)
Others	37 (12.6)	31 (12.4)	40 (14.9)
Laboratory			
Complete blood count	860 (97.3)	815 (97.0)	802 (98.0)
Renal function tests	826 (93.4)	782 (93.1)	765 (93.5)
Liver function tests	811 (91.7)	773 (92.0)	764 (93.4)
Markers of bone metabolism	772 (87.3)	734 (87.4)	724 (88.5)
Tumor markers	698 (79.0)	700 (83.3)	691 (84.5)
Others	8 (0.9)	7 (0.8)	3 (0.4)

^a Bone survey is a series of X-ray of the major bones (axial or cortical bones) in the body

Table 5 Compatibility rate of the present survey results with the BASO guidelines

	Number (%)
Diagnosis of bone metastasis	
Radiology	977 (95.2)
Interventional diagnosis	36 (3.5)
Laboratory	1,010 (98.4)
Staging	
Laboratory	1,019 (99.3)
Radiology	986 (96.1)
Treatment	
Surgery	31 (3.0)
Radiotherapy	580 (56.5)
Chemotherapy or hormonal therapy	997 (97.2)
Methods to evaluate the response to bone metastasis therapy	885 (86.3)

diagnosis, and the rest were diagnosed during the course of the disease. We focused primarily on the diagnosis and treatment of bone metastasis. The findings of the present survey indicated that the practical approach to breast cancer patients with bone metastasis in Turkey was consistent with international guidelines; discrepancies are likely due to insufficient knowledge of the guidelines by physicians and to the lack of equipment at some centers.

Patient-related and disease-related factors, the incurable nature of the disease, and difficulty in implementing the available knowledge in clinical practice complicate the diagnosis and treatment of bone metastases, which cause significant mortality in breast cancer patients [13]. Therefore, bone metastasis of breast cancer is frequently late or misdiagnosed and poorly treated. Nevertheless, timely diagnosis and effective treatment increase patient survival [5–7]. To overcome the obstacles for managing breast cancer that has metastasized to the bone, several guidelines were developed. The BASO guidelines are international guidelines developed by a multidisciplinary group of specialists for the management of metastatic bone disease in breast cancer [11]. These guidelines consider all aspects of care of metastatic bone disease in breast cancer patients, including diagnosis, staging, treatment, and assessing the response to treatment. A recent consensus guideline was published following the First International Consensus Conference for Advanced Breast Cancer in 2011, which focused primarily on metastatic breast cancer and suggested a multidisciplinary approach [12].

In these guidelines, radiological, laboratory, and interventional assessments were recommended for diagnosing bone metastasis in patients with persistent and localized bone pain, depending on the level of clinical suspicion [11, 12]. In our survey, the most common modalities for diagnosing bone

metastasis were bone scintigraphy followed by radiography. Because radiological techniques give reliable results and biopsies are interventional modalities that cause patient discomfort and that are not universally available, bone biopsy and fine-needle aspiration biopsy were applied in only 3.5 % of patients. Tumor markers (CEA, Ca15.3) were detected in 94.9 % of patients as a part of routine oncologic diagnostic procedures for the origin of bone metastasis, and markers of bone metabolism were measured in 90.4 % of patients.

The treatment of bone metastasis derived from breast cancer includes antitumor endocrine and cytotoxic agents, radiotherapy, bisphosphonates, and conservative treatments [14]. The interaction between tumor cells and the bone microenvironment is the main molecular mechanism underlying bone metastasis in breast cancer [15, 16]. Novel therapies based on recent advances in molecular biology were developed recently to prevent and treat bone metastasis in breast cancer [15, 17]; however, they are not yet widely used in clinical practice.

According to the BASO guidelines, optimum treatment of metastatic bone disease should be aimed at identifying patients who are at risk of fracture and identifying prophylactic treatment [11]. Surgery should be performed as prophylactic fixation of metastatic deposits when there is a risk of fracture, for stabilization or reconstruction following pathological fracture, and for decompressing the spinal cord and nerve roots followed by stabilization of the affected vertebra. Of the patients in our survey, only 3.5 % underwent surgery for bone metastasis, compared with 56.5 % who received radiotherapy. The low rate of surgery may be due to an insufficient multidisciplinary approach, including the lack of orthopedic surgeons and neurosurgeons involved in the management of bone metastasis; this should be improved. Although the rate of radiotherapy was higher, it was still less than suggested.

In the literature, several studies have shown a survival benefit from treatment of metastatic breast cancer with chemotherapy; however, most optimum regimen to delay or prevent the development of bone metastases has not been defined [18–20]. In the current survey, 26.4 % of patients received palliative chemotherapy; the most common regimen was docetaxel in combination with capecitabine. Nevertheless, the management practices for bone metastasis in our survey were >95 % compliant with the BASO guidelines, with the exception of the interventional diagnostic and treatment procedures such as biopsy and surgery, which were applied to a much lesser extent in our survey than is recommended by the guidelines [11, 12].

Newer and more efficacious generation of bisphosphonates currently forms the gold standard for treating bone metastasis [14, 17, 21]. Bisphosphonates have antiresorptive action and reduce tumor-associated osteolysis by inhibiting osteoclast function in bone metastases. Furthermore, bisphosphonates can alleviate bone pain in patients with bone metastasis. The effectiveness of bisphosphonates in reducing pain and

increasing quality of life has been recognized in randomized clinical trials [14, 21, 22]; as such, the guidelines suggest that they be used routinely in combination with other systemic therapies in breast cancer patients with bone metastasis [12]. Consistent with the guidelines, most of the patients (96 %) in our survey received bisphosphonates, most commonly ibandronic acid and zoledronic acid. For the postoperative follow-up of bone metastasis, radiography, bone scintigraphy, and CT were three main imaging tools, consistent with the BASO guidelines [11].

In conclusion, the diagnosis and management practices of breast cancer that has metastasized to the bone in Turkey are generally compatible with international guidelines. However, the awareness and knowledge of physicians regarding the current guidelines should be enhanced, and the equipment necessary to perform interventional procedures should be provided to all clinics to achieve optimal and standard management of bone metastasis in breast cancer. A multidisciplinary approach including radiation oncologists, medical oncologists, orthopedic surgeons, neurosurgeons, and radiologists is crucial to achieve the optimum therapeutic approach for bone metastasis; such should be improved in Turkey. A national policy should be developed and implemented to provide the optimum care and to subsequently increase survival and quality of life of breast cancer patients with bone metastasis.

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Conflict of interest Co-authors, Bahadır Pekin and Fatih Ozdener, are currently staff members of Roche, Istanbul, a manufacturer of oncology drugs. Other co-authors had no conflict of interest to declare. The authors have full control of all primary data and they agree to allow the journal to review their data if requested.

References

1. Turkish Ministry of Health (2010) Health statistics year book. 28 p.- [cited 2012 Jan 30]. Available from: <http://www.saglik.gov.tr/TR/dosya/12577/h/saglikistatistikleriyilligi2010.pdf>
2. Coleman RE, Rubens RD (1987) The clinical course of bone metastases from breast cancer. *Br J Cancer* 55:61–66
3. Coleman RE (2001) Metastatic bone disease: clinical features, pathophysiology, and treatment strategies. *Cancer Treat Rev* 27:165–176
4. Theriault RL, Hortobagyi GN (1992) Bone metastasis in breast cancer. *Anticancer Drugs* 3:455–462
5. Giordano SH, Buzdar AU, Smith TL et al (2004) Is breast cancer survival improving? *Cancer* 100:44–52
6. Chia SK, Speers CH, D'yachkova Y et al (2007) The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 110: 973–979
7. Pagani O, Senkus E, Wood W et al (2010) ESO-MBC Task Force. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? *J Natl Cancer Inst* 102:456–463
8. Goldhirsch A, Wood WC, Coates AS et al (2011) Panel members. Strategies for subtypes dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. *Ann Oncol* 22:1736–1747
9. National Comprehensive Cancer Network (2012) NCCN clinical practice guidelines for breast cancer, version 1. Available from: www.nccn.org
10. Harris L, Fritsche H, Mennel R et al (2007) American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 25:5287–5312
11. British Association of Surgical Oncology Guidelines (1999) The management of metastatic bone disease in the United Kingdom. The Breast Specialty Group of the British Association of Surgical Oncology. *Eur J Surg Oncol* 25:3–23
12. Cardoso F, Costa A, Norton L et al (2012) 1st International Consensus Guidelines for advanced breast cancer (ABC 1). *Breast* 21:242–252
13. Cardoso F, Bedard PL, Winer EP, ESO-MBC Task Force et al (2009) International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. *J Natl Cancer Inst* 101:1174–1181
14. Kohno N (2008) Treatment of breast cancer with bone metastasis: bisphosphonate treatment—current and future. *Int J Clin Oncol* 13: 18–23
15. Akhtari M, Mansuri J, Newman KA, Guise TM, Seth P (2008) Biology of breast cancer bone metastasis. *Cancer Biol Ther* 7:3–9
16. Zhang Y, Ma B, Fan Q (2010) Mechanisms of breast cancer bone metastasis. *Cancer Lett* 292:1–7
17. Rose AA, Siegel PM (2010) Emerging therapeutic targets in breast cancer bone metastasis. *Future Oncol* 6:55–74
18. Fumoleau P, Largillier R, Clippe C et al (2004) Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. *Eur J Cancer* 40:536–542
19. Geels P, Eisenhauer E, Bezjak A, Zee B, Day A (2000) Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. *J Clin Oncol* 18:2395–2405
20. Ramirez AJ, Towilson KE, Leaning MS, Richards MA, Rubens RD (1998) Do patients with advanced breast cancer benefit from chemotherapy? *Br J Cancer* 78:1488–1494
21. Costa L, Major PP (2009) Effect of bisphosphonates on pain and quality of life in patients with bone metastases. *Nat Clin Pract Oncol* 6:163–174
22. Oura S, Hirai I, Yoshimasu T, Kokawa Y, Sasaki R (2003) Clinical efficacy of bisphosphonate therapy for bone metastasis from breast cancer. *Breast Cancer* 10:28–32