Clinical nomogram to predict bone-only metastasis in patients with early breast carcinoma

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Background: Bone is one of the most common sites of distant metastasis in breast cancer. The purpose of this study was to combine selected clinical and pathologic variables to develop a nomogram that can predict the likelihood of bone-only metastasis (BOM) as the first site of recurrence in patients with early breast cancer.

Methods: Medical records of patients with non-metastatic breast cancer were retrospectively collected. On the basis of the analysis of patient and tumour characteristics using the Cox proportional hazards regression model, a nomogram to predict BOM was constructed for a 4175-patient-training cohort. The nomogram was validated in an independent cohort of 579 patients.

Results: Among 4175 patients with non-metastatic breast cancer, 314 developed subsequent BOM. Age, T classification, lymph node status, lymphovascular space invasion, and hormone receptor status were significantly and independently associated with subsequent BOM. The nomogram had a concordance index of 0.69 in the training set and 0.73 in the validation set.

Conclusions: We have developed a clinical nomogram to predict subsequent BOM in patients with non-metastatic breast cancer. Selection of a patient population at high risk for BOM could facilitate research of more specific staging approaches or the selective use of bone-targeted therapy.

Bone is the first site of distant disease in 25–40% of patient with metastatic breast cancer, and ~60–80% of patients with recurrent disease have skeletal involvement (Coleman 1997).

Breast cancers are heterogeneous tumours that result from several molecular progression pathways (Esteva et al, 2002). Analyses of breast cancer progression suggest that the disease preferentially metastasises to the bone, with or without metastasis to visceral organs, loco-regional sites, or the brain (Smid et al, 2008; Kennecke et al, 2010). Several hypotheses have been developed to explain this phenomenon, including the favourable chemokine milieu or microenvironment of the bone and intrinsic molecular features of cancer cells (Kang et al, 2003; Jones et al, 2006; Smid et al, 2006; Jamieson-Gladney et al, 2011). Although these hypotheses are promising, clinicians are still determining prognosis on the basis of anatomical characteristics such as tumour size or nodal status, in addition to biological information like...
tumour grade, hormone receptor status, human epidermal growth factor 2 (HER2) status, and proliferation. These factors, however, evaluate the risk of metastasis in general, while predictors of bone-only metastasis (BOM) remain a clinical uncertainty (Galea et al., 1992; Hess et al., 2003; Millar et al., 2009).

Nomograms constructed on the basis of known prognostic factors are increasingly being used to predict specific outcomes (Rouzier et al., 2005; Werkoff et al., 2009; Graesslin et al., 2010). The purpose of this study was to develop and validate a nomogram based on clinical and pathologic variables that is able to predict the likelihood of BOM in patients with early breast cancer. Such a nomogram, after validation, could be used to identify a subgroup of patients who may benefit from adjuvant bisphosphonates (or other bone-specific targeted agents) (Wong et al., 2012), or develop radiologic screening and novel preventive treatment strategies for patients with early-stage breast cancer, potentially improving quality of life measures, if not improving disease outcomes as well.

PATIENTS AND METHODS

Study population. We searched the clinical database of the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center (Houston, Texas) for the medical records of all patients with stage I–III breast cancer at diagnosis who presented to MD Anderson Cancer Center for treatment between January 1997 and December 2004. We identified 4175 consecutive patients with primary non-metastatic breast cancer. This cohort was used as a training set to develop a model to predict BOM in a population of non-metastatic breast cancer patients. A second cohort that consisted of 579 breast cancer patients referred to Tenon Hospital (Paris, France) between January 1997 and December 2004. We searched the clinical database of the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center institutional electronic databases and from Tenon Hospital medical records (Table 1). Clinical tumour stage was determined at presentation by physical examination and standard-of-care imaging modalities (mammography, ultrasonography, computerised tomography (CT), and/or bone scans), and tumour biology (biomarkers) was determined before any treatment initiation. No central pathology review was performed, but for the MD Anderson cohort, a breast pathologist reviewed all outside pathology reports and stained slides at the time of referral to the centre. As institutional policy at MD Anderson Cancer Center, unstained slides are requested on rare occasions when discrepancy exists between the outside report and the review performed at MD Anderson Cancer Center. Similarly, for the Tenon cohort, the outside pathology reports were reviewed only when discordance was found between the diagnostic biopsy and the final report based on the surgical specimen. Oestrogen receptor (ER), progesterone receptor (PR), and HER2 measurements were available for all patients.

As our study period predates the American Society of Clinical Oncology’s recommendation for ER and PR positivity/negativity thresholds (Hammond et al., 2010), ER and PR positivity were each defined as nuclear staining $\geq$10%, and HER2 positivity was defined as 3+ staining on immunohistochemistry or gene amplification by FISH. For our retrospective data analysis, we grouped the tumours according to hormone receptor (HR) status as follows: positive (ER+ and/or PR+) or negative (ER− and PR−). In the MD Anderson cohort, the grade was defined according to the modified Black’s nuclear grade. In the Tenon cohort, the tumour grade was defined according to the modified Black’s nuclear grade. In the Tenon cohort, the grade was defined according to the modified Black’s nuclear grade.

Patient characteristics. The clinical and histologic characteristics of all patients were acquired retrospectively from MD Anderson Cancer Center institution electronic databases and from Tenon Hospital medical records (Table 1). Clinical tumour stage was determined at presentation by physical examination and standard-of-care imaging modalities (mammography, ultrasonography, computerised tomography (CT), and/or bone scans), and tumour biology (biomarkers) was determined before any treatment initiation. No central pathology review was performed, but for the MD Anderson cohort, a breast pathologist reviewed all outside pathology reports and stained slides at the time of referral to the centre. As institutional policy at MD Anderson Cancer Center, unstained slides are requested on rare occasions when discrepancy exists between the outside report and the review performed at MD Anderson Cancer Center. Similarly, for the Tenon cohort, the outside pathology reports were reviewed only when discordance was found between the diagnostic biopsy and the final report based on the surgical specimen. Oestrogen receptor (ER), progesterone receptor (PR), and HER2 measurements were available for all patients.

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| Characteristic | Training set (N = 4175) | Validation set (N = 579) |
|---------------|-------------------------|--------------------------|
| Age, years    |                         |                          |
| Median        | 50                      | 46                       |
| Range         | 19–91                   | 24–90                    |
| %             | €0.001                  | €0.001                   |
| Menopausal status | 2387 57 394 58 | 2129 29 327 56 |
| %             | €0.001                  | €0.001                   |
| Histology     |                         |                          |
| Oestrogen receptor (ER) and/or PR positivity | 2890 69 497 86 | 1285 31 82 14 |
| %             | €0.001                  | €0.001                   |
| HER2 status  |                         |                          |
| Lympohvascular space involvement | 1441 35 156 27 | 2734 65 331 57 |
| %             | €0.001                  | €0.001                   |
| Local breast surgery | 1316 32 382 66 | 2331 56 196 34 |
| %             | €0.001                  | €0.001                   |
| Axillary surgery | 3036 73 410 71 | 586 14 169 29 |
| %             | €0.001                  | €0.001                   |
| Systemic therapy (neoadjuvant and/or adjuvant) | 2221 63 325 56 | 1505 36 73 13 |
| %             | €0.001                  | €0.001                   |
| Endocrine therapy | 722 17 340 59 | 1713 41 158 27 |
| %             | €0.001                  | €0.001                   |
| Adjuvant radiation | 2804 47 356 62 | 1371 33 67 12 |
| %             | €0.001                  | €0.001                   |

Table 1. Patient characteristics for the MDACC cohort (training set) and the Tenon cohort (validation set)

Abbreviations: ER= oestrogen receptor; HER2 = human epidermal growth factor receptor 2; MDACC = The University of Texas MD Anderson Cancer Center; PR = progesterone receptor.

*Histologic grade was determined according to the modified Black’s nuclear grade for the training set and according to the modified Scarff, Bloom, and Richardson for the validation set.

**Status of oestrogen receptor and progesterone receptor was determined by immunohistochemistry.

*Status of HER2 was determined by immunohistochemistry or fluorescence in situ hybridisation.
Nomogram to predict bone-only metastasis

RESULTS

Prediction of bone-only metastases in the MD Anderson cohort (training set). In the MD Anderson cohort, the first site of recurrence was BOM in 314 patients, bone and concurrent visceral or soft tissue metastases in 329 patients, and a non-bone distant metastasis in 658 patients (Table 2). Comparisons were performed between those who developed BOM and the rest of the patient cohort, regardless of disease outcome. The majority of the MD Anderson patients received anthracycline-based adjuvant chemotherapy, in addition to adjuvant hormonal therapy and/or adjuvant radiation therapy (Table 1), as deemed necessary for the individual patient. The probabilities of developing BOM were 5% (95% CI, 5.7–4.3), 8.1% (95% CI, 9.1–7.1), and 10.2% (95% CI, 11.4–9.6) at 3, 5, and 7 years, respectively. The median follow-up times for patients with BOM and patients with non-BOM disease were 66 months (range, 9–259) and 60 months (range, 3–477), respectively.

Upon univariate analysis, BOM was strongly associated with HR-positive tumours (P < 0.001; Table 3). The other factors correlated with BOM were younger age (age <35 years), T2 or T3 classification and standard-of-care recommendations. In the MD Anderson cohort, regardless of disease outcome. The majority of the MD Anderson patients received anthracycline-based adjuvant chemotherapy, in addition to adjuvant hormonal therapy and/or adjuvant radiation therapy (Table 1), as deemed necessary for the individual patient. The probabilities of developing BOM were 5% (95% CI, 5.7–4.3), 8.1% (95% CI, 9.1–7.1), and 10.2% (95% CI, 11.4–9.6) at 3, 5, and 7 years, respectively. The median follow-up times for patients with BOM and patients with non-BOM disease were 66 months (range, 9–259) and 60 months (range, 3–477), respectively.

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Table 3. Univariate and multivariate analysis of factors predicting bone-only metastasis

| Factor                        | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                               | Hazard ratio | 95% CI | P     | Hazard ratio | 95% CI | P     |
| Age, years                    | <0.05        |       |       | <0.05        |       |       |
| >50                           | 1.3          | 1.02–1.66 | 0.03 | 1.3          | 0.95–1.86 | 0.09 |
| 35–50                         | 2.37         | 1.69–3.33 | <0.001 | 2.11 | 1.32–3.38 | <0.001|
| Menopausal status             | <0.05        |       |       | <0.05        |       |       |
| No                            | 0.74         | 0.59–0.93 | 0.008 | 0.99 | 0.71–1.39 | 0.99 |
| Yes                           | 1            |       |       | 1            |       |       |
| T stage                       | <0.05        |       |       | <0.05        |       |       |
| T1                            | 1.89         | 1.48–2.41 | <0.001 | 2.03 | 1.57–2.62 | <0.001|
| T2                            | 2.56         | 1.75–3.71 | <0.001 | 2.59 | 1.75–3.85 | <0.001|
| T3                            | 2.56         | 1.75–3.71 | <0.001 | 2.59 | 1.75–3.85 | <0.001|
| Multifocal tumour             | <0.05        |       |       | <0.05        |       |       |
| No                            | 0.9          | 0.7–1.23 | 0.6   | 0.59          | 0.4   | 0.4 |
| Yes                           | 1            |       |       | 1            |       |       |
| Histology                     | <0.05        |       |       | <0.05        |       |       |
| Ductal carcinoma              | 0.9          | 0.7–1.23 | 0.6   | 0.85          | 0.59–1.22 | 0.4 |
| Lobular carcinoma             | 0.48         | 0.2–1.07 | 0.07  | 0.27          | 0.14  | 0.2 |
| Others                        |              |       |       |              |       |       |
| HR status*                    | <0.05        |       |       | <0.05        |       |       |
| Negative                      | 1.66         | 1.25–2.2 | <0.001 | 1.52 | 1.11–2.1 | 0.001 |
| Positive                      | 1            |       |       | 1            |       |       |
| HER2 status                   | <0.05        |       |       | <0.05        |       |       |
| Negative                      | 0.92         | 0.70–1.23 | 0.6   | 0.6–1.17     | 0.35  | 0.35 |
| Positive                      | 1            |       |       | 1            |       |       |
| Nuclear grade                 |              |       |       |              |       |       |
| 0.9                           | 0.86–1.26    | 0.6   | 1.04  | 0.83–1.31    | 0.7   | 0.7 |
| 1.0                           |              |       |       |              |       |       |
| Lymphovascular space involvement| <0.05        |       |       | <0.05        |       |       |
| No                            | 2.05         | 1.6–2.56 | <0.001 | 1.55 | 1.22–1.96 | <0.001|
| Yes                           | 1            |       |       | 1            |       |       |
| Axillary lymph node involvement| <0.05        |       |       | <0.05        |       |       |
| No                            | 2.57         | 1.88–3.55 | <0.001 | 2.44 | 1.73–4.17 | <0.001|
| Yes                           | 1            |       |       | 1            |       |       |

Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormonal receptor.
*Hormonal receptor positive was defined as estrogen receptor positive and/or progesterone receptor positive.

Figure 1. Nomogram to predict the probability of bone-only metastasis in non-metastatic breast cancer. Abbreviations: HR, hormone receptor status (HR negative was defined as estrogen receptor and progesterone receptor negative); LN, lymph node; LVI, lymphovascular space involvement.

T3 classification at diagnosis, lymphovascular space involvement, and axillary lymph node involvement. However, BOM was not associated with histologic subtype ($P = 0.4$ for ductal carcinoma vs lobular carcinoma), grade ($P = 0.7$), multifocality ($P = 0.7$), or HER2 status ($P = 0.6$).

All of the covariates, except for menopausal status, significant on univariate analysis were still significant after multivariate hazard ratio regression analysis ($P < 0.001$ for all covariates). On the basis of the covariates independently associated with BOM, we constructed a nomogram, and probabilities of BOM were reported at 3, 5, 7, and 10 years (Figure 1). The prediction model had a good concordance index, 0.69 (95% CI, 0.68–0.71), in the training set (internal validation).

External validation of the nomogram. Compared with patients in the MD Anderson cohort, those in the Tenon cohort were older, had smaller (stage T1) and lower-grade (grade I/II) tumours, and had more ER+ and/or PR+ tumours (Table 1). Endocrine therapy alone was more often used in the Tenon cohort than in the MD Anderson cohort, and fewer patients received treatment with chemotherapy alone. Patients in the Tenon cohort had fewer distant recurrences, but the proportion of BOM compared with other sites of metastasis was higher (28 out of 67; 42%) in the Tenon cohort than in the MD Anderson cohort (314 out of 1301; 24%).

The concordance index of the nomogram in the external validation model was 0.73 (95% CI, 0.68–0.79). Of note, the nomogram was well calibrated at 3, 5, 7, and 10 years, with a slight underestimation in the validation set (Figure 2). The mean absolute error in predicted probabilities was 2.3%, and the 0.9 quintile of absolute errors was 4%.

Clinical utility of the nomogram. Once the nomogram had been developed using commonly measured clinical covariates, we sought to use it to identify a subgroup of patients at high risk of developing isolated bone metastasis. Our virtual prevention trial showed that the nomogram would help to select patients with a higher risk of BOM for a clinical trial. As shown in Table 4, the number of patients for clinical/translational trials could be markedly reduced if patient selection was based on the results of this nomogram.
DISCUSSION

Using a large retrospective database, we developed the first clinical nomogram to predict the likelihood of BOM for patients diagnosed with non-metastatic breast cancer. We validated this nomogram with an independent cohort having different tumour characteristics, prognoses, and outcomes, supporting the excellent exportability of our model. Although some models have been developed to predict the risk of breast cancer recurrence (Mazouni \textit{et al.}, 2011), few are validated to specifically predict the risk of bone metastasis in patients with breast cancer. On the basis of 855 breast cancer samples, Zhou and Liu, (2014) identified eight genetic pathways significantly associated with metastasis to bone. By integrating these pathways into one molecular, computational model, patients at high and low risks for developing bone metastasis were identified. Importantly, other genetic pathways, characterised by non-bone metastasis, were also discerned. Further analysis revealed that the major difference between these two metastatic pathways (bone and non-bone) was that certain dysregulated immune genes (\textit{FAS}, \textit{IL2RG}, and \textit{IL7R}) were more strongly associated with bone metastasis from breast cancer.

It has been demonstrated that the ER-positive status is correlated with the development of bone metastasis (Coleman \textit{et al.}, 1998; Diel, 2001; Hess \textit{et al.}, 2003). Our model substantiates such findings, and shows that patients with HR-positive breast cancer have an increased risk of bone metastases (hazard ratio $= 1.66$; 95% CI, 1.25–2.2), as well as a 10.2% absolute probability of developing bone metastasis after 7 years. However, the other factors analysed are also in agreement with those reported by the International Breast Cancer Study Group, which found that a higher number of involved nodes, larger tumour size, and tumour oestrogen expression were associated with BOM as well (Colleoni \textit{et al.}, 2000).

Several studies conducted on murine models have shown that metastatic lesions can lead to further metastatic spread (Klein, 2009). Therefore, preventing metastasis may reduce the risk of subsequent (secondary) metastatic progression. Agents that may interrupt metastasis to certain organs may help to alter the natural history of the disease, such as the inhibition of bone resorption and osteoclast activity on bone metastasis. A meta-analysis showed that the adjuvant use of zoledronic acid improves overall survival, distant metastasis-free survival, bone metastasis-free survival, and the fracture-free rate in patients with early-stage breast cancer (He \textit{et al.}, 2013). Nonetheless, the use of bisphosphonates as adjuvant therapy remains controversial. A growing body of evidence, however, indicates that adjuvant bisphosphonates may be effective in preventing bone metastasis in patients who are postmenopausal for more than 5 years (Gnant \textit{et al.}, 2009, 2011; Eidtmann \textit{et al.}, 2010; Coleman \textit{et al.}, 2011; Marshall \textit{et al.}, 2012). Although the benefits of bisphosphonates are not limited only to those who develop bone disease, by identifying a patient population at higher risk for BOM, this nomogram may be used as a research tool to resolve controversies surrounding the adjuvant use of bisphosphonates, and better understand the prevention or treatment of bone-specific metastasis.

In adult knock-in mice made to express chimeric (murine/human) receptor activator of nuclear factor-$\kappa$B ligand (RANKL), denosumab, a fully human monoclonal antibody to RANKL, suppresses bone resorption and increases bone mineral density (Kostenuik \textit{et al.}, 2009). Similarly, dasatinib, a SRC tyrosine kinase inhibitor, has been shown to block cellular proliferation, along with various activities required for metastasis and osteoclast activity (Araujo and Logothetis, 2010). Therefore, with the availability of drugs that may have a preferential effect on particular metastatic organ sites (e.g., bone), this nomogram can be used to facilitate future clinical trials by enriching the patient population needed, resulting in a smaller study without compromising power (Graesslin \textit{et al.}, 2010). Much like the risk assessment process

![Image](https://example.com/image.png)

Figure 2. External validation by calibration plot of the nomogram to predict bone-only metastasis in patients with non-metastatic breast cancer at 3, 5, 7, and 10 years. The dashed line shows the ideal calibration line.

Table 4. Clinical utility of the nomogram for predicting the need for adjuvant bisphosphonate, as illustrated by a virtual two-sided preventive trial

| Threshold probability of bone metastasis at 7 years | 15% Relative reduction of isolated bone metastases | 25% Relative reduction of isolated bone metastases | 35% Relative reduction of isolated bone metastases |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Rate of isolated bone metastases before 7 years | Rate of isolated bone metastases before 7 years | Number of patients to enrol | Rate of isolated bone metastases before 7 years | Number of patients to enrol | Rate of isolated bone metastases before 7 years | Number of patients to enrol |
| Without nomogram | 6.85 | 5.82 | 11 483 | 5.14 | 6 212 | 4.45 | 11 305 |
| 95% Cutoff | 7.85 | 6.67 | 15 220 | 5.89 | 15 360 | 5.10 | 26 556 |
| 90% Cutoff | 10.59 | 9.00 | 11 224 | 7.94 | 39 08 | 6.88 | 19 224 |
| 85% Cutoff | 12.58 | 10.69 | 9 248 | 9.43 | 32 224 | 8.17 | 15 990 |
| 80% Cutoff | 14.25 | 12.11 | 8 300 | 10.69 | 28 14 | 9.26 | 13 386 |
| 75% Cutoff | 13.99 | 11.89 | 8 210 | 10.49 | 28 66 | 9.09 | 14 11 |
| 70% Cutoff | 19.70 | 16.74 | 5 474 | 14.77 | 19 22 | 12.80 | 9 54 |

$^a$Rate of isolated bones metastasis based on the training set population.

$^b$Assuming the presumed relative risk reduction.

$^c$The sample sizes were calculated to have 80% power to detect a difference between two arms, with a significance level 0.05 and sample size ratio 1 to 1.

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proved successful in selecting patients for preventive trials (Fisher et al., 1998), it can be hypothesised that nomograms will prove to be essential tools in the selection of clinical trial participants.

We validated our nomogram with respect to good discrimination and calibration by testing it in a different population. Because of censored data, the discrimination could not be determined using the classical area under the receiver-operating curve. Thus, we report the concordance index, which indicates whether the relative ranking of individual prediction is in the correct order. The concordance index was good in both the training set and the validation set. The calibration between the training and validation sets gives an idea of a model’s performance when extrapolated to new patient populations. In our case, the Tenon cohort characteristics were clearly different from the MD Anderson ones, but the calibration was still consistent. Consequently, we can speculate that because the nomogram worked in these two different populations, it will work in other groups of patients as well.

There is a complicated interface between breast cancer cells and the bone microenvironment (Korde and Gralow, 2011). Bone marrow can be a sanctuary for cancer cells, and bone marrow micrometastases not only lead to subsequent bone relapse, but also metastasis and overall poor disease outcome as well (Braun et al., 2005; Biddard et al., 2008). Lipton et al. (2011) have reported a biochemical marker of bone resorption, which reflects alterations in bone turnover and predicts bone metastases. Other groups have focused on microarray multigene expression profiles that may also be predictive of bone metastases from breast cancer. However, there is still no validated marker or molecular signature to predict an increased risk of subsequent bone metastasis (Kang et al., 2003; Minn et al., 2005; Smid et al., 2006). Prediction models using routine clinical variables and multigene signatures have been compared and shown to be complementary (Lee et al., 2010). Future studies that combine a clinical nomogram with relevant molecular markers and a genomic signature may be the best solution for obtaining accurate predictions.

This study has several limitations. Patients in both cohorts were retrospectively selected from prospectively maintained databases, and bone metastases were diagnosed as part of routine care. Some patients might have had undiagnosed, asymptomatic, or isolated bone metastases, meaning that the actual rate of isolated bone metastases may have been higher than our findings indicate. Furthermore, nodal status was assessed at the time of surgery, after some patients had received neoadjuvant therapy, but was likely balanced by the very large number of patients that the calibration was still consistent. Consequently, we can speculate that because the nomogram worked in these two different populations, it will work in other groups of patients as well.

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Nomogram to predict bone-only metastasis

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