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Influence of Hormone Receptor Status on Spinal Metastatic Lesions in Breast Cancer Patients

Jenny Lin¹, Leanne Goldstein, DrPH¹, Amanda Nesbit¹, and Mike Y. Chen, M.D., Ph.D.^{1,*}

¹Division of Neurosurgery, City of Hope and Beckman Research Institute, Duarte, CA, 91010

Abstract

Bony metastasis predominantly affects the spinal column and has been commonly associated with breast cancer patients. There are two types of lesions that can occur with spine cancer, osteolytic or osteoblastic. Some patients may have mixed lesions, which include lytic and blastic in one vertebra or lytic and blastic in different vertebrae. Previous studies have shown breast cancer patients have an increased likelihood for development of lytic spinal metastases. A retrospective chart review was conducted to more closely examine the association between hormone receptor status and spinal lesion type. 195 patients were initially identified through the City of Hope Cancer Registry. Out of the 195, only 153 patients had hormone receptor marker status available. Associations between spinal lesion and hormone receptor status were evaluated using Chi-Square tests with $\alpha = .05$ significance level. In a secondary analysis, the OncoPrint Platform[®] was used, which integrated The Cancer Genome Atlas (TCGA) datasets, to identify osteogenic genes that may be relevant to invasive breast cancers. Contrary to previous studies, our findings revealed progesterone receptor positive (PR+) patients were significantly more likely to present with blastic than lytic or mixed lesions. Furthermore using TCGA analysis, COL1A1 and COL1A2 were found to be upregulated, which could provide a molecular explanation for the development of blastic metastases. By integrating both clinical and bioinformatic techniques, this study provides a novel discovery of the relationship between blastic and PR+ breast cancers, which may have important implications for diagnostic strategies concerning vertebral metastases.

Keywords

breast cancer; bone metastasis; spine cancer; hormone receptor status; metastatic lesions

*Corresponding author: Mike Y. Chen, mchen@coh.org, Telephone number: 800-826-4673, (Ext. 67285), Fax number: 800-826-4673 (Ext. 67344).

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The authors declare that they have no conflict of interest.

Introduction

In the United States, breast cancer is one of the most frequently diagnosed types of cancer in women. About 1 in 8 U.S. women will develop invasive breast cancer over the course of her lifetime [1]. Since 2000, more than 220,000 women in the U.S. are diagnosed with breast cancer, of which 40,000 cases result in death [2]. Globally, breast cancer remains the principal cause of death among women with cancer.

Hormone receptor status is a main factor in assessment and treatment of breast cancer, but few have examined its use for prognostic purposes. Though the mechanism is unclear, hormone receptor status has been found to be related to the chance of recurrence. Studies have shown local and regional recurrence may be associated with breast molecular subtype or receptor [3]. Hormone receptor positive tumors have a slightly lower chance of recurrence than hormone receptor-negative tumors in the first five years after diagnosis[4]. Specifically, estrogen receptor (ER) or progesterone (PR) positive, human epidermal growth factor 2 (HER2) negative have the best prognosis and lowest rate of relapse [3]. Thus, hormone receptor status has proven to be a useful prognostic tool for insight on the spread of breast cancer and can facilitate therapeutic decisions.

Additionally, breast cancer patients are most commonly diagnosed by stage. Patients may present with Stage IV breast cancer, or metastatic breast cancer, at diagnosis or months after a previous chemotherapy treatment for early or locally advanced breast cancer (Stage I, II, III) [5]. Rates of metastatic breast cancer are dependent on an individual's biology of the tumor and the stage of original diagnosis. It is estimated that 20–30% of all breast cancer cases will become metastatic[1]. Breast cancer patients who were diagnosed at later stages have lower survival rates, while those diagnosed at Stage I have a median survival of 212 months[6]. Advanced stage diseases and negative hormone receptor status were each associated with poor survival outcome[7]. Therefore, early diagnoses benefit and contribute to therapeutic success and quality of life.

Patients diagnosed with breast cancer are also given a grade, based on results of immunohistochemistry staining of the tumor. Tumor size and high histological grade are independent of patient age [8]. The histological samples indicated how aggressively the tumor may metastasize. We use breast cancer grades to refine our analysis of the association between breast and spine cancer. Grades range from 0–3+, in which 0 or 1 represents low grade cancers, which look similar to normal cells and are less likely to spread[9]. Grade 2 breast cancer indicate a faster growth, while grade 3 breast cancers grow even more rapidly[10]. This scoring method takes into account differentiation, nuclear features, and mitotic activity. [11]

Bony metastasis most commonly involves the spinal column and affects 10–30% of all cancer patients [12]. Skeletal metastases will affect about 70% of women with advanced disease, of those patients, 33% will be diagnosed with metastases to the vertebral column [13, 14]. Spinal metastases dramatically decrease a patient's quality of life and can lead to additional problems such as increased levels of pain, pathological fractures, or neurologic compression [15]. Computed tomography (CT) scans have traditionally been used to assess

the presence and density of vertebral metastases [12]. There are two main types of lesions that can occur with spinal metastases, osteolytic or osteoblastic. Lytic lesions deteriorate areas of the spine, while blastic lesions harden the spine with growth of additional cells [16]. Patients may also have “mixed” lesions, which indicate lytic and blastic lesions on the same vertebrae, or they may be categorized as having “both” lytic and blastic, which signify having lytic in one area of the vertebral column and blastic in another. Based on previous CT scan studies, scientists have confirmed there is an association between type of spinal metastases and breast cancer [17].

Historically, breast cancer patients have been shown to be associated with lytic spinal metastases[18]. However, our studies aimed to delve deeper into the association between spinal metastasis type and breast cancer by examining hormone receptor status. Previous studies have shown patterns of metastatic localization based on hormone receptor status. In one retrospective study, 36 patients were imaged between 1995 and 1998, using contrast-enhanced MRI of the brain and total body skeletal scintigraphy, for possible metastatic breast carcinoma [19]. Researchers categorized patients by estrogen receptor (ER) and progesterone receptor (PR) status and by brain and/or skeletal metastases, and excluded patients with diffuse metastases. Two major patterns of disease spread in metastatic breast carcinoma were identified. Patients with ER+/PR+ tumors more often had skeletal metastases than brain metastases, while patients with ER-/PR- tumors more often had brain metastases [19]. While this study demonstrated increased likelihood of spinal metastases based on hormone receptor status, there are still no known studies reporting on the association between hormone receptor status and spinal lesion type in breast cancer patients.

The aim of our study was use retrospective patient chart analysis to identify the association of hormone receptor status and spinal lesion type. Our findings most notably refuted previous findings of the association between lytic lesions and breast cancer. Through the examination of hormone receptor status, an association between blastic metastases and PR+ breast cancer patients was shown to be more prevalent. However, no known molecular pathways currently explain this phenomenon. To further our understanding, osteogenic genes were examined through a bioinformatics approach for potential contribution to blastic spinal metastases in invasive breast cancer patients.

Methods

Study Design

195 female breast cancer patients diagnosed from 1989–2013 with documented bone metastases were identified from the City of Hope’s cancer registry. A retrospective chart review was performed. CT scans such as in Figure 1 and physician impression notes were used to capture types of spinal metastatic lesions: blastic, lytic, both, or mixed. A review of pathology reports was conducted to identify hormone receptor grading (0 to 3+) for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Reported percentage tubule formations were converted to grades according to methods documented in Bukholm, I.R., et al.: greater than 75% tubule formation was graded as 1, 10–75% was graded as 2, and less than 10% was graded as 3[20]. Reports of grade 1–2+ were considered 2+, and reports of grade 2–3+ were considered 3+. Patients with no

documentation of any hormone receptor grading or spinal metastases type were excluded from the study. This yielded a cohort of 153 patients.

In a secondary analysis to potentially map a molecular pathway of breast to bone metastases, The Cancer Genome Atlas (TCGA) data in OncoPrint Platform[®] by Thermo Fisher Scientific Inc. was used to evaluate osteogenic gene expression levels in normal versus invasive breast cancer patients. Collagen, type I, alpha 1 (COL1A1), and collagen, type I, alpha 2 (COL1A2) were found to be upregulated in the collected sample size of 76 invasive breast cancer patients and were compared to 61 normal breast cancer patients.

Statistical Analysis

Summary statistics were reported on all patients using frequencies and percentages for categorical data and using mean and standard deviation (SD) for continuous age and years to recurrence. Chi-square analyses were performed testing the association of hormone receptor status with spinal metastases type. Hormone receptor was tested as positive versus negative and by grading levels grouped as follows: 0–1+ vs. 3+, 2+ vs. 3+, and 0–1+ vs. 2+ and 3+. Statistical analyses of the cohorts were performed using SAS version 9.4. T-tests in OncoPrint were used to identify statistically significant differences in log₂ median-centered ratio gene expression between normal and invasive breast cancer patients. For all tests, p-values less than 0.05 were considered significant.

Results

Summary statistics of our patient cohort are reported in Table 1. Most patients were White/Non-Hispanic and had late stage breast cancer at onset (Stage 3 or 4). Patients on average had 3 years from time of breast cancer diagnosis to spinal metastases. Unknown hormone receptor status varied from approximately 8% to 12% by receptor type and 4% of patients were unknown with regard to triple negative status. When hormone receptor status was known, patients were more often ER+, PR+, and HER2–. Only 10 patients (6.5%) were triple negative for hormone receptors ER, PR, and HER2.

Table 2 shows associations of hormone receptor status (positive vs. negative) by spinal metastases type. Nearly 60% of PR+ patients as opposed to 45% of PR– patients had blastic metastasis (p=0.0253). No statistically significant associations were found for ER, HER2, and triple negative status with spinal metastases type. Table 3 shows associations of hormone receptor grade and spinal metastases type, PR 3+ patients more often had blastic metastases (70%) than PR 0–1+ patients (45%, p-value 0.0246) and PR 2+ patients (56%, p-value = 0.0131). There were no statistically significant associations between hormone receptor grade and spinal metastases type for ER or HER2, and no statistically significant differences in spinal metastases types between PR2+ and PR3+ patients.

In our secondary analyses using OncoPrint, Figure 2 shows the difference in upregulation of (A) COL1A1 and (B) COL1A2 between (1) normal breast cancer on left panel vs. (2) invasive breast cancer on right panel. Both osteogenic genes had significantly higher expression levels in invasive breast cancer patients than in normal breast cancer patients. For COL1A1, invasive breast cancer patients had 5.483 times the expression levels of normal

breast cancer patients and for COL1A2 invasive breast cancer patients had 3.258 times the expression levels of normal breast cancer patients (both p-values <0.0001).

Discussion

Advanced breast cancer has been known to be associated with development of metastatic spine lesions [21]. Patients with high-grade breast cancers present with spinal metastases earlier, but unfortunately current treatments for bone metastases are palliative and not curative. The prognosis for patients who are diagnosed with metastatic breast to bone cancer is poor, with a reported 15% five year survival rate [22].

Previous findings have highlighted the potential relationship between breast cancer and lytic lesions; however, our study suggests progesterone receptor positive (PR+) patients have a higher tendency to develop blastic lesions alone compared to other spinal metastases. Blastic lesions occur due to additional osteoblasts filling the bone, while lytic lesions destroy the native bone. Recent *in vitro* studies have documented progesterone's ability to promote osteoblast maturation and differentiation and therefore increase osteoblast numbers [23]. Additionally, prior studies have often focused on estrogen's contribution in prevention of bone loss [19]. However, current research has shown that elevated progesterone levels may prevent bone loss, even in the absence of estrogen [24]. For example, in pseudopregnancy cases, in which there are high endogenous progesterone and low estrogen levels, increased periosteal bone formation was observed [24]. The study suggested endogenous progesterone may contribute to maintenance of bone mass by increasing bone formation during periods of low estrogen.

Furthermore, postmenopausal bone loss has been historically associated with low levels of estrogen, and is most often treated with estrogen replacement therapy [25]. However, other studies have shown decreased levels of estrogen may not be the sole reason for bone loss. Progesterone deficiency may also play a role, as progesterone replacement therapy has shown greater increase in bone formation, while estrogen affects bone resorption [26]. Thus, the hardening of the spine or blastic lesions may correspond to an over expression of progesterone's natural role in the body.

Despite the correlative studies, the molecular pathway has remained unknown. Although it is known that the breast cancer tumor cell must attach to and colonize bone, the mechanisms are not clearly defined [27]. Nutter et al. has shown bone colonization is associated with increased fibronectin and upregulation of molecules that may affect signal transduction pathways, which may breakdown the extracellular matrix[27]. The data suggests that during early stages of breast cancer to bone metastasis, specific genes may be altered to facilitate bone formation. Nevertheless, the genes and potential pathway to explain the propensity of PR+ breast cancers to form blastic lesions are still indistinguishable.

By using TCGA, type I collagen osteogenic genes, COL1A1 and COL1A2, were found to be upregulated in invasive breast as compared to normal breast cancer patients. Collagen plays a major role in the composition of the extracellular matrix and contributes to the physical barrier for cell migration and regulates proliferation of both normal and cancer cells[28].

Recently, type I collagen has been studied in terms of its relationship to tumorigenesis of malignant breast cancer[29]. COL1A1 and COL1A2 make up the most abundant protein in bone and the degradation of type I collagen by matrix metalloproteinases (MMPs) have been associated with poor survival and secondary metastasis[30]. Although the process is unclear, type I collagen has been speculated to be associated with invasive breast cancers and their changing characteristics may be involved in the development of later bony lesions [31]. Thus, the regulation of type I collagen genes is key to understanding the development of spinal metastasis and its relationship to breast cancer [32]. Additionally, prior studies have demonstrated the connection between COL1A1 and breast cancer cells as a positively regulated target gene of the Wnt/Beta-catenin pathway [33]. The combined studies highlight the importance of these osteogenic genes, COL1A1 and COL1A2, and their relationship to both breast cancer development and later spinal metastases.

Due to the preliminary nature of our study, direct clinical applications are not currently relevant. Spinal metastasis is a feared consequence of breast cancer, as morbidity is often associated with spinal fractures. Understanding the biology of the fractures potentially would provide an opportunity for patient modulation of the cancer metastasis to a more benign form. For example, an epigenetic modification can theoretically alter phenotype of the tumor to create a blastic rather than lytic metastasis, decreasing the incidence of fractures. Though the molecular relationship between higher grade PR+ breast cancers and spine cancer is unclear, our study indicates a possible explanation for the development of blastic versus lytic lesions and discusses the role of progesterone in relation to increased bone formation, a blastic characteristic. However, for this to become a reality, studies such as ours must be conducted to elucidate potential associations between metastatic breast cancers and development of certain types of spinal lesions.

Conclusion

Prior to our study, it had been established that breast cancer patients may have the propensity to develop lytic spinal lesions. Our findings have shown the contrary through examination of the association between hormone receptor status and the type of metastatic spinal lesion. Our study suggests progesterone receptor positive (PR+) patients have a higher tendency to develop blastic lesions alone compared to other spinal metastases. This is of particular interest as we have looked into the role of progesterone in bone formation and have proposed a link between PR+ breast cancer patients developing blastic metastases. Because the pathway is unclear, we attempt to elucidate our findings using biostatistics. We demonstrated that there are osteogenic genes which are upregulated in invasive breast cancer patients versus other cancers. Our study is in the early stages of mapping out a potential mechanism for the development of blastic lesions in high grade breast cancer patients. Prospective studies through tissue collection may be performed to confirm our findings in a clinical setting. Future basic science experiments will also be performed to investigate our findings of upregulation of osteogenic genes COL1A1 and COL1A2 through use of immunohistochemistry or Western blots. Ideally, by isolating osteogenic genes in metastatic breast cancer tissues, one would be able better understand the molecular pathway and the relationship of progesterone to COL1A1 and COL1A2 in invasive breast cancer patients.

Further studies of the regulatory pathways for breast and spine cancer linked genes, can lead to improved diagnostic and therapeutic strategies for metastatic breast cancer patients.

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Abbreviations

COL1A1	collagen, type I, alpha 1
COL1A2	collagen, type I, alpha 2
CT	Computed tomography
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
PR	progesterone receptor
TCGA	The Cancer Genome Atlas

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Highlights

- Conducted a retrospective chart review of 153 patients to examine the relationship between metastatic breast cancer and type of spinal lesions present.
- Novel discovery that high-grade progesterone receptor positive breast cancers tend to lead to osteoblastic metastases.
- Examined potential breast cancer biomarkers that could explain the relationship, COL1A1 and COL1A2. Biomarkers were found to be upregulated in invasive breast cancer patients.
- Future goals include examining these biomarkers in metastatic breast cancer tissues to better understand the molecular pathway.

Fig. 1. CT scan of Patient with Metastatic Breast Cancer to the Spine

75- year old female patient with metastatic breast carcinoma presents with multiple mixed lytic and blastic lesions in thoracic and lumbar vertebrae. Arrows indicate various lesions present on the spine. Blastic lesions are lighter than lytic lesions, which appear to be the darker spots of the CT scan. Impression notes from the physician describe a stable compression fracture of the L2 vertebral body, as well as stable 7mm anterolisthesis of L4 on L5 associated with degenerative changes of the facet joints.

Fig. 2. Gene Expression Data for Osteogenic Genes in Breast Cancer Patients

593 total breast cancer patients were identified using The Cancer Genome Atlas (TCGA), 76 of which were invasive breast carcinoma. Comparisons between normal breast samples and invasive breast carcinoma are shown through the gene expression bar plots. (a–b) Collagen, type I, alpha 1, A1 and A2 are upregulated in invasive breast carcinoma in comparison to normal breast tissue

Table 1

Summary Statistics of Breast Cancer with Spinal Metastases Cohort (N=153).

	n	%
Age Mean (SD) [Range]	52 (13) [28–94]	
Race		
White/Non-Hispanic	87	56.86
White/Hispanic	30	19.61
Black	7	4.58
Native American	2	1.31
Asian	26	16.99
Unknown	1	0.65
Years until recurrence Mean (SD) [Range]	3.0 (4.1) [0–19]	
Breast Cancer Stage		
I	13	8.50
II	38	24.84
III	27	17.64
IV	64	41.83
Unknown	11	7.18
Hormone Receptor		
Estrogen Receptor (Grade)		
Negative (0)	23	15.03
1+	5	3.27
2+	25	16.34
3+	81	52.94
Unknown	19	12.26
Progesterone Receptor (Grade)		
Negative (0)	60	39.22
1+	13	8.50
2+	25	16.34
3+	36	23.53
Unknown	19	12.42
HER 2 (Grade)		
Negative (0–1+)	75	49.02
2+	43	28.10
3+	23	15.03
Unknown	12	7.84
Triple Negative		
Yes	10	6.54
No	137	89.54
Unknown	6	3.92

Table 2

Hormone Receptor Status by Spinal Metastases Lesion Type

Hormone Receptor Status	Spinal Metastases Type						Chi-Square P-Value
	Blastic		Lytic		Mixed Lytic/Blastic		
	n	%	n	%	n	%	
ER							0.4165
Negative	9	39.1%	4	17.4%	4	17.4%	26.1%
Positive	70	56.0%	21	16.8%	15	12.0%	15.2%
PR							0.0253 *
Negative	27	45.0%	9	15.0%	7	11.7%	28.3%
Positive	52	59.8%	15	17.2%	12	13.8%	9.2%
HER2							0.3411
Negative	43	57.3%	13	17.3%	11	14.7%	10.7%
Positive	35	50.7%	11	15.9%	8	11.6%	21.7%
Triple Negative (ER-/PR-/HER2-)							0.8583
Yes	5	50.0%	2	20.0%	2	20.0%	10.0%
No	74	54.0%	23	16.8%	17	12.4%	16.8%

* Statistically significant p-value <0.05.

Table 3

Hormone Receptor Grade by Spinal Metastases Type

Hormone Receptor Grade	Spinal Metastases Type						Chi-Square Test P-Values		
	Blastic			Lytic			0-1+ vs 3+P-Value		
	n	%	n	%	n	%	0-1+ vs 3+P-Value	2+ vs 3+P-Value	0-1+ vs 2-3+P-Value
ER									
0-1+	10	35.7%	5	17.9%	6	21.4%	7	25.0%	0.1009
2+	11	44.0%	8	32.0%	4	16.0%	2	8.0%	
3+	51	63.0%	11	13.6%	8	9.9%	11	13.6%	
PR									
0-1+	33	45.2%	12	16.4%	10	13.7%	18	24.7%	0.0131*
2+	14	56.0%	7	28.0%	2	8.0%	2	8.0%	
3+	25	69.4%	5	13.9%	5	13.9%	1	2.8%	
Her2									
0-1+	43	57.3%	13	17.3%	11	14.7%	8	10.7%	0.3870
2+	22	51.2%	6	14.0%	6	14.0%	9	20.9%	
3+	11	47.8%	5	21.7%	2	8.7%	5	21.7%	

* Statistically significant p-value <0.05