

# Prediction of Bone Metastasis in Inflammatory Breast Cancer Using a Markov Chain Model

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Breast cancer • Inflammatory breast cancer • Bone metastasis • Prediction model • Markov chain model

## ABSTRACT

**Background.** Inflammatory breast cancer (IBC) is a rare yet aggressive variant of breast cancer with a high recurrence rate. We hypothesized that patterns of metastasis differ between IBC and non-IBC. We focused on the patterns of bone metastasis throughout disease progression to determine statistical differences that can lead to clinically relevant outcomes. Our primary outcome of this study is to quantify and describe this difference with a view to applying the findings to clinically relevant outcomes for patients.

**Subjects, Materials, and Methods.** We retrospectively collected data of patients with nonmetastatic IBC ( $n = 299$ ) and non-IBC ( $n = 3,436$ ). Probabilities of future site-specific metastases were calculated. Spread patterns were visualized to quantify the most probable metastatic pathways of

progression and to categorize spread pattern based on their propensity to subsequent dissemination of cancer.

**Results.** In patients with IBC, the probabilities of developing bone metastasis after chest wall, lung, or liver metastasis as the first site of progression were high: 28%, 21%, and 21%, respectively. For patients with non-IBC, the probability of developing bone metastasis was fairly consistent regardless of initial metastasis site.

**Conclusion.** Metastatic patterns of spread differ between patients with IBC and non-IBC. Selection of patients with IBC with known liver, chest wall, and/or lung metastasis would create a population in whom to investigate effective methods for preventing future bone metastasis. *The Oncologist* 2019;24:1322–1330

**Implications for Practice:** This study demonstrated that the patterns of metastasis leading to and following bone metastasis differ significantly between patients with inflammatory breast cancer (IBC) and those with non-IBC. Patients with IBC had a progression pattern that tended toward the development of bone metastasis if they had previously developed metastases in the liver, chest wall, and lung, rather than in other sites. Selection of patients with IBC with known liver, chest wall, and/or lung metastasis would create a population in whom to investigate effective methods for preventing future bone metastasis.

## INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer in females and the second most common cause of cancer death in women in the U.S. [1]. There are currently an

estimated more than 3.5 million BC survivors living in the U.S. [2], and it is estimated that there will be more than 40,000 deaths in 2017 due to BC [3]. Inflammatory breast

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cancer (IBC) is a very rare subset of the disease (1.5% of all BCs) marked by distinct clinical and biological characteristics [4, 5]. Compared with non-IBC cases, it is extremely aggressive and has a high recurrence rate [5–7]. Because of these factors, once a patient with IBC develops a recurrence or metastasis, a rapid and decisive strategy to prevent further disease progression is needed.

Approximately 10%–15% of patients with estrogen receptor (ER)-negative and 5%–10% of patients with ER-positive invasive breast cancer develop disease recurrence at 5 years regardless of the completion of standard multimodality treatment [8]. In contrast, the 5-year recurrence rates are 65%–75% in patients with hormone receptor-positive IBC and greater than 80% in patients with triple-negative IBC [9]. Current efforts to improve survival outcomes in initially curable BC are aimed at predicting which patients are most susceptible to developing distant metastases and finding efficacious early intervention strategies.

One of these recent efforts includes adjuvant bisphosphonate treatment in patients with early-stage breast cancer [10, 11]. Zoledronic acid is a bisphosphonate that is approved for patients with bone metastasis and used to prevent skeletal-related events [12]. Some data showed that it may affect the bone destruction by inhibiting “vicious cycle” of growth factor and cytokine signaling between tumor and bone cells in the bone marrow microenvironment [13]. Despite this, there was no significant benefit found among patients with breast cancer in general in the context of recurrent disease with the addition of adjuvant zoledronic acid [10, 13]. However, a meta-analysis of 18,766 patients with early-stage breast cancer from 26 randomized clinical trials reported that in postmenopausal women treatment with adjuvant bisphosphonates reduced the rate of recurrence in the bone and improved survival [14]. A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline recommends adjuvant bisphosphonates in postmenopausal patients with nonmetastatic breast cancer [11].

Denosumab, another drug that is approved for patients with bone metastasis, is a humanized monoclonal antibody that binds to and inhibits the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL), which is an essential mediator of osteoclast activity and bone resorption [15, 16]. Randomized clinical trials have shown denosumab to reduce the number of skeletal-related events when it is used in the adjuvant setting [16], and prior studies have reported that it is superior to zoledronic acid in reducing bone-related complications of metastatic BC [17]. In addition to the role of bone remodeling, RANKL plays an important role in enhancing tumorigenic change, cell proliferation, and metastasis [18–20]. In this regard, denosumab might prove a better treatment for the prevention of bone metastasis. Recent study demonstrated that adjuvant denosumab improves disease-free survival of patients with hormone receptor-positive postmenopausal breast cancer who were treated with aromatase inhibitor [21]. However, those studies are for breast cancer in general, and the clinical benefit in IBC is still unclear.

As of now, there are no clinically validated biomarkers to determine which patients will develop bone metastasis in breast cancer. The lack of bone metastases-predictive

biomarkers may impede recommendations for preventive adjuvant zoledronic acid or denosumab. Hence, understanding and predicting metastatic progression patterns is a necessary step in designing a clinical trial model for this set of drugs.

Newton et al. have developed a breast cancer model that predicts the subsequent metastatic sites using a retrospective longitudinal database [22]. To simulate progression, the model makes the assumption that the next state of the disease is only dependent on the current state and nothing prior (no history dependence). The transition probabilities from state to state are then used to quantify the likelihood of each metastatic pathway. Additionally, the model classifies metastatic sites as those that are more likely to receive tumor cells with diminished subsequent dissemination (“sponges”) and those from which tumor cells are more likely to spread to potential metastatic locations (“spreaders”) [22]. The clinical implications of this model with respect to the patterns of metastatic spread may allow for targeted interventions that improve patient outcomes.

We hypothesized that the patterns of metastasis leading to and following bone metastasis differ significantly between patients with IBC and those with non-IBC. In this study, we quantified and described this difference with a view to applying the findings to clinically relevant outcomes for patients.

## SUBJECTS, MATERIALS, AND METHODS

### Patient Selection

This retrospective chart review study was approved by The University of Texas MD Anderson Cancer Center’s Institutional Review Board (protocol number: PA 16-0138), and a waiver of informed consent was granted based on the study’s retrospective nature. We reviewed the Breast Medical Oncology management system database (protocol number: 2004-0541) to identify patients with pathologically confirmed nonmetastatic invasive IBC or non-IBC at the time of diagnosis who developed local recurrence or distant metastasis between January 1980 and January 2016.

From the database, we extracted various clinical, demographic, and temporal data points for each patient, such as age at diagnosis, race/ethnicity, menopausal status at diagnosis, body mass index, histological subtype, clinical stage, ER status, progesterone receptor (PR) status, human epidermal growth receptor 2 (HER2) status, nuclear grade, lymphovascular invasion status, treatments (neoadjuvant, adjuvant, and metastatic settings and radiation), dates and sites of recurrence or metastasis, and dates of initial diagnosis, definitive surgery, death, and last follow-up. The diagnosis of IBC was made by multidisciplinary approach by physicians specialized in IBC in the Morgan Welch Inflammatory Breast Cancer Clinic since 2006. The diagnosis was made by each treatment physician before 2006.

Follow-up information for patients in the Breast Medical Oncology management system database is obtained every 2 years by direct review of the medical records and linkage to the MD Anderson Tumor Registry. The system mails follow-up letters to each patient registered in the system to confirm

that the patient is alive and free of cancer. As a backup, the MD Anderson Tumor Registry also checks the Social Security Death Index and the Texas Bureau of Vital Statistics for the status of patients who do not respond to the letters.

### Statistical Analysis

All Kaplan-Meier survival curves of overall survival (OS) were generated with the R programming language (version 3.3.1; <https://www.r-project.org/>) in RStudio (version 0.99.902; <https://www.rstudio.com/>) using the survival library (version 2.39-4) and compared for statistical differences ( $p < .05$ ) using the log-rank test. Patients with IBC and non-IBC were further subgrouped into those that never developed bone metastasis, those for whom bone metastasis was present when progression was first diagnosed, and those who developed bone metastasis later, not as part of their first identified progression. Python (version 2.7; <https://www.python.org/>) was used to calculate conditional probabilities between bone and each of the sites in the model, and the seaborn module was used to graph the results in a heat map format (version 0.7.1; <https://seaborn.pydata.org/>).

### Spatiotemporal Diagrams

Metastatic progression for the patients with IBC and non-IBC was visualized as circular “tree ring” diagrams with disease diagnosis originating in the center and episodes of progression moving outward in distinct steps with each concentric ring. Sites of progression were grouped based on anatomical similarity and subsequently color-coded for quick visual identification. The “Other” category comprised multiple sites that occur in less than 1% of the population. The circular arc length of each ring represents the percentage of the population that has progressed to that metastatic location from each preceding step. In the event that a patient had developed multiple tumors since their previous doctor’s visit, we listed the tumors of that particular progression in order of decreasing frequency and illustrated them according to this.

### Markov Modeling

The Markov chain models were generated in Python with the use of the Pykov module (version 1.0; <https://github.com/riccardoscalco/Pykov>) using maximum likelihood estimators from direct observations of the data points. The resulting model is visualized as a circular chord diagram with color-coding identical to that of the spatiotemporal diagrams. The one-step transition probabilities were used to calculate and determine the top 30 two-step transition probabilities to create a reduced model. Using these 30 values and computing the ratio between the total outgoing ( $P_{out}$ ) and total incoming ( $P_{in}$ ) probabilities, we classified each anatomical site in the model as either a spreader ( $P_{out}/P_{in} > 1$ ) or a sponge ( $P_{out}/P_{in} < 1$ ), and colored them red or blue, respectively. The numerical ratio is called the spreader/sponge factor and measures the propensity of the site to spread the disease.

For additional analyses, these figures and models were incorporated into an interactive webpage ([http://kuhn.usc.edu/breast\\_cancer/](http://kuhn.usc.edu/breast_cancer/)). All patient data are stored on a secure server in a PostgreSQL database. We use the Python modules psycopg2 (version 2.0.14), pandas (version 0.17.1), and

NumPy (version 1.10.4) to pull subsets of patients and perform all necessary calculations and arrangement of the data. The response output was then used to create interactive visuals via the D3 JavaScript library (<http://d3js.org/>) and displayed in a column format for easy, side-by-side comparison.

## RESULTS

### Patient Characteristics

Within our patient cohort of 3,735 primary patients with BC, there were 299 patients with IBC (8.01%) and 3,436 patients with non-IBC (91.99%). The mean follow-up times were 4.73 years for patients with IBC and 6.34 years for those with non-IBC. The mean ages at initial diagnosis were 48.35 and 48.76 years, respectively. The majority of patients were of white, black, or Hispanic race/ethnicity (~96%), and most had presented with ductal carcinoma (Table 1). Among patients with hormone receptor data available, ER status was positive in the majority of patients with non-IBC (56.52%), but in a smaller proportion of patients with IBC (38.13%). In both IBC and non-IBC populations, the majority were PR negative (64.54% and 50.61%, respectively) and HER2 negative (46.82% and 62.98%, respectively). Of note, a large portion of each group had an unknown HER2 status: 25.42% in the IBC population and 19.53% in the non-IBC population.

The distribution of every metastatic site noted during the course of progression for both IBC and non-IBC is shown in Table 2. The most frequent metastatic site for both groups was the distant lymph nodes, constituting approximately 20% of all metastases. A bone metastasis occurred in 52.21% of patients with non-IBC ( $n = 1,794$ ) as compared with 44.82% of patients with IBC ( $n = 134$ ). Additionally, a chest wall metastasis was twice as probable in patients with IBC (32.78%;  $n = 98$ ) as in those with non-IBC (16.01%;  $n = 550$ ). For both lung/pleura and liver metastases separately, the incidence rates in both groups were comparable. Brain metastasis was more frequent in patients with IBC (25.08%;  $n = 75$ ) than in patients with non-IBC (21.74%;  $n = 747$ ).

### Survival Analysis

Figure 1A shows that the 5-year survival rate of patients with IBC was 35.6%, as compared with 59.0% for those with non-IBC ( $p < .001$ ). To elucidate the role of bone metastases in these populations, we subgrouped each based on whether the patient developed a bone metastasis in their first progression of metastases (Bone First; Total = 1,276, IBC = 79, non-IBC = 1,197), not in their first progression (Bone Not First; Total = 650; IBC = 54, non-IBC = 596), or not at all (No Bone; Total = 1,809, IBC = 166, non-IBC = 1,643). In the IBC group (Fig. 1B), the OS duration in the Bone Not First subgroup was shorter than that in the subgroup with no bone metastasis, but the difference was not statistically significant ( $p = .140$ ). The Bone First IBC subgroup exhibited significantly better OS than Bone Not First ( $p = .038$ ). The difference in OS duration between the Bone First subgroup and the subgroup with no bone metastasis was not significant ( $p = .749$ ). In the non-IBC group (Fig. 1C), developing a bone metastasis, regardless of timing, yielded significantly worse OS compared

**Table 1.** Baseline characteristics for patients with IBC and non-IBC

Characteristics	IBC (n = 299), n (%)	Non-IBC (n = 3,436), n (%)
Age, years		
Mean (SD)	48.35 (10.84)	48.76 (11.81)
Follow-up time, years		
Mean (SD)	4.73 (4.02)	6.34 (4.59)
BMI, kg/m <sup>2</sup>		
Mean (SD)	30.42 (7.15)	28.34 (6.61)
Race/ethnicity		
White	232 (77.59)	2,379 (69.24)
Hispanic	33 (11.04)	394 (11.47)
Black	24 (8.03)	509 (14.81)
Other	3 (1.00)	41 (1.19)
Menopause status		
Premenopausal	147 (49.16)	1,676 (48.78)
Postmenopausal	150 (50.17)	1,697 (49.39)
Unknown	2 (0.67)	63 (1.83)
Clinical stage		
I	0	701 (20.40)
II	0	1,666 (48.49)
III	299 (100)	1,069 (31.11)
Histology		
Ductal	264 (88.29)	2,898 (84.34)
Invasive carcinoma	10 (3.34)	69 (2.01)
Lobular	12 (4.01)	243 (7.07)
Mixed	11 (3.68)	151 (4.39)
Other	2 (0.67)	75 (2.18)
ER status		
Positive	114 (38.13)	1,942 (56.52)
Negative	154 (51.51)	1,334 (38.82)
Unknown	31 (10.37)	160 (4.66)
PR status		
Positive	80 (26.76)	1,501 (43.68)
Negative	187 (62.54)	1,739 (50.61)
Unknown	32 (10.70)	196 (5.70)
HER2 status		
Positive	83 (27.76)	601 (17.49)
Negative	140 (46.82)	2,164 (62.98)
Unknown	76 (25.42)	671 (19.53)
Nuclear grade		
I	4 (1.34)	92 (2.68)
II	50 (16.72)	942 (27.42)
III	226 (75.59)	2,187 (63.65)
Unknown	19 (6.35)	215 (6.26)
Lymphovascular invasion		
Positive	197 (65.89)	1,380 (40.16)
Negative	96 (32.11)	1,980 (57.63)
Unknown	6 (2.01)	76 (2.21)

(continued)

**Table 1.** (continued)

Characteristics	IBC (n = 299), n (%)	Non-IBC (n = 3,436), n (%)
Types of treatments		
Neoadjuvant chemotherapy	285 (95.32)	1,905 (55.44)
Adjuvant chemotherapy	187 (62.54)	1,738 (50.58)
HER2 targeted therapy	30 (10.03)	174 (5.06)
Hormone therapy	95 (31.77)	1,703 (49.56)
Radiation	246 (82.27)	2,375 (69.12)
Survival status		
Alive	42 (14.05)	1,065 (31.00)
Deceased	257 (85.95)	2,371 (69.00)

Abbreviations: BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth receptor 2; IBC, inflammatory breast cancer; PR, progesterone receptor.

with having no bone metastasis ( $p < .005$  for both Bone First and Bone Not First). There was no statistically significant difference in OS between the Bone First and Bone Not First subgroups ( $p = .288$ ).

### Metastatic Progression

We next investigated the sequence of metastatic sites in both patients with IBC and those with non-IBC via their spatiotemporal diagrams (Fig. 2A, 2B, respectively). Both groups' trajectories 20 years after disease diagnosis are shown. A noted difference between the two was that the most common first metastatic sites for IBC were the distant lymph nodes (23.7%), chest wall (19.4%), and bone (19.1%), versus bone (30.4%), distant lymph nodes (22.1%), and lung/pleura (12.4%) for non-IBC. As expected, chest wall metastases were much more common in IBC and also much more frequent as a first metastatic site (19.4% vs. 7.39%).

Analyzing the patterns of progression revealed some interesting differences as well. Patients with IBC that progressed to the breast, bone, and then liver had a 71.43% (15/21) probability of dying without any further metastasis, versus a 37.16% (97/261) probability in non-IBC. The patients with non-IBC that progressed to breast, bone, and then lung developed many additional metastases before death, which has also been observed in previous research [22]. This pattern was not seen in patients with IBC. The models are available online: [http://kuhn.usc.edu/breast\\_cancer](http://kuhn.usc.edu/breast_cancer).

### Conditional Progression

Because our main interest was the patterns of progression in the context of bone metastasis, we focused on pathways to bone metastases as well as pathways afterward. We investigated these dynamics by means of conditional probabilities in two distinct scenarios: (a) development of a bone metastasis prior to metastasis in any of the other sites and (b) development of a nonbone metastasis prior to a bone metastasis.

In the first scenario, the probabilities of developing specific, nonbone metastases after a bone metastasis were calculated with three different given conditions: (a) a bone metastasis was present in the first progression (Bone In First), (b) not present in the first progression (Bone Not

**Table 2.** Profile of the distribution of metastatic sites for patients with IBC and non-IBC

IBC (n = 299)				Non-IBC (n = 3,436)			
Metastatic site	n	% of all sites	% of patients	Metastatic site	n	% of all sites	% of patients
LN (distant)	204	21.79	68.23	LN (distant)	1,991	19.87	57.95
Lung/pleura	157	16.77	52.51	Bone	1,794	17.90	52.21
Bone	134	14.32	44.82	Lung/pleura	1,769	17.65	51.48
Liver	103	11.00	34.45	Liver	1,259	12.56	36.64
Chest wall	98	10.47	32.78	Brain	747	7.46	21.74
Brain	75	8.01	25.08	Chest wall	550	5.49	16.01
Skin	31	3.31	10.37	LN (regional)	464	4.63	13.50
Contra breast	29	3.10	9.70	Ipsi breast	454	4.53	13.21
LN (regional)	28	2.99	9.36	Other	347	3.46	10.10
Other	27	2.88	9.03	Skin	138	1.38	4.02
Other CNS	15	1.60	5.02	Other CNS	129	1.29	3.75
Bone marrow	12	1.28	4.01	Contra breast	114	1.14	3.32
Ipsi breast	10	1.07	3.34	Bone marrow	91	0.91	2.65
Pericardium	5	0.53	1.67	Kidney/adrenal	69	0.69	2.01
Ovary	4	0.43	1.34	Ovary	53	0.53	1.54
Kidney/adrenal	4	0.43	1.34	Pericardium	51	0.51	1.48

Sites are ordered by frequency of occurrence for each group.

Abbreviations: CNS, central nervous system; Contra, contralateral; IBC, inflammatory breast cancer; Ipsi, ipsilateral; LN, lymph nodes.

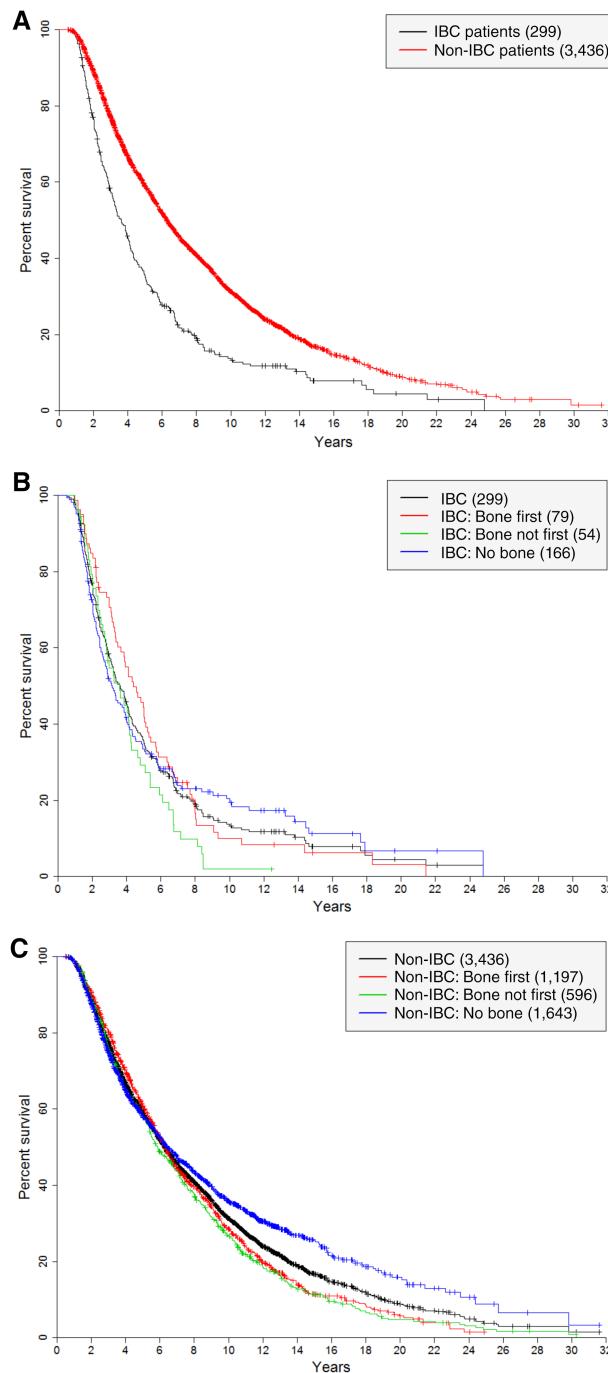
In First), and (c) present at any time of progression (Bone Ever). For each of these, results were divided into specific metastasis patterns: (a) in the immediate next progression (Met Site In Next) and (b) in any following progression (Met Site Ever After; Fig. 3). The highest probabilities for both the IBC and non-IBC groups were for spread to the liver, lung/pleura, regional lymph nodes, or brain. For example, as indicated in the first and second column in Figure 3A, 16% (13/79) of patients with IBC with bone metastasis in their first progression had liver metastasis in their second progression, and 24% (19/79) of patients had liver metastasis at some point in the natural progression of the disease. The third and fourth column in Figure 3A show that of patients with IBC with bone metastasis in their second or later progression, 7% (4/54) had liver metastasis in their immediate next progression. As indicated in the fifth and sixth column in Figure 3A, 13% (17/133) of patients with IBC with bone metastasis at some point of progression developed liver metastasis in their next progression, and 17% (23/133) of patients with IBC with bone metastasis at some point developed liver metastasis at some time point afterward.

For the second scenario, the probabilities of developing a bone metastasis after metastasis in other specific sites were calculated with three different given conditions: (a) a specific nonbone metastasis (listed on the left side of the figure) in the first progression (Met Site In First), (b) a specific nonbone metastasis not in the first progression (Met Site Not In First), and (c) a specific nonbone metastasis present in any progression (Met Site Ever). For each of these, results were divided into the bone metastasis being (a) in the immediate next progression (Bone In Next) and (b) in any following progression (Bone Ever After; Fig. 4). Cases in which bone metastasis had occurred in a prior

progression were excluded. Ignoring the metastasis sites with only a few cases, patients with initial progression to the chest wall, liver, and lung tended to develop bone metastasis at any point afterward. For these three particular metastases, patients developed bone metastasis in the immediate next progression in 15% (12/81), 12% (9/76), and 10% (6/58), respectively, and at any point afterward in 28% (23/81), 21% (16/76), and 21% (12/58), respectively. In patients with non-IBC, the differences between probabilities of each metastasis pattern were not as large as those with IBC (Fig. 4B).

### Markov Modeling

We next modeled the progression for each subpopulation via Markov chain models. The reduced models that were created from two-step transition pathways of the full models are shown in Figure 5. Because these figures were created from the top 30 most probable pathways, it is important to note that both models give a consistent snapshot of the two-step disease dynamics, as indicated by the 71.08% and 69.41% proportions of two-step values represented for IBC and non-IBC, respectively. Anatomical sites in the model were classified as either spreaders or sponges based on the ratio of the total outgoing ( $P_{out}$ ) and total incoming ( $P_{in}$ ) probabilities, indicating the propensity of the site to spread the disease. The IBC model denotes three spreaders (chest wall, bone, and liver) and two sponges (distant lymph nodes and lung), whereas the non-IBC model denotes one spreader (bone) and three sponges (distant lymph nodes, lung, and liver). As shown, the distant lymph nodes and lung were classified as sponges and bone as a spreader in both models. In contrast, liver was classified as a spreader in IBC and a sponge in non-IBC.



**Figure 1.** Kaplan-Meier survival curves over a 35-year period showing duration from diagnosis to death. **(A)**: Patients with IBC and non-IBC; **(B)**: patients with IBC with and without bone metastasis; and **(C)**: patients with non-IBC with and without bone metastasis. Bone First and Bone Not First refer to whether bone metastasis was present upon the first metastatic progression of disease.

Abbreviation: IBC, inflammatory breast cancer.

## DISCUSSION

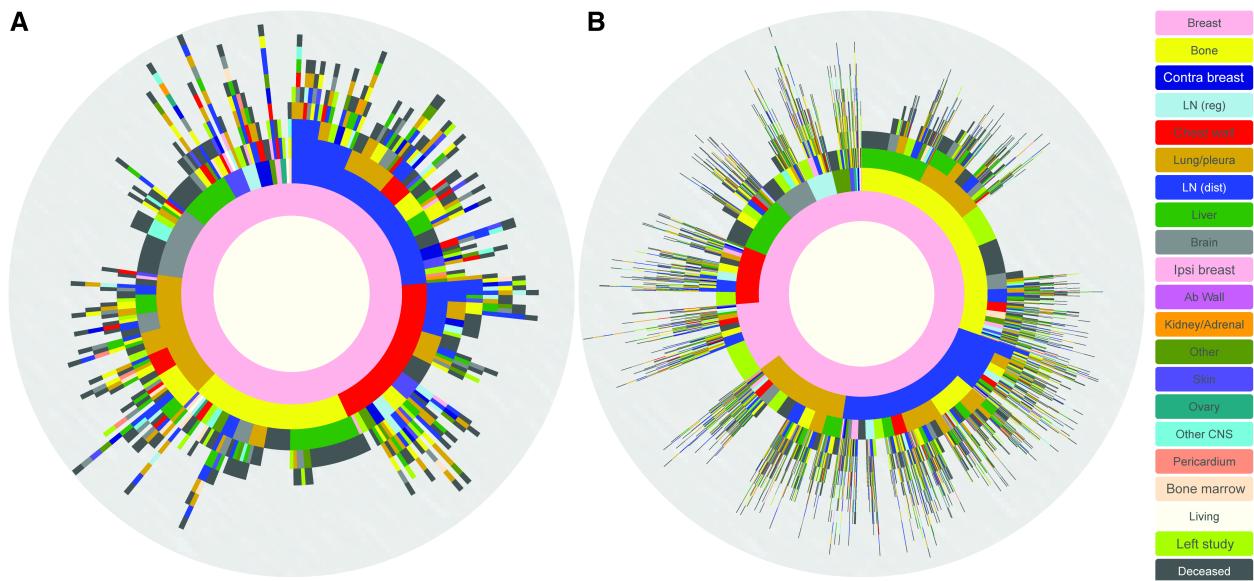
Our hypothesis that the patterns of metastasis leading to and following bone metastasis differ significantly between patients with IBC and those with non-IBC was supported. Patients with IBC had a progression pattern that tended toward the development of bone metastasis if they had

previously developed metastases in the liver, chest wall, and lung, rather than in other sites. No clear pattern of metastatic sites preceding bone metastasis was seen in patients with non-IBC. We found that both patients with IBC and those with non-IBC who had bone metastasis at some point in their disease had a higher frequency of developing liver, lung, and brain metastasis afterward as compared with other sites. Furthermore, in both IBC and non-IBC, bone metastasis was a spreader whereas lung metastasis was a sponge.

Currently, zoledronic acid and denosumab are approved only for patients who have known bone metastasis, and using them for preventive purposes is still controversial [10, 11, 13–16]. The D-CARE study reported that adjuvant denosumab did not reduce breast cancer recurrences or deaths in patients with high-risk early breast cancer [23]. Some preclinical studies have demonstrated that RANK binding to RANKL, which denosumab disrupts, enhanced tumorigenicity, promoted mechanisms of metastasis, and was related to resistance to chemotherapy [18, 19, 24]. One of these mechanisms is that micrometastases attached to the bone surface can activate osteoclasts that lead to metastasis in the bone and potentially at other sites [10, 25, 26]. Bisphosphonates such as zoledronic acid inhibit osteoclast activity both directly and indirectly through effects on osteoblasts [27].

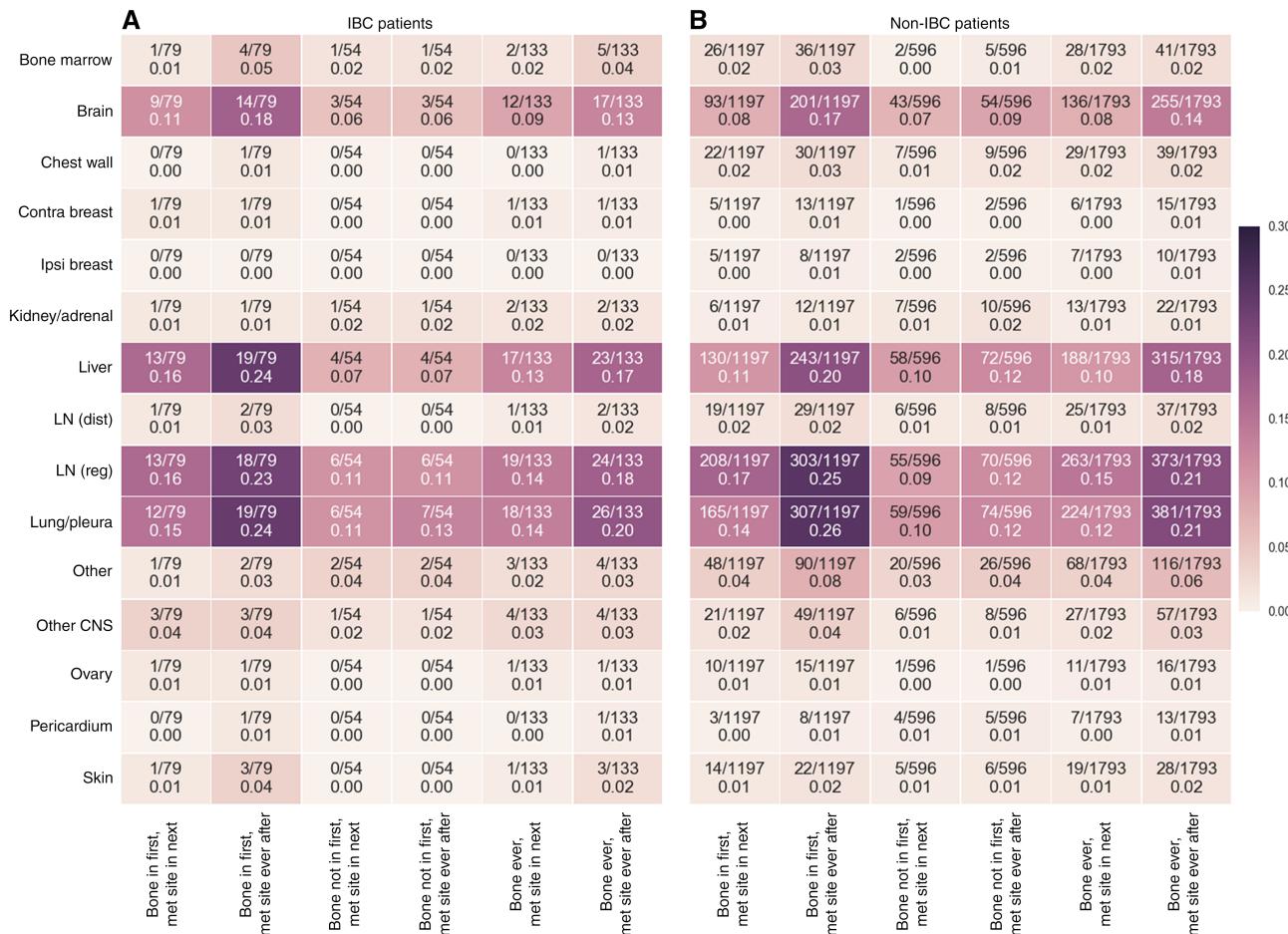
Unfortunately, clinical trials largely have failed to show OS benefit from zoledronic acid [14]. A potential reason that the trials have failed to show significant survival benefit is that an appropriate patient population could not be selected. For example, the studies included patients who did not develop bone metastasis during the course of progression although only those who had disease in the bone may have received benefit from preventive zoledronic acid. As such, one of the current clinical challenges is the lack of predictive models for future metastases, specifically to the bone. We found that among patients with IBC, 28% (23/81) of patients who had chest wall metastasis, 21% (12/58) of patients who had lung metastasis, and 21% (16/76) of patients who had liver metastasis developed bone metastasis at some point of progression. A similar subgroup of patients could serve as a target population in a future clinical trial testing the preventive effects of zoledronic acid and/or denosumab.

In our current study, there are several limitations that need to be addressed before clinical validation. First, as this was a retrospective study with a long follow-up period, the systemic treatments used within the population varied (e.g., cyclophosphamide, methotrexate, and fluorouracil, which was used more before). Second, the HER2 status of many patients was not known. Not treating the appropriate patients within this group with targeted therapy would yield shorter OS times than for those treated with such therapy, thus skewing the survival analyses. Third, the definitions of ER, PR, and HER2 positivity changed during the follow-up period; different categorizations might have affected the interpretation of the results. Fourth, because IBC is a rare disease, the sample size was smaller than that for non-IBC. We could not define targeted subgroups of the IBC population, which would have resulted in smaller sample sizes and less powerful predictive models. Last, the diagnosis of IBC is clinical, and the consistency and accuracy of diagnosis could vary depending on the experience of each physician before 2006. After 2006, the



**Figure 2.** Spatiotemporal progression diagrams over 20 years after diagnosis. **(A):** IBC patients and **(B):** non-IBC patients. Disease diagnosis is represented by the inner pink ring. Metastatic progression to various sites over time is represented by color-coded, concentric rings. The circular arc length of each ring represents the percentage of the population that has progressed to that metastatic location from each preceding step. The models are available online at [http://kuhn.usc.edu/breast\\_cancer](http://kuhn.usc.edu/breast_cancer).

Abbreviations: CNS, central nervous system; Contra, contralateral; dist, distant; Ipsi, ipsilateral; LN, lymph nodes; reg, regional.



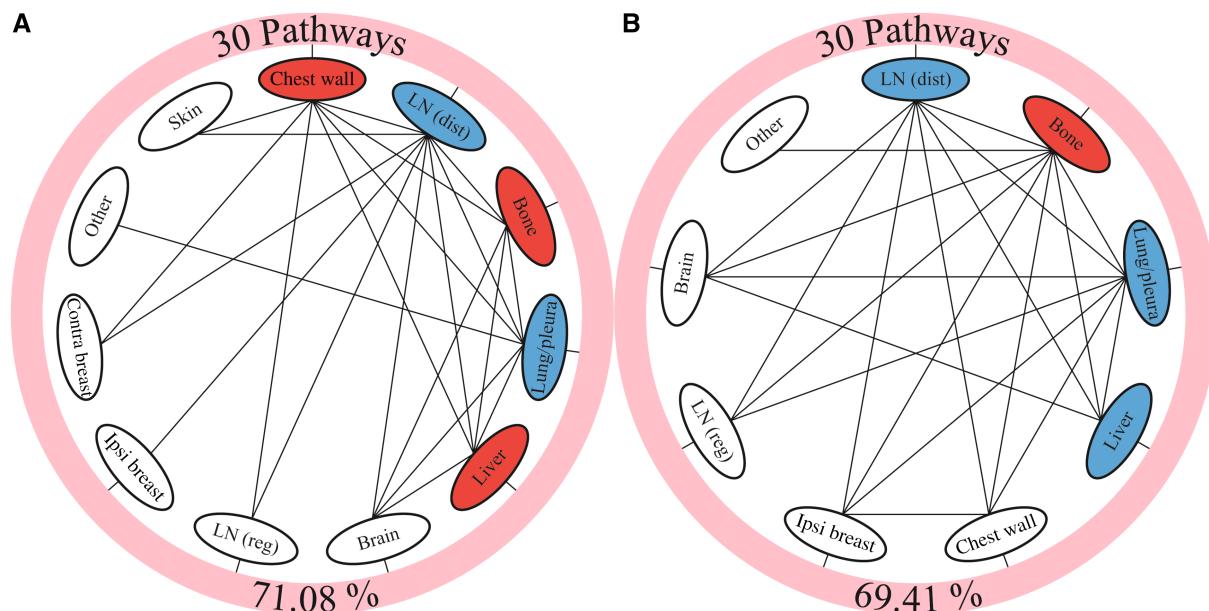
**Figure 3.** Heat map of conditional probabilities in patients with known bone metastasis. **(A):** IBC and **(B):** non-IBC patients with bone metastasis as a given condition in either the first progression (Bone in First), not in the first progression (Bone Not in First), or in any progression (Bone Ever). For each site listed along the left side of the figure, numbers of cases and percentages are given for development of metastasis either in the immediate next progression (Met Site in Next) or in any progression afterwards (Met Site Ever After). Abbreviations: CNS, central nervous system; Contra, contralateral; dist, distant; IBC, inflammatory breast cancer; Ipsi, ipsilateral; LN, lymph nodes; Met, metastasis; reg, regional.

	IBC patients						Non-IBC patients					
	2/3 0.67	2/3 0.67	0/9 0.00	0/9 0.00	2/12 0.17	2/12 0.17	4/33 0.12	6/33 0.18	3/58 0.05	4/58 0.07	7/91 0.08	10/91 0.11
Bone marrow												
Brain	2/33 0.06	3/33 0.09	1/42 0.02	1/42 0.02	3/75 0.04	4/75						
Chest wall	12/81 0.15	23/81 0.28	0/17 0.00	1/17 0.06	12/98 0.12	24/98 0.24						
Contra breast	1/13 0.08	1/13 0.08	1/16 0.06	1/16 0.06	2/29 0.07	2/29 0.07						
Ipsi breast	1/10 0.10	2/10 0.20			1/10 0.10	2/10 0.20						
Kidney/adrenal	1/2 0.50	1/2 0.50	0/2 0.00	0/2 0.00	1/4 0.25	1/4 0.25						
Liver	9/76 0.12	16/76 0.21	3/71 0.04	4/71 0.06	10/124 0.08	17/124 0.14						
LN (dist)	1/14 0.07	5/14 0.36	2/12 0.17	2/12 0.17	2/25 0.08	6/25 0.24						
LN (reg)	9/53 0.17	11/53 0.21	9/50 0.18	9/50 0.18	18/103 0.17	20/103 0.19						
Lung/pleura	6/58 0.10	12/58 0.21	5/81 0.06	7/81 0.09	9/124 0.07	16/124 0.13						
Other	3/16 0.19	4/16 0.25	1/11 0.09	1/11 0.09	4/26 0.15	5/26 0.19						
Other CNS	0/3 0.00	0/3 0.00	0/12 0.00	0/12 0.00	0/15 0.00	0/15 0.00						
Ovary	0/2 0.00	0/2 0.00	0/2 0.00	0/2 0.00	0/4 0.00	0/4 0.00						
Pericardium			0/5 0.00	0/5 0.00	0/5 0.00	0/5 0.00						
Skin	3/13 0.23	3/13 0.23	1/18 0.06	2/18 0.11	4/30 0.13	5/30 0.17						

Met site in first, bone in next  
Met site in first, bone ever after  
Met site not in first, bone in next  
Met site not in first, bone ever after  
Met site ever, bone in next  
Met site ever, bone ever after

Met site in first, bone in next  
Met site in first, bone ever after  
Met site not in first, bone in next  
Met site not in first, bone ever after  
Met site ever, bone in next  
Met site ever, bone ever after

**Figure 4.** Heat map of conditional probabilities in patients with known metastasis other than bone. **(A):** IBC and **(B):** non-IBC patients with a given metastatic site (listed along the left side of the figure) as a condition in either the first progression (Met Site in First), not in the first progression (Met Site Not in First), or in any progression (Met Site Ever). Numbers of cases and percentages are given for development of a bone metastasis in either the immediate next progression (Bone in Next) or in any progression afterwards (Bone Ever After). Abbreviations: CNS, central nervous system; Contra, contralateral; dist, distant; IBC, inflammatory breast cancer; Ipsi, ipsilateral; LN, lymph nodes; Met, metastasis; reg, regional.



**Figure 5.** Reduced Markov models indicating the propensity of the site to spread the disease. **(A):** IBC and **(B):** non-IBC patients showing the top 30 two-step transition probabilities emanating from the breast (pink ring). Nodes are colored as spreaders (red) or sponges (blue) based on the ratio of their outgoing and incoming transition probabilities. The bottom percentage values represent the portion of all the two-step values the diagrams represent.

Abbreviations: Ipsi, ipsilateral; LN, lymph nodes.

IBC diagnosis was determined by multidisciplinary approach using the international IBC diagnosis consensus [28].

## CONCLUSION

Patients who developed bone metastasis at any time point of progression had significantly shorter OS than did patients who had never developed bone metastasis in non-IBC, and patients with IBC who developed liver, chest wall, and lung metastases, more so than other sites of metastasis, tended to develop bone metastasis at some time of progression afterward. Selection of patients with known liver, chest wall, and/or lung metastasis would create a population in whom to investigate effective methods for preventing future bone metastasis. Further prospective studies to confirm the association between initial and subsequent metastatic sites are warranted.

## ACKNOWLEDGMENTS

We thank Sunita Patterson of the Department of Scientific Publications at The University of Texas MD Anderson Cancer Center for providing scientific editing services. This project

was funded in whole or in part with funds from the Morgan Welch Inflammatory Breast Cancer Research Program, a grant from the State of Texas Rare and Aggressive Breast Cancer Research Program, BCRF (Grant No. 3794), BCRF/JKTG (Grant No. 007688-00002), Seven Bridges (Contract No. 007906-00001), Novartis Pharmaceuticals Corporation (PRSUPON/S3410160), the USC Institute of Urology, the USC Michelson Center for Convergent Biosciences, and the Carol Vassiliadis Fellowship.

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## DISCLOSURES

The authors indicated no financial relationships.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.
2. Miller K, Siegel RL, Jemal A. Cancer Treatment & Survivorship Facts & Figures 2016–2017. Atlanta: American Cancer Society, 2016.
3. Siegel RL, Miller KD, Fedewa SA et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin* 2017;67:177–193.
4. Masuda H, Baggerly KA, Wang Y et al. Comparison of molecular subtype distribution in triple-negative inflammatory and non-inflammatory breast cancers. *Breast Cancer Res* 2013;15:R112.
5. Lee AH, Happerfield LC, Millis RR et al. Inflammatory infiltrate in invasive lobular and ductal carcinoma of the breast. *Br J Cancer* 1996;74:796–801.
6. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol* 2001;2:133–140.
7. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: A review. *J Clin Oncol* 1992;10:1014–1024.
8. Yi M, Huo L, Koenig KB et al. Which threshold for ER positivity? A retrospective study based on 9639 patients. *Ann Oncol* 2014;25:1004–1011.
9. Masuda H, Brewer TM, Liu DD et al. Long-term treatment efficacy in primary inflammatory breast cancer by hormonal receptor- and HER2-defined subtypes. *Ann Oncol* 2014;25:384–391.
10. Coleman R, Cameron D, Dodwell D et al. Adjuvant zoledronic acid in patients with early breast cancer: Final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol* 2014;15:997–1006.
11. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017;35:2062–2081.
12. Rosen LS, Gordon D, Kaminski M et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: A randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;98:1735–1744.
13. Coleman R, Gnant M, Morgan G et al. Effects of bone-targeted agents on cancer progression and mortality. *J Natl Cancer Inst* 2012;104:1059–1067.
14. Early Breast Cancer Trialists' Collaborative Group. Adjuvant bisphosphonate treatment in early breast cancer: Meta-analyses of individual patient data from randomised trials. *Lancet* 2015;386:P1353–1361.
15. Delmas PD. Clinical potential of RANKL inhibition for the management of postmenopausal osteoporosis and other metabolic bone diseases. *J Clin Densitom* 2008;11:325–338.
16. Gnant M, Pfeiler G, Dubsky PC et al. Adjuvant denosumab in breast cancer (ABCsG-18): A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:433–443.
17. Martin M, Bell R, Bourgeois H et al. Bone-related complications and quality of life in advanced breast cancer: Results from a randomized phase III trial of denosumab versus zoledronic acid. *Clin Cancer Res* 2012;18:4841–4849.
18. Gonzalez-Suarez E, Jacob AP, Jones J et al. RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis. *Nature* 2010;468:103–107.
19. Tang ZN, Zhang F, Tang P et al. RANKL-induced migration of MDA-MB-231 human breast cancer cells via Src and MAPK activation. *Oncol Rep* 2011;26:1243–1250.
20. Blake ML, Tometsko M, Miller R et al. RANK expression on breast cancer cells promotes skeletal metastasis. *Clin Exp Metastasis* 2014;31:233–245.
21. Gnant M, Pfeiler G, Steger GG et al. Adjuvant denosumab in early breast cancer: Disease-free survival analysis of 3,425 postmenopausal patients in the ABCSG-18 trial. *J Clin Oncol* 2018;36(suppl 15):500–500.
22. Newton PK, Mason J, Venkatappa N et al. Spatiotemporal progression of metastatic breast cancer: A Markov chain model highlighting the role of early metastatic sites. *NPJ Breast Cancer* 2015;1:15018.
23. Coleman RE, Finkelstein D, Barrios CH et al. Adjuvant denosumab in early breast cancer: First results from the international multicenter randomized phase III placebo controlled D-CARE study. *J Clin Oncol* 2018;36(suppl 15):501–501.
24. Palafox M, Ferrer I, Pellegrini P et al. RANK induces epithelial-mesenchymal transition and stemness in human mammary epithelial cells and promotes tumorigenesis and metastasis. *Cancer Res* 2012;72:2879–2888.
25. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004;350:1655–1664.
26. Kaplan RN, Rafii S, Lyden D. Preparing the “soil”: The premetastatic niche. *Cancer Res* 2006;66:11089–11093.
27. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* 2005;23:8219–8224.
28. Dawood S, Merajver SD, Viens P et al. International expert panel on inflammatory breast cancer: Consensus statement for standardized diagnosis and treatment. *Ann Oncol* 2011;22:515–523.