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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

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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 2003 and December 2005 was used as a validation set. The Institutional Review Board of MD Anderson Cancer Center approved the study.

Patient characteristics. The clinical and histologic characteristics of all patients were acquired retrospectively from 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 $\geqslant 10\%$, 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

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

	Training set ($N=4175$)		Validation set ($N=579$)		
Characteristic	No. of patients	%	No. of patients	%	*P*
Age, years					
Median	50		56		<0.001
Range	19–91		24–90		
Menopausal status					
Yes	2387	57	394	68	<0.001
Histology					
Ductal carcinoma	3456	83	473	82	0.35
Lobular carcinoma	568	14	78	13	
Others	151	4	28	5	
T stage					
T1	1839	44	356	61	<0.001
T2	1975	47	197	34	
T3	361	9	22	4	
Axillary lymph node involvement					
Yes	2956	71	252	44	
No	1219	29	327	56	<0.001
Nuclear grade[a]					
1	170	4	181	31	<0.001
2	1494	36	244	42	
3	2511	60	154	27	
Hormonal receptor status[b]					
ER+ and/or PR+	2890	69	497	86	<0.001
ER− and PR−	1285	31	82	14	
HER2 status[c]					
Positive	900	22	77	13	<0.001
Negative	3275	78	489	84	
Triple-negative breast cancer					
Yes	878	21	69	12	<0.001
No	3297	79	504	87	
Lymphovascular space involvement					
Yes	1441	35	156	27	0.2
No	2734	65	331	57	
Unknown	0	0	92	16	
Local breast surgery					
Conservative	1316	32	382	66	<0.001
Mastectomy	2331	56	196	34	
Unknown	529	13	1	0	
Axillary surgery					
Axillary lymph node dissection	3036	73	410	71	<0.001
Sentinel node	586	14	169	29	
Unknown	553	13	0	0	
Systemic therapy (neoadjuvant and/or adjuvant)					
Endocrine therapy and chemotherapy	2221	53	325	56	<0.001
Endocrine therapy alone	282	7	173	30	
Chemotherapy alone	1505	36	73	13	
No systemic treatment	167	4	5	1	
Endocrine therapy					
Aromatase inhibitor	722	17	340	59	<0.001
Tamoxifen	1713	41	158	27	
Endocrine unknown	68	2	0	0	
No endocrine therapy	1672	40	78	13	
Adjuvant radiation					
Yes	2804	67	356	62	<0.001
No	1371	33	67	12	
Unknown	0	0	156	26	

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; MDACC = The University of Texas MD Anderson Cancer Center; PR = progesterone receptor.
[a]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.
[b]Status of oestrogen receptor and progesterone receptor was determined by immunohistochemistry.
[c]Status of HER2 was determined by immunohistochemistry or fluorescence *in situ* hybridisation.

Scarff–Bloom–Richardson system. In both institutions, the number of histologically positive axillary lymph nodes was determined after surgery by examination of serial macroscopic sections of each node.

Patients received neoadjuvant and/or adjuvant systemic therapy (endocrine therapy and/or chemotherapy) according to their TNM classification and standard-of-care recommendations. In the MD Anderson cohort, 1636 patients received neoadjuvant chemotherapy, and all patients underwent breast and axillary surgery. However, some details were missing in 13% of the patients in the MD Anderson cohort.

Overall survival was measured from the date of diagnosis of primary cancer to the date of death from any cause. Patients who were alive at last follow-up were censored. Time to isolated bone metastasis was calculated from the date of diagnosis to the date of BOM. In this study, BOM was defined as the group of patients with bone-only disease, as demonstrated by current standard-of-care staging workup, which entailed the use of bone scans and/or positron emission tomography (PET) scans/PET–CT scans. As needed, confirmatory studies were conducted using CT scans, MRI, and plain X-ray films, as well as biopsy of an identified solitary lesion. Patients with metastasis other than bone (with or without bone metastasis) at the first recurrence were censored.

Nomogram development and statistical analyses. The χ^2-test and Student's *t*-test were used to compare patient characteristics by cohort origin (training cohort *vs* validation cohort).

Univariate analysis was performed using the log-rank test to assess the association between clinical–pathological variables and the risk of BOM. The following variables were tested: age at diagnosis (<35 years, 35–50 years, >50 years), menopausal status, race, T classification at diagnosis (T1, T2, T3), lymphovascular space involvement, axillary lymph node metastasis, nuclear grade, HR status, and HER2 status.

Cox proportional hazards regression was used for multivariate analysis. This model was then used to predict individual patient probability of BOM. Variables were eliminated from the model if their removal improved the overall model quality (as measured by the Akaike information criterion). *P*-values <0.05 were considered significant.

The Cox proportional hazards regression model was used to construct the nomogram. The model performance was quantified with respect to discrimination and calibration. Discrimination (i.e., whether the relative ranking of individual predictions is in the correct order) was quantified using the concordance index. The concordance index ranges from 0 to 1, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and 0 indicating perfect discordance. The 95% confidence interval (CI) was obtained by bootstrapping (1000 repetitions).

There is no accepted test to assess the calibration (i.e., agreement between observed outcome frequencies and predicted probabilities) of a censored model. Calibration was studied with graphical representations of relationships between the predicted probability of BOM and the observed frequencies of BOM in the validation set. The grouped proportions of BOM *vs* the mean predicted probabilities were represented at 3, 5, 7, and 10 years. The average absolute difference between the lowest estimated calibration curve and the line of identity was measured. All analyses were performed using the R package with the survival, r.m.s., and Hmisc libraries (http://lib.stat.cmu.edu/R/CRAN/).

To illustrate whether this nomogram can optimise the design of clinical trials of bone-specific metastasis prevention measures, we designed a virtual prevention trial. We determined the theoretical sample size required to test the efficacy of an experimental bone-modifying drug, such as a bisphosphonate, for preventing bone metastases in a population of patients with early breast cancer at 7 years after diagnosis. The sample size in the virtual trial was calculated using a two-arm binomial design. (http://www.swogstat.org/stat/public/binomial_twoarm.htm) to demonstrate a benefit with $\alpha = 5\%$ and a power of 80%. The nomogram at 7 years was used to select several subgroups of patients at risk for BOM according to different cutoffs of probability. The rate of BOM in each group was calculated based on the training set before year 7. Relative risk reductions (15, 25, and 35%) of isolated bone metastases were tested.

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%) 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

Table 2. First relapse characteristics and follow-up

	Training set (*N* = 4175)		Validation set (*N* = 579)		
Characteristic	**No. of patients**	**%**	**No. of patients**	**%**	***P***
Sites of 1st metastases[a]					
Bone	643	15.4	48	8.2	<0.001
Liver	137	3.2	21	3.6	
Lung	201	4.8	22	3.7	
Brain	110	2.6	8	1.4	
Others sites[b]	593	14.2	NA	—	
Number of metastatic sites per patient					
1	938	22.4	45	7.8	<0.001
2	343	8.2	14	2.4	
3	20	0.4	6	1.0	
4	0	0.0	2	0.3	
Distant metastasis					
Yes	1301	31.1	67	11.6	<0.001
No	2874	68.8	512	88.4	
Bone metastasis					
Isolated bone metastasis	314	7.5	28	4.9	0.2
Bone metastasis associated with another site	320	7.7	20	3.5	
Delay between diagnosis and first distant metastasis (months)					
Median	26.4		32.5		<0.001
Range	1–426		1.4–76		
Follow-up (months)					
Median	60.3		63		0.1
Range	3.3–477		1–93		

Abbreviation: NA = not applicable.
[a]Patients had several metastatic sites.
[b]Includes soft tissues, other visceral localisation, contralateral breast.

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

	Univariate analysis			Multivariate analysis		
Factor	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age, years						
⩾50	1			1		
35–50	1.3	1.02–1.66	0.03	1.33	0.95–1.86	0.09
<35	2.37	1.69–3.3	<0.001	2.11	1.32–3.38	<0.001
Menopausal status						
No	1	0		1		
Yes	0.74	0.59–93	0.008	0.99	0.71–1.39	0.99
T stage						
T1	1			1		
T2	1.89	1.48–2.41	<0.001	2.03	1.57–2.62	<0.001
T3	2.56	1.75–3.7	<0.001	2.59	1.75–3.85	<0.001
Multifocal tumour						
No	1			1		
Yes	1.061	0.77–1.46	0.7	0.9	0.62–1.24	0.5
Histology						
Ductal carcinoma	1			1		
Lobular carcinoma	0.9	0.7–1.23	0.6	0.85	0.59–1.22	0.4
Others	0.48	0.2–1.07	0.07	0.62	0.27–1.4	0.2
HR status[a]						
Negative	1			1		
Positive	1.66	1.25–2.2	<0.001	1.52	1.11–2.1	0.001
HER2 status						
Negative	1					
Positive	0.92	0.70–1.23	0.6	0.87	0.6–1.17	0.35
Nuclear grade	1.04	0.86–1.26	0.6	1.04	0.83–1.31	0.7
Lymphovascular space involvement						
No	1			1		
Yes	2.05	1.6–2.56	<0.001	1.55	1.22–1.96	<0.001
Axillary lymph node involvement						
No	1			1		
Yes	2.57	1.88–3.5	<0.001	2.44	1.7–3.41	<0.001

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

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.

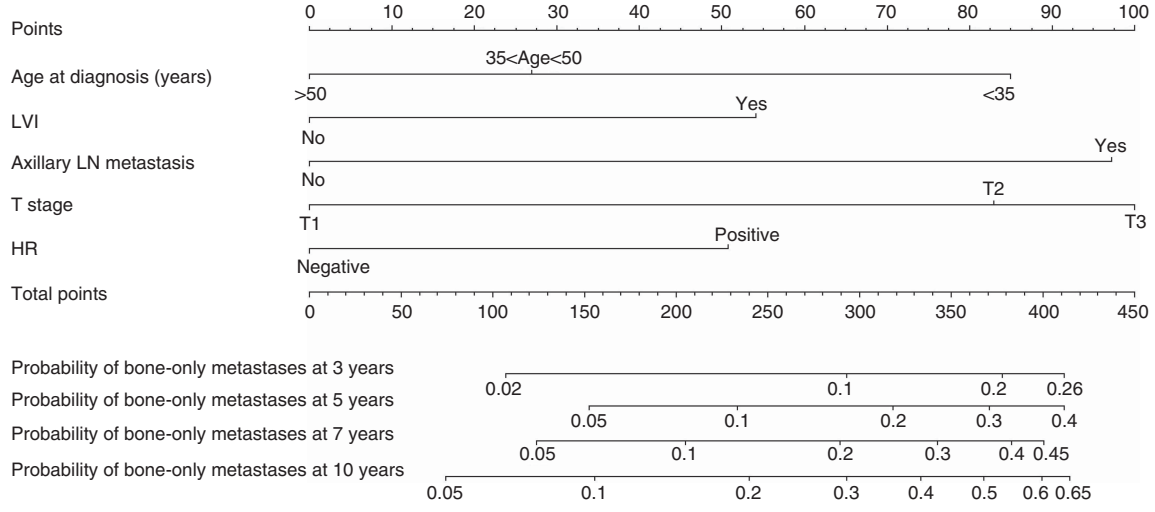

Figure 1. Nomogram to predict the probability of bone-only metastasis in non-metastatic breast cancer. Abbreviations: HR, hormone receptor status (HR negative was defined as estrogen receptor and progesterone receptor negative); LN, lymph node; LVI, lymphovascular space involvement.

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 *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 (*FAS*, *IL2RG*, and *IL7R*) were more strongly associated with bone metastasis from breast cancer.

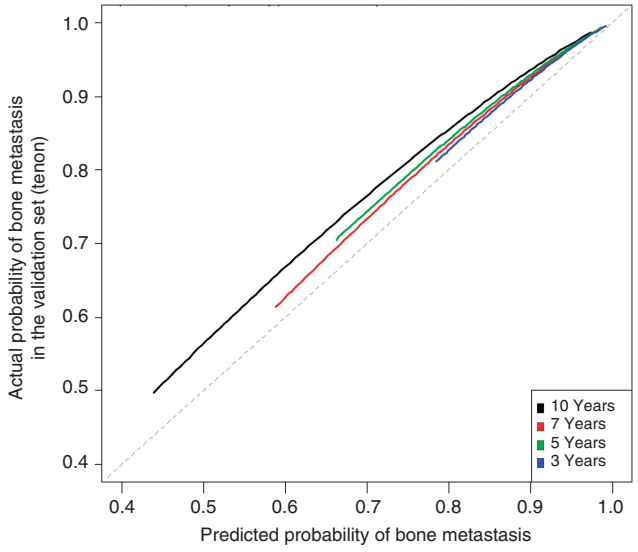

Figure 2. External validation by calibration plot of the nomogram to predict bone-only metastasis in patients with non-metastatic breast cancer at 3, 5, 7, and 10 years. The dashed line shows the ideal calibration line.

It has been demonstrated that the ER-positive status is correlated with the development of bone metastasis (Coleman *et al*, 1998; Diel, 2001; Hess *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 *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 *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 *et al*, 2009, 2011; Eidtmann *et al*, 2010; Coleman *et al*, 2011; Marshall *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-κB ligand (RANKL), denosumab, a fully human monoclonal antibody to RANKL, suppresses bone resorption and increases bone mineral density (Kostenuik *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 *et al*, 2010). Much like the risk assessment process

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

	15% Relative reduction of isolated bone metastases			25% Relative reduction of isolated bone metastases		35% Relative reduction of isolated bone metastases	
Threshold probability of bone metastasis at 7 years	Rate of isolated bone metastases before 7 years[a]	Rate of isolated bone metastases before 7 years[b]	Number of patients to enrol[c]	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	17 948	5.14	6282	4.45	3070
95% Cutoff	7.85	6.67	15 520	5.89	5430	5.10	2656
90% Cutoff	10.59	9.00	11 224	7.94	3908	6.88	1924
85% Cutoff	12.58	10.69	9248	9.43	3224	8.17	1590
80% Cutoff	14.25	12.11	8030	10.69	2814	9.26	1386
75% Cutoff	13.99	11.89	8210	10.49	2866	9.09	1414
70% Cutoff	19.70	16.74	5474	14.77	1922	12.80	954

[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.

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 distant metastasis and overall poor disease outcome as well (Braun *et al*, 2005; Bidard *et al*, 2008). Lipton *et al*, (2011) have reported a biochemical marker of bone resorption, which reflects alterations in bone turnover and predicts bone metastasis. 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. However, we think that this potential source of bias makes our results more relevant for everyday practice because systematic screening is not currently recommended. A small proportion of patients may also have received bisphosphonates for concomitant osteoporosis. This confounding factor would make the correlation between the covariates and the BOM outcome more difficult to detect, and therefore renders the observed significant associations even more remarkable. Finally, nodal status was assessed at the time of surgery, after some patients had received neoadjuvant chemotherapy. This may have generated an underestimation of nodal status, which is a parameter in the final model. This potential bias concerns patients who achieved a pathologic complete response, but was likely balanced by the very large number of patients in the cohort. In conclusion, we have developed a nomogram that is able to predict isolated bone metastases in patients diagnosed with non-metastatic breast cancer. Use of this nomogram could enrich the selection of patient populations for clinical trials.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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