

Assessment of the Performance of the Stanford Online Calculator for the Prediction of Nonsentinel Lymph Node Metastasis in Sentinel Lymph Node-Positive Breast Cancer Patients

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BACKGROUND: Several models for the prediction of nonsentinel lymph node (NSLN) metastasis in sentinel lymph node (SLN)-positive breast cancer patients have been proposed. In this study, the authors evaluate the Stanford Online Calculator (SOC), which was designed to predict the likelihood of NSLN metastasis using only 3 variables: primary tumor size, SLN metastasis size, and angiolymphatic invasion status. They compared it with the Mayo and Memorial Sloan-Kettering Cancer Center (MSKCC) nomograms. **METHODS:** The SOC was used to calculate the probability of NSLN metastasis in 464 breast cancer patients with SLN metastasis who underwent completion axillary lymph node dissection at the Mayo Clinic. The area under the receiver operating characteristic curve (AUC) was calculated for each model. Mean probabilities of patients with and without NSLN metastasis were compared. Patients with $\leq 5\%$, $\leq 10\%$, and 100% NSLN metastasis probabilities were examined. **RESULTS:** The AUCs of the Stanford, MSKCC, and Mayo models were 0.72, 0.74, and 0.77, respectively ($P = .13$). The mean Stanford probabilities for patients with and without NSLN metastasis were 0.75 (range, 0.06-1.0) and 0.50 (range, 0.05-1.0), respectively ($P < .0001$). The false-negative rates for patients with a Stanford probability of $\leq 5\%$ and $\leq 10\%$ were 0% and 13%, respectively. Of the patients with a Stanford probability of 100%, 26% did not have NSLN metastasis. **CONCLUSIONS:** Despite using only 3 variables, the Stanford nomogram appears to perform on a par with, but not better than, the MSKCC and Mayo nomograms. Further validation in other patient populations is needed. **Cancer 2009;115:4064-70. © 2009 American Cancer Society.**

KEY WORDS: prediction model, nomogram, nonsentinel lymph node, breast cancer.

The surgical treatment of breast cancer has evolved greatly over the past century. In place of the radical Halstead mastectomy, patients are now routinely treated and staged with either lumpectomy or mastectomy combined with sentinel lymph node (SLN) surgery. Axillary lymph node dissection (ALND), in clinically lymph node negative patients, is typically performed only when a pathologically positive SLN is

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found. Of those patients who are found to have metastatic disease in the SLN, 40% to 60% will not have any additional nonsentinel lymph node (NSLN) metastases found at completion ALND.¹ Furthermore, several large randomized trials with 20 to 25 years of follow-up have failed to demonstrate a survival benefit for patients undergoing ALND.^{2,3}

Some authors have proposed that patients with a positive SLN and a low likelihood of having metastasis beyond the SLN could be spared ALND because of its low yield and considerable morbidities. The estimated false-negative (FN) rate of SLN surgery of 5% to 10% has been suggested as the benchmark for deciding whether to perform ALND in patients with a positive SLN.^{4,5} To aid in the stratification of a patient's risk of having NSLN metastasis, multiple predictive models and nomograms have been proposed.^{1,4-28}

The most well-validated nomogram is from Memorial Sloan-Kettering Cancer Center (MSKCC) and requires 10 variables (frozen section, tumor size, tumor type, tumor grade, number of positive SLNs, SLN method of detection, number of negative SLNs, lymphovascular invasion status, multifocality, and estrogen receptor status) to determine a patient's risk of having NSLN metastasis.^{11,12,19,24,29-36} Another model with discriminatory power similar to the MSKCC nomogram is the Mayo model.¹² This model uses 7 variables (patient age, estrogen receptor status, SLN metastasis size, primary tumor size, number of positive and negative SLNs, and presence of extracapsular extension).

In a previous report, we demonstrated that 2 models that use only 2 to 3 criteria for predicting the probability of having NSLN metastasis are not as accurate as models that use multiple variables.³⁷ However, a new model, the Stanford Online Calculator (SOC), was recently published. It uses 3 variables and is reported to perform better than the MSKCC nomogram.¹⁶ The SOC was developed by multivariate logistic regression analysis informed by Classification and Regression Trees using data from the Bay Area SLN Database and published in 2008.

Since the initial publication, it has not been validated in an independent patient population. The Stanford model calculates the probability of NSLN metastasis in patients with a positive SLN using the following 3 variables: primary breast tumor size, size of SLN metastasis

(ie, isolated tumor cell [≤ 0.2 mm], micrometastasis [>0.2 mm and ≤ 2 mm], and macrometastasis [>2 mm]), and the presence or absence of angiolymphatic invasion (ALI). The SOC is available via the Internet and allows clinicians to easily calculate a patient's probability of having metastasis beyond the SLN.³⁸ The purpose of the current study was to assess the performance of the Stanford model in an independent patient population and to compare its performance with the MSKCC and Mayo models in this same population.

MATERIALS AND METHODS

With the approval of the Mayo Clinic Institutional Review Board, we reviewed our database of 465 consecutive, clinically lymph node-negative breast cancer patients with positive SLN(s) who underwent completion ALND from November 1997 through June 2004. The inclusion criteria, method of SLN identification, pathologic review, and tumor and SLN features are described in detail in a previously published report.¹² The MSKCC model was previously validated, and the Mayo model was developed in this population.¹² Briefly, SLNs were identified using radioisotope and/or blue dye according to surgeon preference. Intraoperative frozen section and permanent hematoxylin and eosin (H&E) stains were performed on all SLNs. Immunohistochemical stains were performed on all SLNs that were negative by frozen section and permanent H&E. SLNs were considered to be positive if metastasis were noted on immunohistochemistry or H&E. The database also includes age, pathologic size of primary invasive breast tumor, tumor type, number of positive and negative SLNs, and number of positive NSLNs for each patient (Table 1).

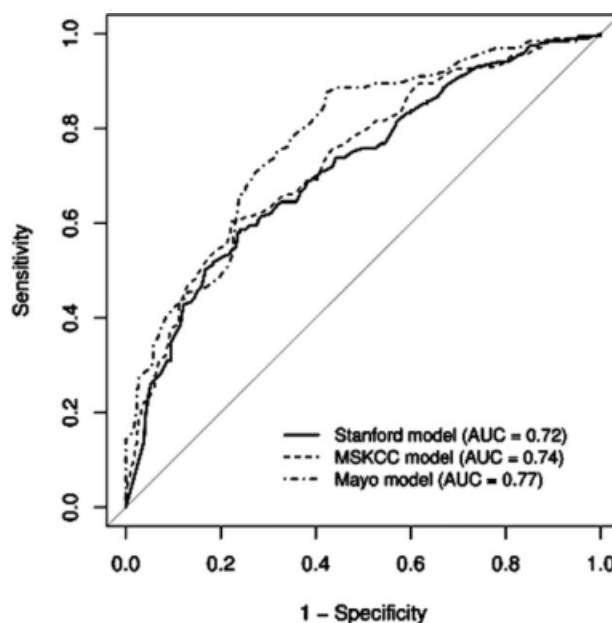
For each patient, the primary breast tumor size, size of SLN metastasis, and presence or absence of ALI were manually entered into the SOC by 1 of the authors (J.S.S.) to calculate the probability of NSLN metastasis.³⁸ Model discrimination of the SOC was assessed by calculating the area under the receiver operating characteristic curve (AUC) with 95% confidence interval (95% CI) for each model. AUCs were compared among models using the method of DeLong et al.³⁹ Mean probabilities of patients with and without positive NSLN were compared using 2-sample Student *t* tests, and probabilities were compared between models within each NSLN category

Table 1. Overall Patient and Tumor Characteristics

Variable	
Age, y, No. (%)	
≤50	162 (35)
>50	302 (65)
Tumor classification, No. (%)	
T1a	13 (3)
T1b	50 (11)
T1c	179 (39)
T2	181 (39)
T3	41 (9)
Tumor type, No. (%)	
Ductal	369 (80)
Lobular	95 (20)
Positive SLNs, No. (%)	
1	359 (77)
>1	105 (23)
Negative SLNs, No. (%)	
0	225 (48)
1	115 (25)
2	62 (13)
>2	62 (13)
Size of SLN metastasis, mm	
≤0.2, No. (%)	37 (8)
0.21-2.0, No. (%)	109 (23)
>2.0, No. (%)	318 (69)
Mean	5.8
Range	0.05-26
Lymphovascular invasion, No. (%)	
Yes	206 (44)
No	258 (56)
Additional +NSLNs, No. (%)	
Yes	202 (44)
No	262 (56)
Mean tumor size ±SD, cm	2.6±2.0
Tumor size, range, cm	0.1-15
Mean No. of SLNs removed ±SD	2.4±1.6
Median No. of SLNs removed, [range]	2 [1-11]

SLN indicates sentinel lymph node; NSLNs, nonsentinel lymph nodes; SD, standard deviation.

using Student *t* tests for paired data. To examine model performance in low-probability patients, the NSLN status of patients with predicted probabilities ≤5% and ≤10% were reported, and FN rates were calculated as the number of patients with positive NSLNs divided by the number of patients meeting the criteria for low predicted probability. Analysis was performed using SAS (version 9.1.3; SAS Institute Inc, Cary, NC) and R (version 2.6.1; R Foundation for Statistical Computing, Vienna, Austria) statistical software. *P* values <.05 were considered statistically significant.

**FIGURE 1.** The areas under the curve (AUCs) for receiver operating characteristic curves based on the Stanford, Memorial Sloan-Kettering Cancer Center (MSKCC), and Mayo models are shown.

RESULTS

For 1 patient, the primary tumor size could not be determined. Therefore, complete variable data were available for 464 of the 465 patients in our SLN database (Table 1). Approximately 44% of patients had NSLN metastasis, 38% of whom had only 1 additional positive lymph node at completion ALND. The mean number of additional positive NSLNs was 4 (range, 1-22 NSLNs) in patients with NSLN metastasis. The mean number of axillary lymph nodes resected was 21 (range, 4-52 axillary lymph nodes).

The AUC of the Stanford model was 0.72 (95% CI, 0.67-0.77) when its criteria were applied to our patient population. This was similar, but not superior to the AUCs of the MSKCC and Mayo nomograms of 0.74 and 0.77, respectively. The AUCs of the 3 models were not significantly different (*P* = .13) (Fig. 1).

The mean Stanford probabilities for patients with and without NSLN disease were 0.75 (range, 0.06-1.0) and 0.50 (range, 0.05-1.0), respectively. These values were significantly different (*P* < .0001). In addition, these values were significantly higher than the respective mean values of the MSKCC and Mayo models (Table 2).

Table 2. Mean Calculated Probability of NSLN Metastasis in Patients With and Without NSLN Metastasis

Model	Without NSLN Metastasis		With NSLN Metastasis	
	% (Range)	P (vs MSKCC)	% (Range)	P (vs MSKCC)
Stanford	50 (5-100)	<.0001	75 (6-100)	<.0001
Mayo	34 (5-82)	.09	56 (9-98)	.28
MSKCC	36 (2-91)		55 (9-95)	

NSLN indicates nonsentinel lymph node; MSKCC, Memorial Sloan-Kettering Cancer Center.

Table 3. Stanford, Mayo, and MSKCC Models at 5%, 10%, and 100% Predicted Probability Cutoff Values Applied to Mayo Data

Predicted Probability of NSLN Metastasis	Model	No.	TN	FN	FN, %
≤5%	Stanford	1/464	1	0	0
	Mayo	1/464	1	0	0
	MSKCC	9/464	9	0	0
≤10%	Stanford	47/464	41	6	13
	Mayo	32/464	11	1	8
	MSKCC	12/46	28	4	13
			TP	FP	FP, %
100%	Stanford	38/464	28	10	26

MSKCC indicates Memorial Sloan-Kettering Cancer Center; NSLN, nonsentinel lymph node; TN, true-negative; FN, false-negative; TP, true-positive; FP, false-positive.

When patients with a low risk ($\leq 10\%$ and $\leq 5\%$) of having NSLN disease were examined, we found that, based on the SOC, 47 patients in the current study cohort had a $\leq 10\%$ predicted probability of having NSLN metastasis. Of these 47 patients, 6 had a positive NSLN, for an FN rate of 13%. At this level of predicted probability, the FN rates of the MSKCC and Mayo models were 13% and 8%, respectively. There was only 1 patient who had a Stanford probability $\leq 5\%$, and this patient did not have a positive NSLN, indicating a FN rate of 0% for the single patient who fit this very low-risk category. Nine patients by the MSKCC model and 1 patient by the Mayo model were found to have predicted probabilities of $\leq 5\%$. None of these patients had NSLN metastasis, for a 0% FN rate for both models (see Table 3).

At the other end of the spectrum, when patients with a high probability of NSLN metastasis were examined, there were 38 patients with a predicted probability of 100% by the SOC. Twenty-eight (74%) of these patients were found to have NSLN metastasis. Ten

patients did not have NSLN metastasis, for a false-positive rate of 26% (Table 3).

DISCUSSION

To be of clinical utility, a model should have an AUC > 0.7 . A model with an AUC of 0.81 to 0.9 is considered to have excellent discrimination.⁴⁰ In multiple validation studies, including those performed outside of the US, the MSKCC nomogram has been shown to have an AUC of 0.58 to 0.86 and is currently considered the “gold standard” of NSLN metastasis prediction.^{12,29-34,36,41} Multiple other models have been developed. To our knowledge, to date, the majority of models with a low number of variables have performed inferiorly to models with more variables. The SOC is of significant interest to clinicians because it incorporates the size of the metastases in the SLN, whereas previous models have not differentiated between micrometastases and macrometastasis in the SLN, or not included isolated tumor cells. The results of

the current study demonstrate that the SOC had an AUC of 0.72, which was similar to the MSKCC and Mayo nomograms. Although the SOC did not have a significantly higher AUC than the MSKCC or Mayo models, it is interesting that the SOC, using only 3 variables, has an AUC that was comparable to the MSKCC and Mayo models, which require 10 and 7 variables, respectively. In addition, it appears that the SOC is much more accurate than previously proposed models that use only 2 to 3 variables.^{4,5,37}

Models always perform best in the population on which they are based. It should be noted that the Mayo model was constructed from the database used for this analysis.¹² Considerable variation is typically observed when they are applied to independent populations. Therefore, the validation of models in independent populations is imperative before widespread utilization. To our knowledge, the current study is the first report evaluating the performance of the SOC since its publication in 2008. The performance of the SOC in our patient population is especially notable given the differences between the patient population in which the SOC was developed and our population. For instance, more of our patients had ALI (44% vs 33%) and SLN macrometastasis (69% vs 7%) than did those in the population used by Kohrt et al to develop the SOC. In addition, more of our patients without ALI had NSLN metastasis (34% vs 19%), whereas fewer of our patients with ALI had NSLN metastasis (55% vs 74%). Our patients were less likely to have isolated tumor cells (8% vs 23%) or micrometastasis (24% vs 70%).

Patients with and those without metastasis beyond the SLN were found to significantly differ with regard to mean predicted probability as determined by the SOC. However, the ranges of these 2 groups completely overlapped. This indicates that there is no probability score above which one can be certain that NSLN metastases are present. In addition, there is no score under which one can be certain that NSLN metastases are not present. In addition, the mean predicted probabilities of the SOC were significantly higher than those predicted by either the MSKCC or Mayo models.

When patients with a low predicted risk for NSLN metastasis were examined, actual rates of NSLN metastasis were found to be higher than predicted. Therefore, based solely on probability scores, the SOC does not

appear to adequately discriminate between patients with and without NSLN metastases to the extent that ALND could be omitted with a high degree of certainty. Several authors have suggested using a threshold of predicted probability of NSLN metastasis of 5% to 10% as the cut-off for omitting ALND, citing the documented FN rate of SLN surgery.^{4,5,42} Given the greater morbidity of ALND compared with SLN surgery and the lack of survival advantage, it may be satisfactory to omit ALND in low-risk patients if they could be properly identified by a rigorously tested model that was proven to be accurate in multiple patient populations.^{2,3,43} Although ALND is not associated with improved survival, the staging information from ALND plays an important role in recommendations for adjuvant treatment, both for chemotherapy and for postmastectomy radiation. If a higher threshold was picked, the staging and prognostic information normally gained from ALND would be incomplete and may result in inadequate treatment for patients. In terms of risks of local recurrence, in a recent retrospective review performed at the study institution, a group of patients with SLN metastases with a mean MSKCC predicted probability of 20% who did not undergo ALND were found to be without any axillary lymph node recurrences with a mean follow-up of 30 months.⁴⁴

Interestingly, for patients with certain parameters (ie, a tumor size of ≥ 5 cm, SLN macrometastasis, and presence of ALI), the SOC will give a predicted probability of 100%. A predicted probability of 100% would suggest that a patient will definitely have NSLN metastasis. However, 10 (26%) of 38 patients with this result in the current study cohort did not have additional positive NSLNs. It is interesting that Kohrt et al chose to allow their calculator to give a predicted probability of 100%, because it implies a level of certainty that could be misleading when applying their model to real patients. Neither the MSKCC nor the Mayo model reports a predicted probability of 100% for any combination of variables. At the other end of the spectrum (ie, a tumor size of 0.01 cm, SLN isolated tumor cells, and no ALI), the lowest probability of NSLN metastasis that the SOC is capable of delivering is 0.045 (4.5%). For this reason, only 1 of 464 patients in our database had a predicted probability of $\leq 5\%$ by the SOC.

The SOC appears to have significant clinical potential, given that it requires only 3 variables and appears to

perform on a par with the MSKCC nomogram in our independent patient population. At this time neither model is sufficiently discriminatory to allow clinicians to confidently omit ALND. The MSKCC nomogram has been shown to be better than a clinician's best prediction.⁴⁵ Likely the same is true of the SOC, given its performance in our patient population. These models allow clinicians to help patients understand their risk of having NSLN metastasis. The other attractive feature of the SOC is that it incorporates whether the SLN metastasis fits into the category of isolated tumor cells, micrometastases, or macrometastases. However, before widespread clinical use and acceptance, the SOC requires further validation in varied patient populations, as has been done with the MSKCC nomogram. At this juncture, ALND should remain the standard of care for the staging and treatment of patients who have SLN metastasis.

Conflict of Interest Disclosures

The authors made no disclosures.

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