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

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■ OBJECTIVE: **Bony metastasis predominantly affects the spinal column and has been commonly associated in patients with breast cancer. 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 that patients with breast cancer have an increased likelihood for development of lytic spinal metastases.**

■ METHODS: **A retrospective chart review was conducted to more closely examine the association between hormone receptor status and spinal lesion type. A total of 195 patients were initially identified through the City of Hope Cancer Registry. Of the 195, only 153 patients had hormone receptor marker status available. Associations between spinal lesion and hormone receptor status were evaluated using χ^2 tests with alpha = 0.05 significance level. In a secondary analysis, the Oncomine Platform was used, which integrated The Cancer Genome Atlas (TCGA) datasets, to identify osteogenic genes that may be relevant to invasive breast cancers.**

■ RESULTS: **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 up-regulated, which could provide a molecular explanation for the development of blastic metastases.**

■ CONCLUSIONS: **By integrating 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.**

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 during the course of her lifetime.[1] Since 2000, more than 220,000 women in the United States 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 investigators have examined its use for prognostic purposes. Although 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 5 years after diagnosis.[4] Specifically, estrogen receptor (ER) or progesterone receptor (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.

Key words
- Bone metastasis
- Breast cancer
- Hormone receptor status
- Metastatic lesions
- Spine cancer

Abbreviations and Acronyms
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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In addition, patients with breast cancer 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 patients with breast cancer will become metastatic.[1] Patients with breast cancer who were diagnosed at later stages have lower survival rates, whereas 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 histologic grade are independent of patient age.[8] The histologic 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 to 3+, in which 0 or 1 represents low grade cancers. These look similar to normal cells and are less likely to spread.[9] Grade 2 breast cancer indicates a faster growth, whereas 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, pathologic fractures, or neurological 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, whereas 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, patients with breast cancer 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 1 retrospective study,[19] 36 patients were imaged between 1995 and 1998, using contrast-enhanced magnetic resonance imaging of the brain and total body skeletal scintigraphy, for possible metastatic breast carcinoma. Researchers categorized patients by ER and 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, whereas patients with ER-/PR- tumors more often had brain metastases.[19] Although that 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 patients with breast cancer.

The aim of our study was to 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 patients with PR + breast cancer 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 patients with invasive breast cancer.

METHODS

Study Design

A total of 195 female patients with breast cancer diagnosed from 1989 to 2013 with documented bone metastases were identified from the City of Hope's cancer registry. A retrospective chart review was performed. CT scans (**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 ER, PR, and HER2. Reported percentage tubule formations were converted to grades according to methods documented in et al[20]: >75% tubule formation was graded as 1, 10%–75% was graded as 2, and <10% was graded as 3. 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 Oncomine Platform by Thermo Fisher Scientific Inc. (Grand Island, NY) 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 up-regulated in the collected sample size of 76 patients with invasive breast cancer and were compared to 61 patients with normal breast cancer.

Statistical Analysis

Summary statistics were reported on all patients using frequencies and percentages for categorical data and using mean and standard deviation for continuous age and years to recurrence. The χ^2 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+ versus 3+, 2 + versus 3+, and 0–1+ versus 2+ and 3+. Statistical analyses of the cohorts were performed using SAS version 9.4. The *t*-tests in Oncomine were used to identify statistically significant differences in log2 median-centered ratio gene expression between normal and

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