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Breast Cancer

Prognostic Factors in Patients with Metastatic Breast Cancer with Bone-Only Metastases

Amanda Parkes,[a] Carla L. Warneke,[b] Katherine Clifton,[a] Aydah Al-Awadhi,[a] Oluchi Oke,[a] Roberto Carmagnani Pestana,[a] Omar Alhalabi,[a] Jennifer K. Litton,[c] Gabriel N. Hortobagyi[c]

Departments of [a]Cancer Medicine, [b]Biostatistics, and [c]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

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Key Words. Breast cancer • Metastasis • Cancer of the bone • Prognostic factors

Abstract

Background. Patients with metastatic breast cancer with bone-only metastases (BOM) are a unique patient population without consensus regarding high-risk characteristics, which we sought to establish.

Methods. We identified 1,445 patients with BOM followed for at least 6 months at MD Anderson Cancer Center from January 1, 1997, to December 31, 2015.

Results. Seventy-one percent (n = 936) of the 1,325 patients with BOM with available pain characterization were symptomatic at time of BOM diagnosis. Pain was more common in patients with lytic compared with blastic or sclerotic metastases (odds ratio [OR], 1.79; 95% confidence interval [CI,] 1.26–2.53) and multiple versus single bone metastases (OR, 1.37; 95% CI, 1.03–1.83). Poorer overall survival (OS) was also noted in patients with multiple bone metastases (median OS, 4.80 years; 95% CI, 4.49–5.07) compared with single bone metastasis (median OS, 7.54 years; 95% CI, 6.28–10.10) and in patients with metastases in both the axial and appendicular skeleton (median OS, 4.58 years; 95% CI, 4.23–4.96) compared with appendicular-only (median OS, 6.78 years; 95% CI, 5.26–7.96) or axial-only metastases (median OS, 5.62 years; 95% CI, 4.81–6.69). Black/non-Hispanic patients had poorer outcomes, and patients aged 40–49 years at time of breast cancer diagnosis had significantly better OS compared with both younger and older patient groups.

Conclusion. Overall, several risk features for decreased OS were identified, including multiple bone metastases and both axial and appendicular skeleton involvement. Multiple bone metastases and lytic bone metastases were associated with increased pain. ***The Oncologist*** 2018;23:1282–1288

Implications for Practice: Patients with metastatic breast cancer and bone-only metastases (BOM) represent a poorly characterized patient subset. The ability to identify unique patient characteristics at time of BOM diagnosis associated with increased morbidity or mortality would allow for recognition of patients who would benefit from more aggressive therapy. In this study, the largest sample of patients with BOM thus far reported is characterized, highlighting several higher-risk BOM groups, including those with multiple bone metastases and bone metastases in both the axial and appendicular skeleton at time of BOM diagnosis. In addition to tailoring current practices for these high-risk patients, ongoing studies of these patients are indicated.

Introduction

Bone metastases are common in metastatic breast cancer (MBC), noted in 60%–80% of patients with MBC and representing the first site of metastatic disease in 25%–40% [1,2]. Metastases to the bone are often complicated by bone pain and skeletal-related events (SREs). SREs are defined as pathological fractures, spinal cord compression, and the need for surgery or radiotherapy to bone; however, using older definitions of SREs that also included bone pain and hypercalcemia, over 50% of patients with MBC and bone metastases have SREs [3,4].

The significant number of patients with MBC with bone metastases and subsequent SREs is particularly notable when considering impact on mobility and quality of life [5,6]. In patients with advanced cancer and symptomatic bone metastases, increased pain has been correlated with reduced quality of life [7]. Beyond this increased morbidity, bone pain from skeletal metastases in MBC has also been associated with increased mortality, with a 2010 paper by Koizumi et al. of 666 patients with skeletal metastases from MBC showing a positive association between bone

Correspondence: Amanda Parkes, M.D., 1400 Holcombe Blvd., FC11.3055, Houston, Texas 77030, USA. Telephone: 713-794-1547; e-mail: amparkes@mdanderson.org, amparkes@medicine.wisc.edu Received February 12, 2018; accepted for publication May 31, 2018; published Online First on August 17, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0085

pain at time of bone metastasis diagnosis and decreased survival compared with patients without bone pain [8].

These findings have not been well documented in patients with MBC with bone-only metastases (BOM), a patient population that has been previously shown to have increased SREs and increased need for radiation for bone pain compared with patients with MBC without disease confined to the skeleton [9,10]. Patients with BOM have previously been shown to have unique characteristics among patients with MBC, including improved survival compared with patients with MBC with nonosseous metastases [10,11]. We recently showed a median overall survival (OS) in BOM patients from breast cancer diagnosis of 8.7 years, which varied significantly by tumor subtype [12]. There have been a few BOM studies evaluating prognostic factors, including a study of 110 patients with BOM that showed number of bone metastases and bisphosphonate treatment to be associated with survival [13]; however, these studies were limited by their small sample size. Given this, methods to stratify patients with BOM regarding the probability of symptomatic disease or predicting the duration of survival are lacking.

Therefore, we aimed to describe the association between pain attributable to bone metastasis and location, number, and type of bone metastases at time of bone metastasis diagnosis in patients with MBC and BOM. We further sought to determine whether these variables were associated with differences in OS. Based on this knowledge, we hope to better define outcomes for patients with BOM using characteristics available at time of BOM diagnosis and identify subsets at increased risk for bone pain as well as decreased survival. This would allow for earlier interventions or identification for clinical trial involvement.

Materials and Methods

Patient Selection

Patients with BOM were identified as previously detailed [12]. Briefly, patients with bone as first and only site of metastasis at time of MBC diagnosis were identified using a prospectively maintained database of patients with breast cancer followed at MD Anderson Cancer Center (MDACC) from January 1, 1997, to December 31, 2015. Patients were required to have at least 6 months of follow-up at MDACC and could not have a coexisting malignant neoplastic diagnosis, and patients with BOM with a single bony metastasis were required to have biopsy-proven metastatic disease. The Institutional Review Board approved the study; informed consent requirement was waived given the retrospective study design. The study was conducted in accordance with all relevant guidelines and procedures and approved by the University of Texas MDACC ethical committee.

Patient Characteristics

Retrospective chart review identified patient demographic and clinical characteristics. Bone metastasis characteristics identified included metastasis sites, type (blastic/sclerotic, lytic, or mixed) and number at time of BOM diagnosis [12]. Single bone metastasis was defined as one bone metastatic lesion restricted to a single site. Multiple bone metastases were defined as two or more lesions, including more than one lesion in the same bone. Mixed bone metastases were defined as two or more types of bone metastases in a patient at a single point in time. Chart review identified SREs, specifically pathologic fractures, cord compression, surgery to bone, and radiation to bone. The date of last follow-up was designated as either the last patient contact noted in the electronic medical record or the date of death. The last patient contact could include both clinic visits and other forms of patient communication.

Pain Assessment

Pain and use of pain medications at time of bone metastasis diagnosis was determined through review of clinician notes. In patients without direct notation of pain status at time of BOM diagnosis, pain medication use at time of BOM diagnosis was used as a surrogate with patients on pain medications classified as symptomatic and patients not on pain medications classified as asymptomatic. Pain medication use included both nonopiate (including nonsteroidal anti-inflammatory agents) and opiate pain medications.

Treatment Characteristics

Review of medical records identified patients treated with bone modifying agents (BMAs), including bisphosphonates, denosumab, and pamidronate.

Statistical Analysis

We used logistic regression to predict symptomatic versus asymptomatic pain using bone metastasis number (single or multiple), location (axial, appendicular, or both), and type (blastic/sclerotic, lytic, or mixed) as independent variables. Results included odds ratios and 95% confidence intervals along with the Nagelkerke adjusted coefficient [14]. OS from distant disease diagnosis was analyzed using the Kaplan-Meier method. Patients who were alive at the end of follow-up were censored at the date of last known vital status. Equality across strata was tested using the log-rank test. Seven-year survival point estimates are presented with corresponding 95% confidence intervals that were obtained by applying the log-log transformation to the survivor function. We adjusted pairwise tests for multiple comparisons based on Tukey's Studentized range test. Cox proportional hazard regression models were used to evaluate bone metastasis characteristics on OS from distant disease diagnosis while adjusting for age at breast cancer diagnosis, race/ethnicity, BMI, and smoking status. Independent variables were assessed to identify and address any violations to functional form or proportional hazard assumptions and to detect interactions with time and between covariates. Two-tailed p values <.05 were considered statistically significant, and all analyses were conducted using SAS for Windows (release 9.4, SAS Institute, Cary, NC).

Results

We identified 2,543 potential patients with BOM in the departmental database and excluded 1,098 for failure to meet inclusion criteria: 640 did not have 6 months of follow-up at MDACC, 172 had evidence of nonbone metastases at time of MBC diagnosis, 164 had a single bone metastasis at diagnosis without confirmatory bone biopsy, 83 had a coexisting malignant neoplasm, and 39 did not have a documented bone metastasis at time of MBC diagnosis. A total of 1,445 patients with BOM met inclusion criteria and were evaluated for our

study. The median age at breast cancer diagnosis was 49.3 years (range, 20–94 years), and median age at BOM diagnosis was 53.5 years (range, 21–95 years). All but 13 of the patients were female, and 73.5% of the sample was white, 10% black, 12% Hispanic, and 4.5% another race/ethnicity. Clinical characteristics of these patients were presented in our previous manuscript, which detailed survival differences among patients with BOM with respect to tumor subtype based on hormone receptor (HR) and HER2 status [12]. In that study, we had data to characterize the tumor subtype for 1,048 of the 1,445 patients. The majority were HR+/HER2− (78%), followed by HR+/HER2+ (11%), HR+/HER2+ (7%), and HR−/HER2− (3%).

Bone Metastasis Characterization at Time of BOM Diagnosis

In our sample of 1,445 patients with BOM, 808 had available information regarding type of bone metastasis at BOM diagnosis: 389 (48%) had lytic bone metastases, 270 (33%) had sclerotic/blastic metastases, and 149 (18%) had mixed bone metastases. At time of BOM diagnosis, 290 patients (20%) were found to have a single bone metastasis, whereas 1,141 patients (79%) had multiple bone metastases (14 patients did not have information available on number of bone metastases at time of BOM diagnosis). Regarding the location of bone metastases at BOM diagnosis, 511 patients (36%) had bone metastases only in the axial skeleton, 153 patients (11%) had bone metastases only in the appendicular skeleton, and 770 patients (54%) had bone metastases in both the axial and appendicular skeleton (11 patient records were missing information on location of bone metastases at time of BOM diagnosis). The majority of patients with a single bone metastasis had metastasis to the spine (35%) followed by metastasis to the pelvis (22%), sternum (20%), femur (8%), rib (7%), humerus (6%), skull (1%), mandible (<1%), clavicle (<1%), and scapula (<1%).

Pain Assessment

Review of medical records allowed for characterization of pain at time of BOM diagnosis for 1,325 patients. Of these, 1,238 patients had direct notation of pain status at time of BOM diagnosis in clinical notes. An additional 87 patients had notation regarding use of pain medications at time of BOM diagnosis. With this characterization, 936 (71%) patients were symptomatic for pain at time of BOM diagnosis, and 389 (29%) were asymptomatic for pain. There were 120 patients whose pain status was unknown.

Association Between Pain and Bone Metastasis Characteristics

Based on the 767 patients with available information on both type of bone metastasis and pain status at BOM diagnosis, we found that pain was significantly associated with bone metastasis type (Wald $\chi^2(2) = 10.79$; $p = .0045$). Patients with lytic bone metastases had a significantly higher odds of pain than patients with blastic/sclerotic metastases (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.26–2.53; $\chi^2(1) = 10.78$; $p = .001$; Table 1). Among patients with available pain status and number of bone metastases ($n = 1{,}317$), patients with multiple bone metastases at time of BOM diagnosis had 37% increased odds of having pain compared with patients with single bone metastasis (OR, 1.37; 95% CI, 1.03–1.83; $\chi^2(1) = 4.62$; $p = .0316$). The overall effect of location of bone metastases on pain trended toward statistical significance (Wald $\chi^2(2) = 4.92$; $p = .0853$), with higher odds of pain in patients with both axial and appendicular metastases versus those with pain confined to the axial skeleton (OR, 1.32; 95% CI, 1.02–1.70; $\chi^2(1) = 4.49$; $p = .0340$).

In multivariable analysis, we included metastasis location and type as independent variables to predict binary pain status. Among 766 patients with complete observations, 538 (70%) reported pain at time of BOM diagnosis. The likelihood ratio test of the full model compared with a constant-only model was statistically significant ($\chi^2(4) = 21.17$; $p = .0003$). Using this model, patients with metastasis in both appendicular and axial locations had significantly greater odds of experiencing pain at BOM diagnosis than did patients with metastases confined to axial locations (OR, 1.73; 95% CI, 1.22–2.47). Patients with lytic metastases had almost double the odds of experiencing pain at BOM diagnosis relative to those with blastic or sclerotic metastases (OR, 1.97; 95% CI, 1.38–2.81; Table 2). Patients with lytic metastases in both appendicular and axial locations had an 80% (95% CI, 75%–84%) predicted probability of pain, and patients with blastic or sclerotic metastases confined to the axial skeleton had a 54% (95% CI, 45%–63%) predicted probability of pain.

Skeletal Related Events

Of the 1,445 patients with BOM meeting inclusion criteria in our study, 765 (53%) had at least one documented SRE. Of these 765 patients, 444 patients (58%) had one SRE, 196 (26%) had two SREs, 87 (11%) had three SREs, and 38 (5%) had four SREs. The most common SRE was radiation to bone, noted in 71% of patients with BOM with SREs, followed by pathologic fracture (20%), surgery to bone (16%), and cord compression (4%).

Overall Survival by Bone Metastasis Characteristics

OS of this BOM population is described in our previous manuscript, which details survival differences in these patients with BOM with respect to tumor subtype [12].

OS from distant disease did not differ significantly by bone metastasis type (log-rank test $\chi^2(2) = 4.53$; $p = .10$) or pain at BOM diagnosis (log-rank test $\chi^2(1) = 1.75$; $p = .19$). However, using other characteristics available at time of BOM diagnosis, we found OS differences between several unique BOM subgroups. Patients with a single metastasis versus multiple bone metastases at time of BOM diagnosis had improved OS from distant disease diagnosis (log-rank test $\chi^2(1) = 34.76$; $p < .0001$). Median survival for patients with a single bone metastasis was 7.54 years (95% CI, 6.28–10.10) compared with 4.80 years (95% CI, 4.49–5.07) for patients with multiple bone metastases (Fig. 1).

OS from distant disease diagnosis also differed by location of bone metastases at time of BOM diagnosis (log-rank test $\chi^2(2) = 31.75$; $p < .0001$), with poorer OS in patients with metastases in both the axial and appendicular skeleton compared with patients with appendicular-only or axial-only metastases. Median OS from distant disease diagnosis was 6.78 years (95% CI, 5.26–7.96) for appendicular-only bone

Table 1. Univariable logistic regression to test associations between pain and bone metastasis characteristics

Variable	Asymptomatic, *n* (%)	Symptomatic, *n* (%)	Total, *n*	Odds ratio (95% CI)	Chi-square	*p* value
Type of bone metastasis[a]						
Lytic	92 (40.17)	280 (52.04)	372	1.79 (1.26–2.53)	10.78	.001
Mixed	43 (18.78)	98 (18.22)	141	1.34 (0.86–2.08)	1.69	.19
Blastic/sclerotic	94 (41.05)	160 (29.74)	254	1.00		
Single or multiple bone metastasis[b]						
Multiple	295 (76.42)	760 (81.63)	1,055	1.37 (1.03–1.83)	4.62	.03
Single	91 (23.58)	171 (18.37)	262	1.00		
Bone metastasis location[c]						
Appendicular	44 (11.43)	95 (10.17)	139	1.03 (0.69–1.55)	0.023	.88
Both appendicular and axial	189 (49.09)	521 (55.78)	710	1.32 (1.02–1.70)	4.49	.03
Axial	152 (39.48)	318 (34.05)	470	1.002		

[a]Missing, 678 (47%); adjusted R^2, .020.
[b]Missing, 128 (9%); adjusted R^2, .005.
[c]Missing, 126 (9%); adjusted R^2, .005.
Abbreviation: CI, confidence interval.

Table 2. Multivariable logistic regression model to predict pain based on metastasis location and type (*n* = 766)

Parameter	Estimate (standard error)	Wald chi-square	*p* value	Odds ratio (95% CI)
Intercept	0.1511 (0.1839)	0.6750	.4113	
Location				
Appendicular	0.0707 (0.2955)	0.0572	.8110	1.07 (0.61–1.94)
Both appendicular and axial	0.5505 (0.1798)	9.3745	.0022	1.73 (1.22–2.47)
Axial				*reference*
Type				
Lytic	0.6761 (0.1814)	13.8859	.0002	1.97 (1.38–2.81)
Mixed	0.3036 (0.2274)	1.7828	.1818	1.36 (0.87–2.13)
Blastic or sclerotic				*reference*

Abbreviation: CI, confidence interval.

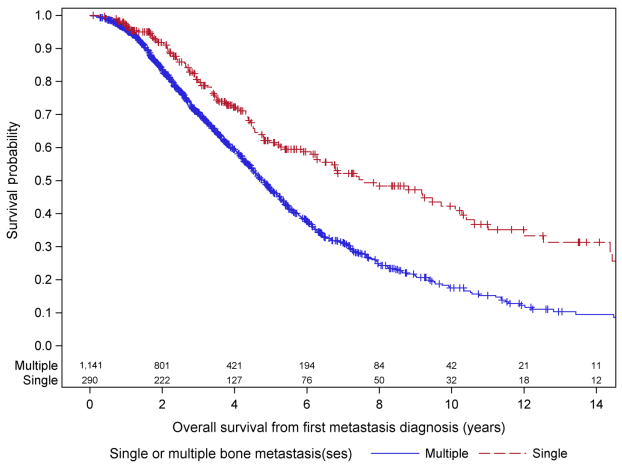

Figure 1. Overall survival from first metastasis diagnosis by number of bone metastases among patients with breast cancer and bone-only metastases (*n* = 1,445).

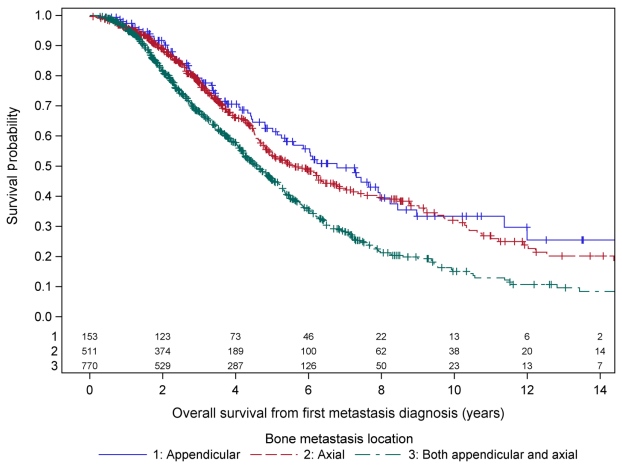

Figure 2. Overall survival from first metastasis diagnosis by bone metastasis location among patients with breast cancer and bone-only metastases (*n* = 1,434).

metastases, 5.62 years (95% CI, 4.81–6.69) for axial-only bone metastases, and 4.58 years (95% CI, 4.23–4.96) for both appendicular and axial bone metastases (Fig. 2).

Combining bone metastasis location and number at time of BOM diagnosis, OS was significantly poorer for patients with multiple metastases located in both the

Table 3. Seven-year overall survival rates from distant diagnosis among patients with breast cancer and bone-only metastases

Number of metastases	Location	7-year survival estimate (95% CI)
Single	Appendicular	0.4834 (0.3528–0.6022)
Single	Axial	0.5426 (0.4445–0.6306)
Multiple	Appendicular	0.5267 (0.3634–0.6662)
Multiple	Axial	0.3438 (0.2701–0.4185)
Multiple	Both appendicular and axial	0.2821 (0.2398–0.3257)

Abbreviation: CI, confidence interval.

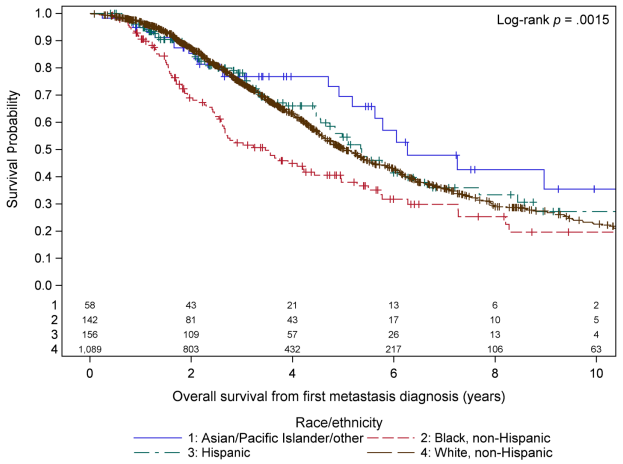

Figure 3. Overall survival from first metastasis diagnosis among patients with breast cancer and bone-only metastases by race/ethnicity (n = 1,445). Plot was truncated at 10 years because of sparse data beyond 10 years.

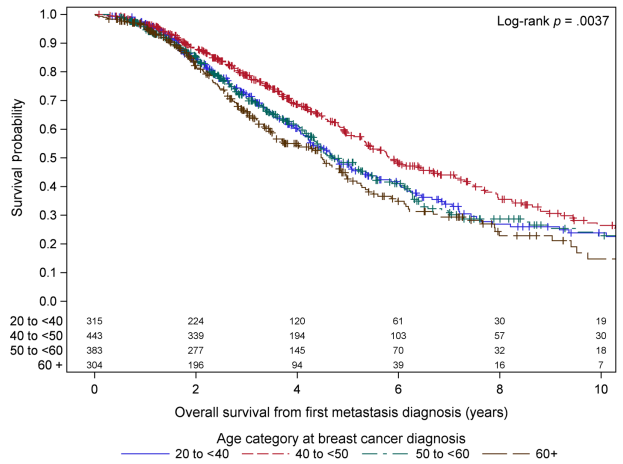

Figure 4. Overall survival from first metastasis diagnosis among patients with breast cancer and bone-only metastases by age at breast cancer diagnosis (n = 1,445). Plot was truncated at 10 years because of sparse data beyond 10 years.

appendicular and axial skeleton, with an OS of 4.58 years (95% CI, 4.22–4.96) and a 7-year survival rate of 28% (95% CI, 24%–33%). The longest 7-year survival was seen in patients with BOM with a single bone metastasis (Table 3).

Overall Survival by Patient Characteristics

Race/ethnicity was significantly associated with OS (log-rank test $\chi^2(4) = 16.17$; $p = .0028$), with black, non-Hispanic patients having a poorer OS from distant disease diagnosis compared with all other race/ethnicity groups (Fig. 3). Median OS for black, non-Hispanic patients was 3.46 years (95% CI, 2.62–4.43), whereas the estimated median survival for all other race/ethnicity groups was greater than 5 years. Age was also significantly associated with OS ($\chi^2(1) = 5.14$; $p = .0234$). By age category (20–39, 40–49, 50–59, and ≥60 years), patients aged 40–49 years at time of breast cancer diagnosis had significantly better OS compared with both younger and older patient groups (Fig. 4). Smoking status and BMI were not significantly associated with OS (smoking status: log-rank test $\chi^2(2) = 2.99$; $p = .2247$; BMI: log-rank test $\chi^2(3) = 1.26$; $p = .7376$).

Overall Survival from Distant Disease Diagnosis by Bone Metastasis Characteristics, Adjusting for Age, Race/Ethnicity, Smoking Status, and BMI

Number of metastases remained a statistically significant predictor of OS after adjusting for age, race, BMI, and smoking status. In a univariable analysis, patients with multiple metastases had an 82% increased hazard of death (hazard ratio, 1.82; 95% CI, 1.49–2.23), and after adjusting for age at breast cancer diagnosis, race/ethnicity, BMI, and smoking status, patients with multiple versus single bone metastases had a 78% increased hazard of death (hazard ratio, 1.78; 95% CI, 1.44–2.20).

Similarly, location of metastases remained a statistically significant predictor of OS after adjusting for age, race, BMI, and smoking status. In a univariable analysis, metastasis location was significantly associated with OS (type 3 test Wald $\chi^2(2) = 31.22$; $p < .0001$), and patients with both axial and appendicular metastasis at time of BOM diagnosis had a 69% increased hazard of death relative to patients with metastases confined to the appendicular skeleton (hazard ratio, 1.69; 95% CI, 1.31–2.19; $p < .0001$). There was no significant difference in OS among patients who had axial-only versus appendicular-only metastases ($p = .3212$). After adjusting for age at breast cancer diagnosis, race/ethnicity, BMI, and smoking status, patients with both axial and appendicular metastases had a 65% increased hazard of death (hazard ratio, 1.65; 95% CI, 1.26–2.17) relative to patients with metastases confined to the axial skeleton.

Overall Survival for Patients Previously Excluded for Lack of 6-Month Follow-Up

In order to assess for the possibility of altered OS based on our inclusion criteria requiring 6-month follow-up at MDACC, we analyzed OS from distant disease diagnosis in the 640 patients excluded for lack of 6-month follow-up. Among these patients, 462 deaths were recorded and

178 were censored at last follow-up. OS from distant metastasis diagnosis was 3.1 years (95% CI, 2.8–3.4), which was significantly shorter than the median OS of 5.0 years (95% CI, 4.7–5.4) observed in patients included in our study (log-rank $\chi^2(1) = 148.34$; $p < .0001$).

Bone Modifying Agents

Of the 1,445 patients with BOM identified in our study, 93 patients (6%) did not receive BMAs, 217 (15%) had unknown BMA usage, and 1135 (79%) received BMAs. Patients who were more likely to receive BMAs had multiple metastases (93% vs. 89% among patients with a single metastasis, $p = .041$) and had bone metastases in both the appendicular and axial skeleton (94% vs. 90% BMA use in patients with appendicular-only or axial-only metastases; $p = .048$). Also, there was a trend towards an increased likelihood of receiving BMAs if a patient was symptomatic (93% vs. 90% BMA use by asymptomatic patients; $p = .085$). Coexisting osteoporosis or osteopenia was documented in 98 patients; 96% received BMAs versus 92% BMA use among patients without a coexisting osteoporosis or osteopenia diagnosis ($p = .231$).

Discussion

Bone is the most common site of metastatic disease associated with breast cancer, with postmortem studies suggesting that up to 70% of patients with breast cancer have some form of skeletal metastasis [15]. Given this high frequency, we sought to evaluate prognostic factors associated with bone metastases in MBC with BOM, focusing on factors present at BOM diagnosis affecting both pain at diagnosis and OS.

Although many metastatic bone lesions are associated with few or no symptoms, bone metastases can be associated with a wide range of symptoms and increased morbidity in the form of pain, pathologic factures, and spinal cord compression. Identifying patients at increased risk of pain attributable to bone metastases would allow for improved therapeutic strategies. We sought to evaluate patients with MBC and BOM given that this is a unique patient population, with prior studies showing improved outcomes compared with patients with visceral or central nervous system metastases [10,11]. Because of increased life expectancy, disruption of quality of life in BOM is more protracted and compromises the value of prolonged survival. Our study showed higher odds of pain in patients with BOM with multiple bone metastases and metastases that were lytic in nature, both identifiers that are routinely available at time of BOM diagnosis. Consistent with prior literature, our BOM series showed a majority of lytic bone metastases [16], with osteolytic metastases more likely to cause symptomatic pain. We also observed that a substantial number of patients with BOM experienced SREs, most commonly radiation to bone.

Although prior studies have suggested an association between pain from skeletal metastasis in MBC and survival [8], our study did not find a correlation between pain at BOM diagnosis and OS from distant disease. We did, however, find that poorer OS was associated with having multiple bone metastases and bone metastases located in both the axial and appendicular skeleton at time of BOM diagnosis. The association of OS with location of bone metastases held true even controlling for number of sites of bone metastases. The finding of poorer outcome associated with multiple sites of bone metastases is consistent with prior studies in the general MBC population [17], and several studies have looked at the association between number of bone metastases and SREs, but the outcomes have been mixed [18,19]. Our study uniquely found prognostic implication in the sites of bone metastases at time of BOM diagnosis using the axial and appendicular skeleton as a way to uniformly characterize locations of these lesions. Prior to this study, little information was available regarding prognostic implications of sites of bone metastases, none in the BOM population.

Other patient characteristics associated with survival in this BOM subset included race/ethnicity and age. Similar to what is seen in the general breast cancer population, black, non-Hispanic patients with BOM had poorer OS compared with all other race/ethnicity groups [20], a finding that has not previously been defined in this large a subset of patients with MBC and BOM. To delineate the reason for this poorer outcome, we compared tumor subtype distributions, as these have previously been shown to be associated with outcome [12]. In our initial BOM study [12], tumor subtypes associated with poorer outcomes included HR−/HER− and HR−/HER2+ tumors. Of the 142 black, non-Hispanic patients in our study, a greater proportion (18%) had HR−/HER− or HR−/HER2+ tumors compared with the proportion (8%) in white, non-Hispanic patients. We hypothesize that the poorer outcome seen in black, non-Hispanic patients with BOM in this study is possibly due to this difference in biology, rather than other factors such as access to or quality of treatment. Age was similarly found to have a significant association with OS in this BOM subset, with patients aged 40–49 years at time of breast cancer diagnosis having significantly improved OS compared with both younger and older patient groups. Similar findings have been seen in the general breast cancer population, with a study by Brandt et al. showing poorer prognosis in women less than 40 years of age at breast cancer diagnosis [21].

BMAs such as zoledronic acid, denosumab, and pamidronate are recommended in patients with MBC and bone metastases [22]. In addition to lower risk of SREs with BMAs [23], there has been some suggestion of modest pain control with BMAs [24,25]. Our BOM population had a high rate of BMA usage at 92%, with those patients who received BMAs more likely to have more extensive disease (multiple bone metastases), bone metastases in both the appendicular and axial skeleton, and more painful bone metastases at time of BOM diagnosis. Only 8% of patients had no BMA administration. BMA usage was unknown for 15% of our study sample, which is a limitation of the retrospective nature of this study.

In addition, the retrospective study design resulted in missing study data. This included documentation of pain status at time of BOM diagnosis for a small subset of patients. Without formal pain intensity assessment, conclusions regarding the relationship between bone metastasis characteristics and pain are approximate. Missing data also limited our ability to study the relationship between patient characteristics and SREs.

Another study limitation is the use of a study population from a single large referral institution, which is likely to have characteristics distinct from other centers, thus limiting broad generalizations. In addition, our study excluded patients with

lack of 6-month follow-up at MDACC, a necessity to ensure appropriate knowledge of the clinical course of these patients. The shorter OS in patients excluded for lack of 6-month follow-up compared with patients meeting study inclusion criteria suggests that our study overestimates OS for the total population of patients with BOM.

Using the largest subset of patients with BOM to date, this study found several unique characteristics predicting increased pain or poorer prognosis. Given that these factors are present at BOM diagnosis, they serve as unique identifiers for patients who potentially could benefit from more aggressive therapy and suggest unique BOM populations that deserve further investigation.

Conclusion

We have analyzed the largest reported cohort of patients with MBC and BOM and identified having multiple bone metastases and metastases in both axial and appendicular skeleton as factors predicting poorer OS. Similarly, age and race/ethnicity were associated with poorer OS, the latter possibly explained by the distribution of adverse tumor subtypes. These prognostic factors should assist the treating physician in tailoring treatment to individual patients, with higher-risk patients probably requiring more aggressive multidisciplinary management.

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Author Contributions

Conception/design: Amanda Parkes, Carla L. Warneke, Jennifer K. Litton, Gabriel N. Hortobagyi

Provision of study material or patients: Gabriel N. Hortobagyi

Collection and/or assembly of data: Amanda Parkes, Katherine Clifton, Aydah Al Awadhi, Oluchi Oke, Roberto Carmagnani Pestana, Omar Alhalabi

Data analysis and interpretation: Amanda Parkes, Carla L. Warneke

Manuscript writing: Amanda Parkes, Carla L. Warneke

Final approval of manuscript: Amanda Parkes, Carla L. Warneke, Katherine Clifton, Aydah Al-Awadhi, Oluchi Oke, Roberto Carmagnani Pestana, Omar Alhalabi, Jennifer K. Litton, Gabriel N. Hortobagyi

Disclosures

Katherine Clifton: Wellcare (E—spouse). The other authors indicated no financial relationships.

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