

Doctor, What Are My Chances of Having a Positive Sentinel Node? A Validated Nomogram for Risk Estimation

José Luiz B. Bevilacqua, Michael W. Kattan, Jane V. Fey, Hiram S. Cody III, Patrick I. Borgen, and Kimberly J. Van Zee

ABSTRACT

Purpose

Lymph node metastasis is a multifactorial event. Several variables have been described as predictors of lymph node metastasis in breast cancer. However, it is difficult to apply these data—usually expressed as odds ratios—to calculate the probability of sentinel lymph node (SLN) metastasis for a specific patient. We developed a user-friendly prediction model (nomogram) based on a large data set to assist in predicting the presence of SLN metastasis.

Patients and Methods

Clinical and pathologic features of 3,786 sequential SLN biopsy procedures were assessed with multivariable logistic regression to predict the presence of SLN metastasis in breast cancer. The model was subsequently applied to 1,545 sequential SLN biopsies. A nomogram was created from the logistic regression model. A computerized version of the nomogram was developed and is available on the Memorial Sloan-Kettering Cancer Center (New York, NY) Web site.

Results

Age, tumor size, tumor type, lymphovascular invasion, tumor location, multifocality, and estrogen and progesterone receptors were associated with SLN metastasis in multivariate analysis. The nomogram was accurate and discriminating, with an area under the receiver operating characteristic curve of 0.754 when applied to the validation group.

Conclusion

Newly diagnosed breast cancer patients are increasingly interested in information about their disease. This nomogram is a useful tool that helps physicians and patients to accurately predict the likelihood of SLN metastasis.

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INTRODUCTION

Axillary lymph node status is the most influential prognostic factor in patients with invasive breast cancer.¹⁻⁴ Axillary sentinel lymph node (SLN) biopsy is a standard of care for patients with early-stage breast cancer, replacing traditional axillary lymph node dissection when the SLN is negative.⁵⁻⁷

Lymph node metastasis (LNM) is a multifactorial event. Several variables have been described as predictors of LNM in breast cancer (Appendix Table A1, online only). Usually the results of multivariate analyses of predictors of LNM are expressed as odds ratios, which make it difficult to apply and calculate the probability of SLN metastases for a specific patient.

Newly diagnosed breast cancer patients are increasingly interested in information about their disease. In 2004, eight of 10 Internet users searched online for information on at least one

major health topic, which translates to about 100 million American adults who use the Internet to obtain health information.⁸ Breast cancer is one of the most common health topics researched online, and breast oncologists are likely to encounter more patients who have used the Internet in the context of their diagnosis.⁹⁻¹⁹

With an increased focus on consumer and patient use of information technologies (eg, Internet, multimedia home-care informatics, computerized educational programs) for medical information, tailoring this information appropriately to individuals' cancers, literacy, and culture-specific needs should be a priority.²⁰

The new web-oriented patient demands more precise answers for her questions. Therefore, even with many studies on prediction of LNM, it is a quite challenge to answer precisely (numerically) the simple question: Doctor, what are my chances of having a positive sentinel node?

From the Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; the Department of Quantitative Health Sciences Cleveland Clinic, Cleveland, OH; and the Departamento de Cirurgia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

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Address reprint requests to Kimberly J. Van Zee, MS, MD, FACS, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, MRI 1026, New York, NY 10021; e-mail: vanzeeek@mskcc.org.

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Nomogram for Predicting SLN Metastases

Table 1. Descriptive Characteristics of Modeling and Validation Groups

Characteristic	Modeling		Validation	
	No.	%	No.	%
No. of Patients	3,786	100.0	1,545	100.0
Sex				
Female	3,754	99.2	1,532	99.2
Male	32	0.8	13	0.8
Age, years				
Median	56		56	
Range	20-91		25-90	
≤ 40	374	9.9	181	11.7
41-69	2,732	72.2	1,066	69.0
≥ 70	680	18.0	298	19.3
Tumor size, cm				
Median	1.2		1.3	
Range	0.1-11.0		0.1-9.5	
T1mic	131	3.5	51	3.3
T1a	422	11.1	199	12.9
T1b	963	25.4	362	23.4
T1c	1,582	41.8	624	40.4
T2 ≤ 3.0 cm	495	13.1	215	13.9
T2 > 3.0 cm	160	4.2	80	5.2
T3	33	0.9	14	0.9
Laterality				
Right	1,903	50.3	749	48.5
Left	1,883	49.7	796	51.5
Bilateral				
No	3,530	93.2	1,428	92.4
Yes	256	6.8	117	7.6
Palpability				
No	1,332	35.2	NC	
Yes	1,594	42.1	NC	
Tumor location				
UOQ	2,154	56.9	879	56.9
LOQ	480	12.7	211	13.7
UIQ	564	14.9	264	17.1
LIQ	271	7.2	135	8.7
Central	285	7.5	56	3.6
Unknown	32	0.8	0	
Surgery				
Conservative	2,710	71.6	1,033	66.9
Mastectomy (MRM or TM)	1,076	28.4	512	33.1
Tumor type				
Ductal	3,244	85.7	1,339	86.7
Lobular	372	9.8	166	10.7
Colloid/medullary/tubular	170	4.5	40	2.6
Histologic grade*				
I	331	8.7	97	6.3
II	1,033	27.3	375	24.3
III	1,782	47.1	810	52.4
Unknown	268	7.1	97	6.3
Nuclear grade*				
I	298	7.9	89	5.8
II	1,732	45.7	661	42.8
III	1,073	28.3	522	33.8
Unknown	311	8.2	107	6.9
Estrogen receptor				
Negative	640	16.9	273	17.7
Positive	2,471	65.3	1,186	76.8
Unknown	675	17.8	86	5.6

(continued in next column)

Table 1. Descriptive Characteristics of Modeling and Validation Groups (continued)

Characteristic	Modeling		Validation	
	No.	%	No.	%
Progesterone receptor				
Negative	1,230	32.5	600	38.8
Positive	1,866	49.3	858	55.5
Unknown	690	18.2	87	5.6
HER-2/neu				
Negative	1,887	49.8	NC	
Positive	612	16.2	NC	
Multifocality				
No	2,943	77.7	1,155	74.8
Yes	843	22.3	390	25.2
Lymphovascular invasion				
No	2,989	78.9	1,205	78.0
Yes	797	21.1	340	22.0
SLN metastases				
No	2,535	67.0	966	62.5
Yes	1,251	33.0	579	37.5

NOTE. The histologic and cytologic variables were classified using the criteria defined by the Association of Directors of Anatomic and Surgical Pathology.¹ Tumor size was defined as the size of the invasive component in centimeters as a continuous variable. We also classified tumor size as a categorical variable, using T stage according to the 2002 TNM classification system.³ Multifocality was defined as foci of carcinoma separate from primary tumor; no distinction was made between multifocality or multicentricity. In cases of multifocal tumors or unifocal tumors that involved more than 1 quadrant, the tumor location was classified in the following order of priority: UOQ, central quadrant (central), LOQ, LIQ, and UIQ. For example, a tumor in the UIQ and central quadrants would be classified as central. A tumor involving the central quadrant and UOQ would be classified as UOQ. If all quadrants were involved, the tumor was classified as UOQ. Histologic tumor types were categorized as ductal, lobular, and special. The latter includes pure tubular, pure colloid (mucinous), or typical medullary carcinomas. Other histologies, such as atypical medullary carcinoma or carcinoma with ductal and lobular features, were classified as ductal. Lobular carcinomas are generally not assigned a nuclear grade. Therefore, for the purpose of our analysis, lobular histology and nuclear grade were combined into a single variable defined as nuclear grade: I, II, III, and lobular. Positivity of estrogen and progesterone receptors was defined as at least 10% or more immunostained cells. Positive SLNs were categorized as immunohistochemical (IHC) only (SLN metastases found exclusively by IHC), serial section (SLN metastases found on serial sections by H&E or hematoxylin-eosin [H&E] as a result of IHC), H&E routine (SLN metastases detected by routine single-section H&E or by the frozen-section control), and H&E frozen (SLN metastases found on intraoperative frozen section). No cytology imprints were used.

Abbreviations: MRM, modified radical mastectomy; TM, total mastectomy; UOQ, upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; SLN, sentinel lymph node; NC, not collected.

*Excluding lobular carcinomas.

The goal of this study is to create, using a large data set, a validated nomogram to assist in predicting the presence of SLN metastasis in breast cancer, and to develop a user-friendly software program to allow easy calculation of the risk predicted by the nomogram.

PATIENTS AND METHODS

This project was reviewed and approved by the Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) institutional review board. Data were obtained from retrospective review of a database in which data were prospectively collected for each procedure. The patients were arbitrarily separated into two groups by date of SLN biopsy: the modeling group and the validation group.

Our modeling study population consisted of the 4,608 breast cancer procedures of axillary SLN biopsy performed at MSKCC between September 12, 1996, and July 31, 2002. The inclusion criteria were patients with invasive breast carcinoma who had not undergone neoadjuvant treatment, and who underwent a successful SLN biopsy. A total of 3,786 SLN procedures were eligible for our study and were considered the modeling group.

The validation study population consisted of 2,037 SLN biopsies performed at MSKCC between August 1, 2002 and May 1, 2004. The inclusion and exclusion criteria were identical to those in the modeling population, except for the date of SLN biopsy. There were 1,545 eligible procedures, and these were classified as the validation group. Detailed information for exclusions is listed in Appendix Table A2 (online only). Clinicopathologic characteristics of the modeling and validation groups are described in Table 1.

We utilized each of the following variables: age, sex, primary tumor size, laterality, palpability, histologic tumor type, histologic grade, nuclear grade, tumor location within the breast (quadrant), lymphovascular invasion (LVI), multifocality, estrogen receptor (ER) status, progesterone receptor (PR) status, *HER-2/neu* status, and type of surgery.

The method of pathologic evaluation of SLNs has not changed after the first 78 cases of the sentinel node protocol (institutional review board protocol No. 96-049). Beginning with case 79, frozen section and immunohistochemical (IHC)-stained sections were routinely performed. IHC staining was done retrospectively in the first 78 cases.

The technique of SLN biopsy and histopathologic analyses have been described elsewhere.²¹

Statistical Methods

The variables analyzed for the prediction of SLN metastasis are listed in Table 1. Statistical analyses were done using the statistical software program SPSS, version 10.0.5 (SPSS Inc, Chicago, IL), StatXact, version 4.0.1 (Cytel

Software Corporation, Cambridge, MA) and S-Plus, version 2000, professional edition with design library (Mathsoft, Data Analysis Products Division, Seattle, WA).

Logistic regressions, using interaction between the predictor and data set, tested whether a significant shift in the relationship between each predictor and SLN positivity occurred across data sets.

A nomogram for predicting SLN metastases was developed based on the patients in the modeling group, and then validated with the patients in the validation group. In the modeling group (n = 3,786), logistic regression was used to analyze the association of each variable with the likelihood of SLN metastases. We used restricted cubic splines to relax the linearity assumption when fit was improved. This model was applied to the validation group (n = 1,545) by inserting all postoperative data into the model and calculating each individual patient's probability of having positive SLNs. The discrimination of the model was measured by using the area under the receiver operating characteristic (ROC) curve. The calibration of the model was assessed graphically. Patients were grouped into deciles based on their nomogram predictions. For each decile, the mean predicted probability was compared with the proportion of patients who actually had positive SLNs (actual probability).

A bootstrapping analysis was also performed. First, we computed the apparent accuracy of the full model on the entire data set. Second, we computed the accuracy on a sample of the same size but with replacement, refitting these data. Third, we then calculated the accuracy of this second model, using the original data set. Optimism is the difference between the second and third accuracies. After repeating this process 200 times, the mean optimism was subtracted from the first model accuracy to arrive at a nearly unbiased estimate.

A user-friendly software program was developed to facilitate the calculation of the probability of SLN metastases for each patient.

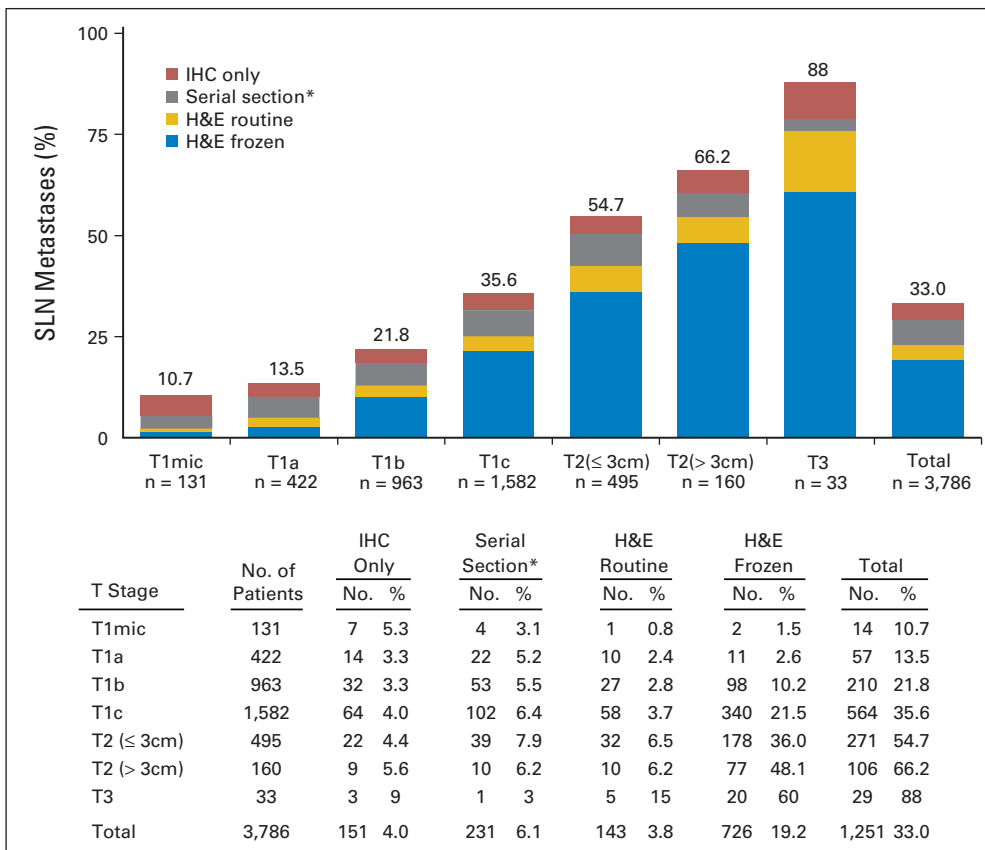


Fig 1. Frequency of sentinel lymph node (SLN) metastasis by T stage and method of detection of metastases in modeling group. The table provides the precise patient numbers and percentages represented graphically in the figure. (*) Serial section: includes SLN metastases found on serial sections by hematoxylin and eosin (H&E) or H&E as a result of immunohistochemistry (IHC).

Nomogram for Predicting SLN Metastases

Table 2. Incidence of SLN Metastases for Modeling and Validation Groups by Patients and Pathologic Characteristics

Characteristic	Modeling			Validation			P
	No.	SLN +		No.	SLN +		
		No.	%		No.	%	
No. of patients	3,786	1,251	33.0	1,545	579	37.5	.0023*
Sex							.127
Female	3,754	1,236	32.9	1,532	569	37.1	
Male	32	15	47	16	10	77	
Age, years							.803
≤ 40	374	172	46.0	181	88	48.6	
41-69	2,732	909	33.3	1,066	406	38.1	
≥ 70	680	170	25.0	298	85	28.5	
Tumor size							.580
T1mic	131	14	10.7	51	11	22	
T1a	422	57	13.5	199	31	15.6	
T1b	963	210	21.8	362	84	23.2	
T1c	1,582	564	35.7	624	263	42.1	
T2 ≤ 3.0 cm	495	271	54.7	215	121	56.3	
T2 > 3.0 cm	160	106	66.3	80	56	70	
T3	33	29	88	14	13	93	
Laterality							.642
Right	1,903	608	31.9	749	277	37.0	
Left	1,883	643	34.1	796	302	37.9	
Bilateral							.264
No	3,530	1,176	33.3	1,428	533	37.3	
Yes	256	75	29.3	117	46	39.3	
Palpability							
No	1,332	320	24.0	NA	NA	NA	
Yes	1,594	642	40.3	NA	NA	NA	
Tumor location							.191
UOQ	2,154	726	33.7	879	330	37.5	
LOQ	480	181	37.7	211	91	43.1	
UIQ	564	143	25.4	264	74	28.0	
LIQ	271	81	29.9	135	49	36.3	
Central	285	100	35.1	56	35	62	
Unknown	32	20	62	—	—	—	
Surgery							.769
Conservative	2,710	739	27.3	1,033	312	30.2	
Mastectomy (MRM or TM)	1,076	512	47.6	512	267	52.1	
Tumor type							.970
Ductal	3,244	1,092	33.7	1,339	514	38.4	
Lobular	372	150	40.3	166	61	36.7	
Colloid/medullary/tubular	170	9	5.3	40	4	10	
Histologic grade†							.955
I	331	41	12.4	97	11	11	
II	1,033	341	33.0	375	139	37.1	
III	1,782	688	38.6	810	346	42.7	
Unknown	268	31	11.6	97	22	23	
Nuclear grade†							.319
I	298	38	12.8	89	16	18	
II	1,732	558	32.2	661	236	35.7	
III	1,073	446	41.6	522	234	44.8	
Unknown	311	59	19.0	107	32	29.9	
Estrogen receptor							.880
Negative	640	216	33.8	273	99	36.3	
Positive	2,471	884	35.8	1,186	462	39.0	
Unknown	675	151	22.4	86	18	21	
Progesterone receptor							.670
Negative	1,230	401	32.6	600	219	36.5	
Positive	1,866	694	37.2	858	342	39.9	
Unknown	690	156	22.6	86	18	21	

(continued on next page)

Table 2. Incidence of SLN Metastases for Modeling and Validation Groups by Patients and Pathologic Characteristics (continued)

Characteristic	Modeling			Validation			P
	No.	SLN +		No.	SLN +		
		No.	%		No.	%	
<i>HER-2/neu</i>							
Negative	1,887	678	35.9	NA	NA	NA	
Positive	612	240	39.2	NA	NA	NA	
Multifocality							.159
No	2,943	877	29.8	1,155	403	34.9	
Yes	843	374	44.4	390	176	45.1	
Lymphovascular invasion							.156
No	2,989	767	25.7	1,205	344	28.5	
Yes	797	484	60.7	340	235	69.1	

Abbreviations: SLN, sentinel lymph node; SLN+, sentinel lymph node positive; NA, not available; UIQ, upper inner quadrant; UOQ, upper outer quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant; MRM, modified radical mastectomy; TM, total mastectomy.

*Fisher's exact test.

†Excluding lobular carcinomas.

RESULTS

The overall frequency of SLN metastasis was 33%. The frequency of SLN metastasis by T stage and method of detection of metastases is demonstrated in Figure 1. The great majority of metastases were identified by frozen section of the SLN. The enhanced pathologic analysis identified additional metastases in 10% of patients, 4% by IHC only, and 6% by serial section. There was no statistical difference (Pearson χ^2 , 3.357; $P = .34$) between the frequencies of method of detection of the modeling (Fig 1) and validation groups (Appendix Fig A1, online only).

There was a higher incidence of SLN metastases in the validation group (37.5% v 33.0%; $P < .05$). No significant shift in the relationship between each predictor and SLN positivity occurred across data sets (all $P > .05$; Table 2).

In multivariate analysis, variables that were associated with SLN metastasis in breast cancer were tumor type, LVI, tumor size, tumor location, age, multifocality, and ER and PR status ($P < .05$ for all variables). There was no difference in frequency of SLN metastases between ductal and lobular tumor types ($P > .25$).

In Appendix Table A3, we list the results of the final logistic regression models for predicting SLN metastasis in breast cancer. We also created a model that does not include ER and PR because this information may not be available before the definitive surgery.

Two nomograms based on these models were developed in the modeling group ($n = 3,786$) and appear in Figures 2A and 3A. The overall predictive accuracy of the models applied to the validation population, as measured by the area under ROC curve was 0.754 for both nomograms. For each model we built a calibration curve (Figs 2B and 3B) and a plot of the distribution of predicted probabilities (Figs A2 and A3, online only). The bootstrapping analysis demonstrated concordance indices of 0.753.

Using the Nomogram

The nomogram consists of rows. The first row (POINTS) is the point assignment for each variable. For example, in Figure 2A, rows 2 to 10 represent the variables included in the model. For an individual patient, each variable is assigned a point value (uppermost scale, POINTS) based on the clinicopathologic characteristics. A vertical line

is made between the appropriate variable value and the POINTS line. The assigned points for all nine variables are summed and the total is found in row 11 (TOTAL POINTS). Once the total is located, a vertical line is made between TOTAL POINTS and the final row, row 12 (Predicted Probability of +SLN).

Below each nomogram is its corresponding calibration plot. The nomogram developed using the modeling group of patients ($n = 3,786$) was applied to the validation group ($n = 1,545$). A histogram of the calculated probabilities for the validation group is shown along the horizontal axis. These 1,545 patients are grouped in deciles of their predicted probabilities, and the actual incidence of additional SLN metastases was calculated for each decile. The vertical axis represents the actual observed incidence (Actual Probability), and the horizontal axis represents the probability calculated by the nomogram (Predicted Probability). For each decile of the validation group, a triangle is plotted to show actual probability. If the model were perfect, all triangles would lay on the dotted line with a slope of 1. The version of the nomogram in Figure 2 is for use when information on ER and PR status are available; that in Figure 3 is for those patients where ER and PR status are not available.

To facilitate ease of use in clinical setting, in addition to the graphic nomograms, we have made an application (software) for personal computers, Palm (Palm Inc, Sunnyvale, CA), pocket personal computers, and Macintosh computers (Apple Inc, Cupertino, CA). These applications will be made available at our web site (www.mskcc.org/nomograms).

DISCUSSION

The frequency of axillary lymph node metastases (ALNM) by T stage (American Joint Committee on Cancer)³ varies among the studies of pre-SLN era. In the larger studies, the frequency is 10% in T1mic,²² 9% to 13% in T1a,²³⁻²⁸ 13% to 19% in T1b,²³⁻²⁹ 26% to 29% in T1c,^{23,24,27,29} 39% to 50% in T2 less or equal 3 cm,^{23,24,27,29} 48% to 59% in T2 larger than 3 cm,^{27,29} and 71% to 80% in T3.^{24,27}

The frequency of ALNM in each T stage in the SLN era appears higher than the corresponding frequency from the pre-SLN era. This

Nomogram for Predicting SLN Metastases

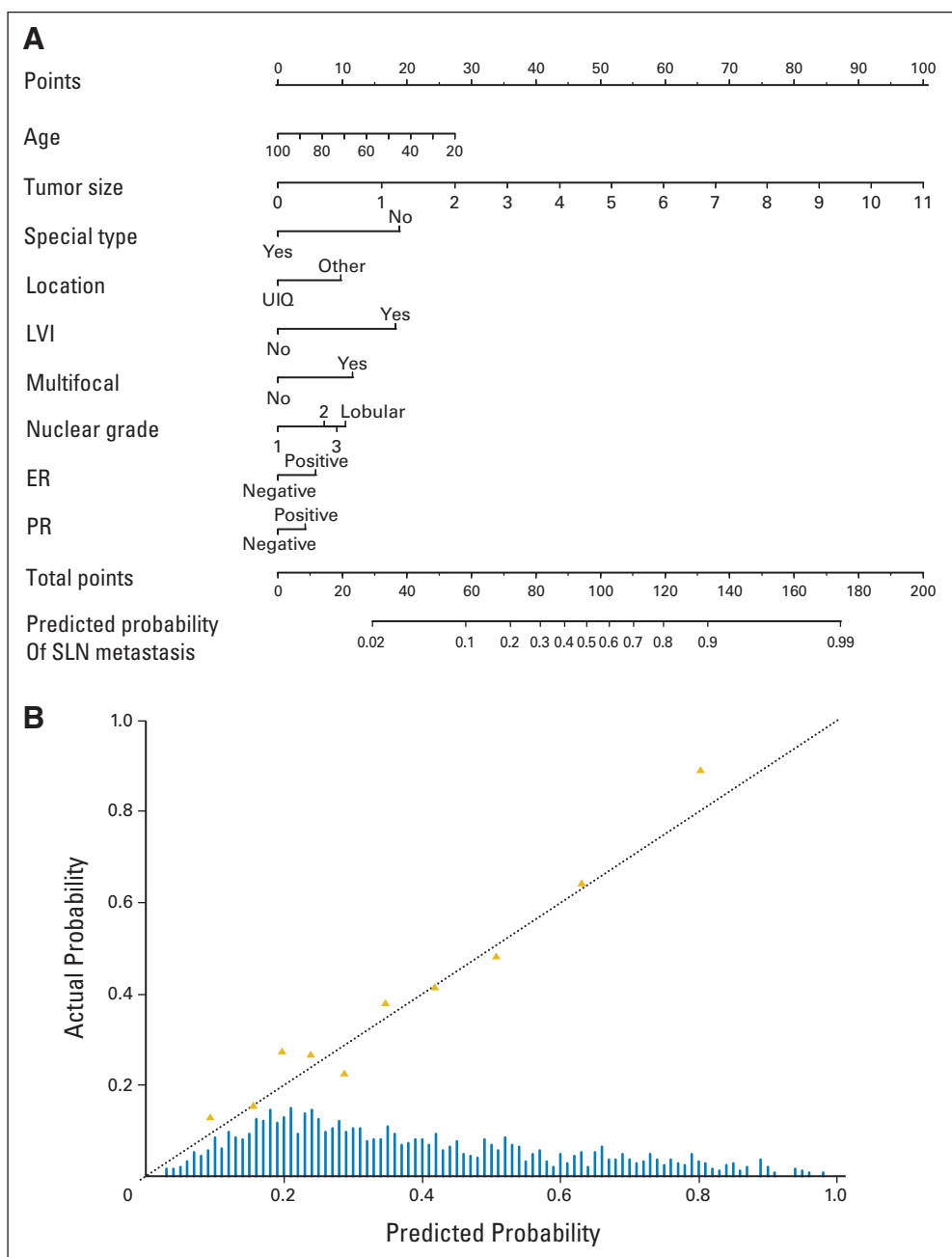


Fig 2. Nomogram to predict likelihood of sentinel lymph node (SLN) metastases. Below the nomogram is its calibration plot. See Using the Nomogram in the Results section for instructions on nomogram use and for an additional explanation. Age, patient's age in years; Tumor size, size of invasive carcinoma in cm; Special type, colloid, medullary, or tubular, defined as "Yes" (ductal and lobular are defined as "No"); Location, UIQ quadrants or other quadrants (outer or central); LVI, lymphovascular invasion; Multifocal, multifocality of primary tumor; ER, estrogen receptor status; PR, progesterone receptor status; Nuclear grade, nuclear grade (I, II, III, and lobular).

is likely attributable to the use of enhanced histopathologic analysis in the SLN era, which allows detection of so-called occult metastases, not usually seen in the past with conventional pathologic analyses. Many studies have demonstrated an increase of 10% to 52% in the detection of SLN metastasis owing to the addition of serial sectioning and IHC analyses.³⁰⁻³⁵ Although the clinical relevance of these micrometastatic deposits is the subject of controversy, data from large studies with long follow-up periods suggest that occult metastases may be associated with a small but significant decrease in overall and/or disease-free survival.³⁶⁻⁴⁰ Maibenco et al,⁴¹ analyzing the Surveillance, Epidemiology, and End Results data, confirm the impact of micrometastases in long-term survival, but found no difference among patients with tumors smaller than 1 cm. However, other studies did not show

any impact of lymph node micrometastases on survival.^{42,43} Large, ongoing prospective studies such as the National Surgical Adjuvant Breast and Bowel Project trial B32 (NSABP B-32), the American College of Surgeons Oncology Group trial Z0010 (ACOSOG-Z0010), and the International Breast Cancer Study Group trial 23-01 will better define the significance of micrometastatic lymph node disease.

The inclusion of IHC-only positive SLNs may cause the nomogram to falsely predict for a positive node. Current AJCC staging criteria labels an IHC-only positive node as N0(i+). However, in our previous study, of patients with an IHC-only positive sentinel node, 12% had additional hematoxylin and eosin (H&E) metastases (macrometastases) on completion axillary dissection, which would have been missed if the patient did not undergo completion axillary

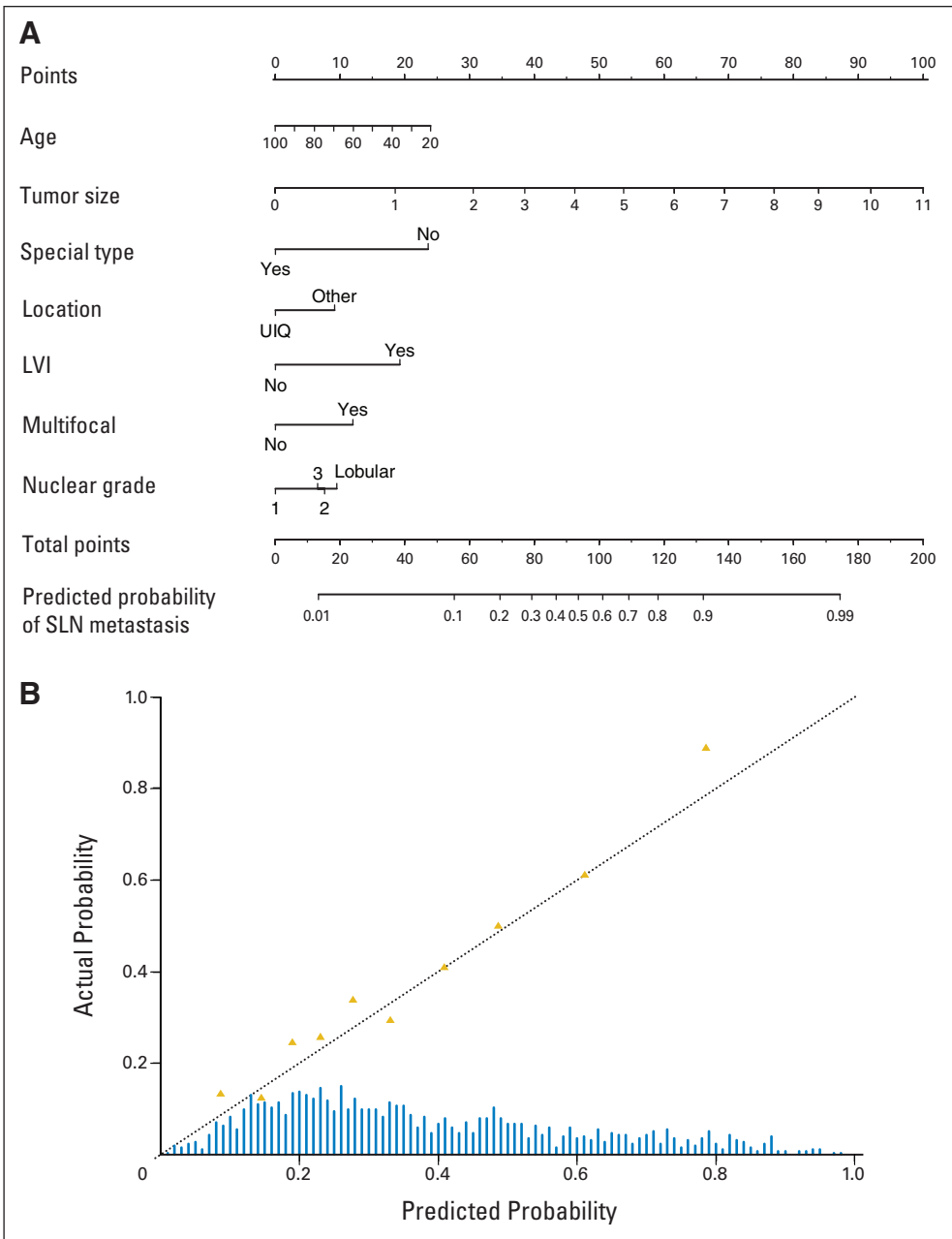


Fig 3. Nomogram without estrogen receptor (ER) and progesterone receptor (PR) information. Below the nomogram is its calibration plot. See Using the Nomogram in the Results section for instructions on nomogram use and for an additional explanation. Age, patient's age in years; Tumor size, size of invasive carcinoma in cm; Special type, colloid, medullary, or tubular, defined as "Yes" (ductal and lobular are defined as "No"); Location, UIQ quadrants or other quadrants (outer or central); LVI, lymphovascular invasion; Multifocal, multifocality of primary tumor; Nuclear grade, nuclear grade (I, II, III, and lobular).

dissection.²¹ Since this information may be relevant, we chose to include both IHC and H&E positive sentinel nodes in the nomogram.

We reviewed the published studies that address the predictors for ALNM in the pre-SLN and SLN eras (Appendix Table A1, online only). The great majority of these studies either collected the data retrospectively, did not mention how the data were collected, or had no central pathology review. In these studies, tumor size, age, LVI, and histologic subtype were the variables most commonly described as independently associated with ALNM. Only two studies, Ravdin et al⁴⁴ and Gann et al,⁴⁵ validated their statistical models in another data set. In SLN studies, the variables associated with SLN metastases were, as expected, quite similar. Our study confirms these results, with the additional findings of tumor location (fewer SLN metastases in patients with upper inner quadrant

[UIQ] tumors), ER status, and PR status as independent predictor factors associated with SLN metastasis.

The frequencies of SLN metastases in ER/PR-positive tumors were higher than those for ER/PR-negative tumors, corresponding to a small, but significant, increase of 2.0% for ER and 4.6% for PR. Although this observation seems counterintuitive, it actually is in agreement with the findings of other large studies. Ravdin et al⁴⁴ studied data from 26,683 patients of the National Breast Cancer Tissue Resource. Gann et al⁴⁵ analyzed data from 18,025 patients of the nationwide Patient Care Evaluation survey of the American College of Surgeons. Viale et al⁴⁶ from Veronesi's group in Milan, studied the prediction of sentinel LNM for 4,351 patients, and they identified the same order of differences (2.8% for ER; 5.7% for PR).

The lower frequency of SLN metastasis in UIQ location tumors observed in this study suggests the possibility of alternative routes of lymphatic flow, especially to the internal mammary chain. In an earlier comprehensive review of the literature on internal mammary nodes, we have addressed the importance of UIQ tumors in terms of survival and their relation to LNM.⁴⁷ Two large data set studies highlight the importance and clinical implications of internal mammary sentinel nodes when identified on preoperative lymphoscintigraphy.^{48,49} Nevertheless, this issue is quite controversial, and it is beyond the scope of this study.

We have developed a nomogram and a corresponding computer application that predict the likelihood of SLN metastases; in the validation test, they performed well (calibration plots in Figs 2 and 3).

The application utilizes nine readily available clinical variables: age, tumor size, tumor type, LVI, multifocality, nuclear grade, tumor location, and ER and PR status. This allows quick and easy calculation. Our patients can now estimate their individual likelihood of having SLN metastases.

It has been suggested that patients with a low risk of axillary lymph node involvement should be spared SLN biopsy.⁴⁶ While SLN biopsy is an extremely safe procedure with low morbidity, there are some patients, typically elderly, in whom consideration is given to avoiding SLN biopsy because of comorbid conditions. In this small patient population, the nomogram could help to weigh the risks and benefits of SLN biopsy. This application could potentially help physicians to select precisely those patients at very low risk for SLN involvement who could be spared an SLN biopsy. Alternatively, it could encourage a physician to reconsider an initial decision to spare a patient an SLN biopsy in the event that a higher than expected risk is identified. Clearly staging the axilla is more accurate than any predictive model. However, in patients with significant comorbidities, and in whom avoidance of standard axillary staging is being considered, the predicted probability might help the clinician weigh the risks and benefits more appropriately.

One could argue that pathologic information such as tumor size, LVI, and multifocality are available only after a surgical biopsy. Indeed, many patients have excisional biopsies before SLN biopsy, and for these women, all necessary predictive variables are available. For those who have only a core biopsy result available, it has been demonstrated that evaluation of tumor size and multifocality preoperatively with mammography, ultrasound, and/or magnetic resonance imaging is accurate and provides a good estimation of tumor size and the possibility of multifocality.⁵⁰⁻⁶⁰ With the quality of breast imaging available today, it is unlikely to identify large differences between imaging and pathological tumor sizes that would impact dramatically in the estimated probability of the nomogram. However, we agree that this is a limitation of the applicability of the nomogram. A practical solution is to enter values into the nomogram from either end of the range of estimates that seem reasonable for a given variable. For example, if the mammogram suggests a 4-cm spiculated mass, but the sonogram

estimates a 2-cm hypoechoic mass, the user can put in both values, and obtain a range of estimates, depending on the final pathology size. Or, if the presence of LVI cannot be precisely assessed, a range of estimates can be calculated with and without LVI.

One could point out that there are differences between the two data sets, in terms of variable distributions and shifts over time; however, these differences put more pressure on the prediction model to be accurate in the validation data set. If the prediction model is accurate, it will properly adjust the predictions to compensate. More important, the results of Table 2 reveal no evidence of a shift in the relationship between any of the predictors and SLN positivity across the development and validation data sets.

Our model is imperfect. The area under the ROC curve was 0.754. This means that if we randomly select two women, one of whom has at least one positive SLN, and one of whom has negative SLNs, there is a 75.4% chance that the model will predict a higher probability for the positive woman. This is a scale that ranges from 0.5, which would be achieved by tossing a coin, to 1.0, which would require perfect ability to distinguish the woman with positive nodes from the one with negative nodes. Another example, for comparison: the area under ROC curve for film and digital mammography is, 0.61 and 0.82, respectively, for the detection of breast cancer.⁶¹ Therefore, our nomograms are as accurate for the prediction of a positive sentinel node as mammography is accurate for the detection of breast cancer.

Nevertheless, this nomogram provides an accurate, accessible, multivariate predictive model that has been prospectively validated in a large independent data set. This model and its computer application represent a significant improvement over our intuition or theorization based on subjectivity of guesstimates. Finally, it provides the precise and deserved answer to our patient's question: Doctor, what are my chances of having a positive sentinel node?

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: José Luiz B. Bevilacqua, Kimberly J. Van Zee
Financial support: Hiram S. Cody III
Administrative support: Hiram S. Cody III
Provision of study materials or patients: Jane V. Fey, Hiram S. Cody III, Kimberly J. Van Zee
Collection and assembly of data: José Luiz B. Bevilacqua, Michael W. Kattan, Jane V. Fey
Data analysis and interpretation: José Luiz B. Bevilacqua, Michael W. Kattan, Patrick I. Borgen, Kimberly J. Van Zee
Manuscript writing: José Luiz B. Bevilacqua
Final approval of manuscript: José Luiz B. Bevilacqua, Michael W. Kattan, Jane V. Fey, Hiram S. Cody III, Patrick I. Borgen, Kimberly J. Van Zee

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).