Published in final edited form as:

Ann Diagn Pathol. 2011 April ; 15(2): 79–83. doi:10.1016/j.anndiagpath.2010.06.010.

Breast Carcinomas with Isolated Bone Metastases Have Different Hormone Receptor Expression Profiles than Those with Metastases to Other Sites or Multiple Organs

Shi Wei, M.D., Ph.D.¹, Yufeng Li, Ph.D.², Gene P. Siegal, M.D., Ph.D.^{1,3,4,5,6}, and Omar Hameed, MBChB^{1,3,5}

¹Department of Pathology, University of Alabama at Birmingham, Birmingham, AL

²Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

³Department of Surgery, University of Alabama at Birmingham, Birmingham, AL

⁴Department of Cell Biology, University of Alabama at Birmingham, Birmingham, AL

⁵Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL

⁶The Center for Metabolic Bone Disease, University of Alabama at Birmingham, Birmingham, AL

Abstract

Breast carcinoma (BC) is one of the most common osteotropic tumors. The subset of BC patients with isolated bone metastasis (IBM) forms a clinically distinct group and often has a favorable clinical outcome as compared to others with metastatic BC. We analyzed all BC patients with distal organ metastasis in our institution between 1997 and 2003 (N=198) to identify the clinicopathologic features of BC with IBM and compare them to those with metastasis to other sites. We found that 63% of BC patients with advanced disease had bone metastases, and 44% of those were IBM. The proportion of cases with IBM that expressed estrogen receptor (ER) and/or progesterone receptor (PR) (47/52; 90%) was significantly higher than those with non-bone metastases ($p<0.0001$) and than those with multiple metastases involving bone ($p<0.0001$). The distribution of BC molecular subtypes in cases of IBM was again significantly different from that of the remainder. By univariate and multivariate analysis of the clinicopathologic factors examined, only ER and PR status of the primary tumor was predictive for IBM. The median survival after diagnosis of metastatic disease was significantly longer in cases with IBM than that of any other group. Our results indicate that the diversity in receptor expression patterns reflects not only the biological diversity of mammary tumors but may also predict their metastatic potential and thus could potentially be utilized in surveying women patients with non-metastatic disease.

Keywords

breast cancer; estrogen receptor; progesterone receptor; HER2; bone metastasis

Introduction

Breast carcinoma (BC) is the most common cancer in women in developed countries, and is responsible for over 40,000 deaths in the United States each year.[1] BCs, along with prostate carcinomas, are the most common osteotropic tumors.[2] In addition, bone represents the first site of relapse for approximately 50% of patients with BC.[3] Different from prostate, however, BC more often metastasizes to other organs as well, with liver and/or lung involvement seen in at least 25% of patients at the time of diagnosis.[4] In recent years, there has also been a reportedly higher rate of central nervous system (CNS) metastases, which is thought to be secondary to the fact that many of the new therapeutic agents used to treat BC may fail to penetrate the blood-brain barrier.[5]

The distant organs to which BC preferentially metastasize to is of clinical and biological importance. For instance, once located in bone, metastatic BC is incurable but remains relatively indolent. However, it may cause significant morbidity due to skeletal complications, including bone pain, hypercalcemia, pathologic fractures, and spinal cord compression.[6–8] The subset of patients with bone-only metastasis at the time of diagnosis forms a clinically distinct group.[9–15] These patients often have prolonged survival, and usually benefit from palliative systemic therapy. Importantly, coexisting and subsequent nonosseous metastatic disease is critical in prognosticating differences among BC patients of the same morphologic type. The patients with isolated bone metastasis (bone-only metastasis at the first relapse and remained clinically confined to the skeleton; IBM) appeared to have significantly prolonged survival.[7, 8, 16]

The biology of primary BC relapsing in bone is poorly understood. The association of bone relapse and estrogen receptor (ER) status of BC has been suggested by a number of human and animal studies.[17–20] However, little has been done to compare BCs with associated with IBM to those that give rise to non-bone metastases and to those with multiple organ metastases which may also involve bone. Thus, the aim of this study was to identify the clinical and pathological features of BC patients with IBM and compare them to those in patients with metastases at other distal sites and at multiple sites.

Materials and Methods

Study design

After approval by the Institutional Review Board, the Tumor Registry and Surgical Pathology database of the authors' institution were searched to identify cases of BC with associated metastasis. Of 2,738 patients with BC diagnosed between 1997 and 2003, 356 had metastatic disease. Those with locoregional recurrence (skin, soft tissue/chest wall adjacent to breast) or lymph node metastasis were excluded. The cases with associated distant metastasis (N=198) were then classified into one of three subgroups, i.e., 1) IBM; 2) non-bone metastasis (NBM), including isolated or multiple visceral organ metastasis (IVM/MVM) or CNS metastasis (CNSM, either isolated or combined with visceral organ metastasis); 3) multiple metastases (MM) involving bone, including those with bone and visceral organ metastasis (BM + VM), and those with bone and CNS metastases (BM + CNSM) regardless of VM.

ER and PR expression of tumors were examined by immunohistochemistry (IHC), and HER2 protein expression and/or gene amplification was evaluated by IHC or fluorescence in situ hybridization (FISH), respectively, as previously described.[21] The patients' demographic data were retrieved from the tumor registry database.

Classification of BC molecular subtypes

Molecular classification of the breast tumors was based on results of ER, PR and HER2 testing as previously reported.[22] In brief, tumors were defined as luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER2+), HER2+ (ER-, PR-, HER2+), and triple negative (ER-, PR-, HER2-). The triple negative group was not further subclassified.

Statistical analysis

The categorical data obtained were statistically evaluated using either the χ^2 -test, or the Fisher's exact test, as appropriate, while continuous data were evaluated using the student t test. A *P*-value of 0.05 was considered statistically significant.

Systemic metastasis-free survival (from date of diagnosis until date of first systemic recurrence; MFS) and overall survival (OS) post-metastasis (from date of first systemic recurrence until death) were determined by creation of a Kaplan-Meier (K-M) curve. Patients who survived or were lost to follow up were censored in the analysis. The log rank test was used to compare groups.

The likelihood of having IBM was further modeled with logistic regression analysis excluding 5 cases with missing data for ER or PR status. The Cox proportion hazard model was utilized to associate OS or MFS with other factors. Statistical analysis was performed by utilizing SAS v9.1 software.

Results

Classification of BC cases with associated metastases and clinicopathologic characteristics

Sixty-three percent of the patients with distant metastasis had bone metastasis, either at the time of diagnosis or subsequently, and 45% of those with bone metastasis were IBM (Table 1). No statistical difference was found between IBM and any other subgroup in regard to the clinicopathologic factors examined (Table 2).

Expression of ER/PR and molecular subtypes

The proportion of cases with IBM that expressed ER and/or PR was significantly higher than that of any other group (Table 3). As shown in Table 4, the cases associated with IBM were predominantly luminal A and B subtypes (30/33; 91%). The distribution of molecular subtypes in cases of IBM was again significantly different from any subgroup of NBM or MM with BM.

Factors associated with IBM

Among the clinicopathologic factors examined (as shown in Table 2) as well as ER, PR and HER2 status, both ER expression (odds ratio (OR) 4.8, 95% CI 2.1–10.9, *p*=0.0002) and PR expression (OR 6.4, 95% CI 3.1–13.2, *p*<0.0001) in the primary tumor were significant predictive factors for IBM by univariate analysis. The significant association of IBM and ER or PR status was further validated by multivariate analysis (OR 3.8, 95% CI 1.1–13.6, *p*=0.03; OR 3.2, 95% CI 1.2–8.5, *p*=0.02, respectively).

Clinical outcomes

Of patients originally metastasis free, the median MFS in IBM group was significantly longer than that in CNSM group (Figure 1) but similar to that appreciated in the other groups (data not shown). The median OS was significantly longer in IBM group than that in

any other group (Figure 2). Of the patients with IBM, those with luminal A and B molecular subtypes had significantly longer survival than those with other subtypes (Figure 3).

Discussion

Bone metastasis is of particular clinical importance in BC because of its high prevalence. While the prognosis after the development of IBM in BC is considerably better than that in other organs, the presence of coexisting or subsequent nonosseous metastatic disease imparts a less favorable outcome.[7, 8, 16] On the other hand, although bone metastasis may be occult and silent in the early stages, it may develop a devastating consequence in the course of BC because of significant morbidity due to catastrophic skeletal complications.[6–8] Thus, it is crucial to identify the group of BC patients with isolated bone metastatic potential in those free of distant metastasis at initial presentation.

Despite the fact that BC has a predilection to spread to bone, the biological mechanisms that might explain the osteotropic nature of BC cells remain poorly understood. Over a century ago, Paget proposed the “seed and soil” hypothesis to explain the marked affinity of BC for bone.[23] While this concept has remained a basic principle in the field of cancer metastasis, it has been challenged by the recent discovery of “pre-metastasis niches” that are formed prior to the arrival of metastatic tumor cells, suggesting that the communication between tumor cells and target organs may occur before the arrival of tumor cells at distant sites.[24, 25]

There is a large body of scientific data regarding the clinical and biological aspects of BC bone metastasis. However, very few studies have investigated BC clinical and pathological factors in association with IBM. Previous studies have shown that bone relapse was more commonly associated with ER+ tumors, suggesting a protective role for ER in tumor progression associated with bone metastasis.[14, 19] A recent microarray analysis found that bone relapse was most abundant in the luminal subtypes, indicating a clear association of bone relapse with ER status.[20] Noteworthy is the fact that the up-regulated genes in the bone relapse patients of the HER2 subtype are entirely different from those found in the luminal subtypes, suggesting that the HER2 subtype may metastasize to bone via a process different from the luminal tumors. However, none of these studies separated IBM from multiple organ metastases involving bone. A previous study found that the patients with bone-only metastases were more likely to be older, with lobular carcinoma and initially with little or no axillary lymph node involvement.[7] However, none of these factors was associated with IBM in our study. Our data clearly suggested that the ER/PR status of the primary tumor were the only clinicopathologic factors associated with the subsequent development of IBM, and that BC with multiple organ involvement including bone may be due to a mechanism different from that BC with IBM but similar to those with non-bone metastases. Thus, BCs with bone metastatic potential likely form two distinguished biological groups that correspond to their distinct respective clinical courses. On the other hand, a significant proportion of ER/PR+ BCs did not undergo bone metastasis. This represents a great clinical interest and an imperative target for further investigation.

It is important to note that hormonal receptor status may be discordant in primary and metastatic BCs (16–56% for ER and 14–44% for PR), whereas HER2 discordance appears to be less common (0–33% by IHC and 0–16% by FISH).[26–32] The mechanisms responsible for the change have yet to be completely understood but possible explanations include effects of adjuvant treatment, intratumoral heterogeneity, and testing conditions.[28, 31, 33]

In conclusion, our data indicate that the diversity in receptor expression patterns not only reflects the biological diversity of tumors, but may also predict their metastatic potential. Relating receptor expression patterns to clinical outcomes is a key issue in understanding this diversity, and thus could potentially be utilized in determining the appropriate survey regimen for follow up of patients with non-metastatic disease. Further understanding of the molecular mechanisms of BC bone metastasis would be essential to developing treatment strategies that can either prevent or treat these lesions.

Acknowledgments

The study was presented in part at the 98th Annual Meeting of the United States and Canadian Academy of Pathology, Boston, Massachusetts, 2009. This work was supported in part by NIH Grants CA089019, CA108585 and AR46031.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. *CA: a cancer journal for clinicians*. 2006; 56(2):106–130. [PubMed: 16514137]
2. Galasko, C. The anatomy and pathways of skeletal metastases. In: Weiss, L.; Gilbert, A., editors. *Bone metastases*. Boston: GK Hall; 1981. p. 49–63.
3. Kriege M, Seynaeve C, Meijers-Heijboer H, Collee JM, Menke-Pluymers MB, Bartels CC, Tilanus-Linthorst MM, van den Ouweland A, van Geel B, Brekelmans CT, et al. Distant disease-free interval, site of first relapse and post-relapse survival in BRCA1- and BRCA2-associated compared to sporadic breast cancer patients. *Breast cancer research and treatment*. 2008; 111(2):303–311. [PubMed: 17952592]
4. Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, Abbruzzese JL. Metastatic patterns in adenocarcinoma. *Cancer*. 2006; 106(7):1624–1633. [PubMed: 16518827]
5. Palmieri D, Smith QR, Lockman PR, Bronder J, Gril B, Chambers AF, Weil RJ, Steeg PS. Brain metastases of breast cancer. *Breast disease*. 2006; 26:139–147. [PubMed: 17473372]
6. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res*. 2006; 12(20 Pt 2):6243s–6249s. [PubMed: 17062708]
7. Coleman RE, Smith P, Rubens RD. Clinical course and prognostic factors following bone recurrence from breast cancer. *British journal of cancer*. 1998; 77(2):336–340. [PubMed: 9461007]
8. Domchek SM, Younger J, Finkelstein DM, Seiden MV. Predictors of skeletal complications in patients with metastatic breast carcinoma. *Cancer*. 2000; 89(2):363–368. [PubMed: 10918167]
9. Swenerton KD, Legha SS, Smith T, Hortobagyi GN, Gehan EA, Yap HY, Gutterman JU, Blumenschein GR. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. *Cancer Res*. 1979; 39(5):1552–1562. [PubMed: 427797]
10. Smalley RV, Scogna DM, Malmud LS. Advanced breast cancer with bone-only metastases: a chemotherapeutically responsive pattern of metastases. *Am J Clin Oncol*. 1982; 5(2):161–166. [PubMed: 7091041]
11. Sherry MM, Greco FA, Johnson DH, Hainsworth JD. Breast cancer with skeletal metastases at initial diagnosis. Distinctive clinical characteristics and favorable prognosis. *Cancer*. 1986; 58(1):178–182. [PubMed: 2423224]
12. Sherry MM, Greco FA, Johnson DH, Hainsworth JD. Metastatic breast cancer confined to the skeletal system. An indolent disease. *The American journal of medicine*. 1986; 81(3):381–386. [PubMed: 2428242]
13. Scheid V, Buzdar AU, Smith TL, Hortobagyi GN. Clinical course of breast cancer patients with osseous metastasis treated with combination chemotherapy. *Cancer*. 1986; 58(12):2589–2593. [PubMed: 3779609]
14. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *British journal of cancer*. 1987; 55(1):61–66. [PubMed: 3814476]
15. Chiedozi LC. Prognostic significance of exclusive skeletal metastases in stage IV primary carcinoma of the breast. *Surgery, gynecology & obstetrics*. 1988; 167(4):303–306.

16. Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer. implications for management. *Eur J Cancer*. 2000; 36(4):476–482. [PubMed: 10717523]
17. Kang Y, Siegel PM, Shu W, Drobnjak M, Kakonen SM, Cordon-Cardo C, Guise TA, Massague J. A multigenic program mediating breast cancer metastasis to bone. *Cancer cell*. 2003; 3(6):537–549. [PubMed: 12842083]
18. Smid M, Wang Y, Klijn JG, Sieuwerts AM, Zhang Y, Atkins D, Martens JW, Foekens JA. Genes associated with breast cancer metastatic to bone. *J Clin Oncol*. 2006; 24 (15):2261–2267. [PubMed: 16636340]
19. Koenders PG, Beex LV, Langens R, Kloppenborg PW, Smals AG, Benraad TJ. Steroid hormone receptor activity of primary human breast cancer and pattern of first metastasis. The Breast Cancer Study Group. *Breast cancer research and treatment*. 1991; 18(1):27–32. [PubMed: 1854977]
20. Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn JG, Foekens JA, Martens JW. Subtypes of breast cancer show preferential site of relapse. *Cancer Res*. 2008; 68 (9):3108–3114. [PubMed: 18451135]
21. Hameed O, Chhieng DC, Adams AL. Does using a higher cutoff for the percentage of positive cells improve the specificity of HER-2 immunohistochemical analysis in breast carcinoma? *Am J Clin Pathol*. 2007; 128(5):825–829. [PubMed: 17951206]
22. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006; 295(21):2492–2502. [PubMed: 16757721]
23. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet*. 1889; 133(3421): 571–573.
24. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald DD, Jin DK, Shido K, Kerns SA, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature*. 2005; 438(7069):820–827. [PubMed: 16341007]
25. Kaplan RN, Rafii S, Lyden D. Preparing the “soil”: the premetastatic niche. *Cancer Res*. 2006; 66(23):11089–11093. [PubMed: 17145848]
26. Brunn Rasmussen B, Kamby C. Immunohistochemical detection of estrogen receptors in paraffin sections from primary and metastatic breast cancer. *Pathol Res Pract*. 1989; 185(6):856–859. [PubMed: 2616369]
27. Wu JM, Fackler MJ, Halushka MK, Molavi DW, Taylor ME, Teo WW, Griffin C, Fetting J, Davidson NE, De Marzo AM, et al. Heterogeneity of breast cancer metastases: comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. *Clin Cancer Res*. 2008; 14 (7):1938–1946. [PubMed: 18381931]
28. Idirisinghe PK, Thike AA, Cheok PY, Tse GM, Lui PC, Fook-Chong S, Wong NS, Tan PH. Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. *Am J Clin Pathol*. 133(3):416–429. [PubMed: 20154280]
29. Broom RJ, Tang PA, Simmons C, Bordeleau L, Mulligan AM, O'Malley FP, Miller N, Andrulis IL, Brenner DM, Clemons MJ. Changes in estrogen receptor, progesterone receptor and Her-2/neu status with time: discordance rates between primary and metastatic breast cancer. *Anticancer Res*. 2009; 29(5):1557–1562. [PubMed: 19443366]
30. Amir E, Ooi WS, Simmons C, Kahn H, Christakis M, Popovic S, Kalina M, Chesney A, Singh G, Clemons M. Discordance between receptor status in primary and metastatic breast cancer: an exploratory study of bone and bone marrow biopsies. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2008; 20(10):763–768. [PubMed: 18824337]
31. Guarneri V, Giovannelli S, Ficarra G, Bettelli S, Maiorana A, Piacentini F, Barbieri E, Dieci MV, D'Amico R, Jovic G, et al. Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: impact on patient management. *The oncologist*. 2008; 13(8):838–844. [PubMed: 18650259]
32. Lower EE, Glass E, Blau R, Harman S. HER-2/neu expression in primary and metastatic breast cancer. *Breast cancer research and treatment*. 2009; 113(2):301–306. [PubMed: 18273700]

33. Lower EE, Glass EL, Bradley DA, Blau R, Heffelfinger S. Impact of metastatic estrogen receptor and progesterone receptor status on survival. *Breast cancer research and treatment*. 2005; 90(1): 65–70. [PubMed: 15770528]

Figure 1. Systemic metastasis-free survival (MFS) from time of diagnosis, IBM group vs. CNSM group.

Figure 2.

Overall survival from time of first systemic recurrence. The difference in median survival remains significant when the IBM group is compared to any other individual group (IBM vs. IVM, $p=0.001$; IBM vs. MVM, $p<0.0001$; IBM vs. CNSM, $p<0.0001$; IBM vs. MM with BM, $p=0.03$).

Figure 3.
Overall survival from time of first systemic recurrence in BC of different molecular subtypes within the IBM group.

Table 1

Classification of metastatic BC cases

Metastatic organ	Metastasis-free at diagnosis	Metastasis at diagnosis	Total
IBM	34	21	55
NBM			
IVM	26	18	44
MVM	8	3	11
CNSM	15	4	19
MM involving bone			
BM + VM	35	13	48
BM + CNSM	16	5	21
Total	134	64	198

Table 2

Clinical and histopathological characteristics

	IBM	IVM	MVM	CNSM	BM + VM	BM + CNSM
Age at diagnosis: mean, median (range)	55, 53 (21–82)	56, 56 (35–81)	52, 49 (30–83)	52, 52 (25–79)	49, 46 (26–82)	50, 48 (31–73)
Race						
White	47	38	6	18	34	14
Black	7	6	5	1	14	7
Others	1					
Tumor size (No. of cases examined)	3.7 cm (45)	3.9 cm (37)	5.4 cm (10)	2.7 cm (16)	4.0 cm (40)	3.6 cm (16)
Tumor type						
Ductal	43	38	9	15	39	16
Lobular	6	1	0	1	2	3
Ductal & Lobular	1	2	0	1	3	1
Unclassified	5	4	2	2	4	1
Tumor grade						
I	3	1	1	0	3	0
II	29	22	1	3	19	8
III	20	20	9	11	22	9
Unclassified	3	1		5	4	4
No. of positive nodes (No. of cases examined)	3.6 (31)	5.4 (29)	2 (7)	3.8 (12)	3.7 (32)	7.4 (14)

Table 3

ER/PR Expression

Organ	ER/PR+	P (vs. IBM)
IBM	90% (47/52)	
NBM*		
IVM	55% (23/42)	0.0002
MVM	45% (5/11)	0.002
CNSM	56% (10/18)	0.003
MM involving bone*		
BM + VM	57% (26/46)	0.0003
BM + CNSM	55% (11/20)	0.002

* When NBM group (or MM involving bone group) is combined, $p < 0.0001$.

Table 4

Molecular Subtypes

Organ	Luminal A	Luminal B	HER2	Triple Negative	P (vs. IBM)
IBM	16	14	1	2	
NBM					
IVM	15	6	9	8	0.05
MVM	2	1	2	4	0.004
CNSM	2	4	2	6	0.003
MM involving bone					
BM + VM	12	9	10	10	0.003
BM + CNSM	4	6	4	5	0.01