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

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Received: 1 October 2013 / Accepted: 9 April 2014 / Published online: 22 April 2014
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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.
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 bisphosphonates. 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 (≥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 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, Ca2+) were measured in 927 (90.4 %). The use of diagnostic tests for bone metastasis is summarized in Table 2.

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

| Time since diagnosis of breast cancer (years) | Mean±SD (range) or n (%) |
| Time since diagnosis of bone metastasis (years) | 1.3±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

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
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 diagnosis. Due to the limitations of our study, we cannot determine the exact prevalence of bone metastasis in breast cancer patients in Turkey. However, our findings suggest that there is a need for improved diagnostic and therapeutic strategies to address the high prevalence of bone metastasis in breast cancer patients. The survey also highlighted the importance of interventional procedures, such as biopsy, for diagnosing bone metastasis and surgical treatment in the management of bone metastasis. Overall, our study provides valuable insights into the clinical practice for the diagnosis and management of breast cancer patients with bone metastasis in Turkey.
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

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

| Method                        | 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 |
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.

Acknowledgments This study was financially supported by Roche, Turkey.

Conflict of interest Co-authors, Bahadir 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.

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