

Can Sentinel Node Biopsy Be Avoided in Some Elderly Breast Cancer Patients?

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Objective: The purpose of this study was to determine factors associated with lymph node metastasis among hormonally-responsive breast cancer patients ≥ 70 years old, and to develop and validate a clinical prediction rule to predict the risk of lymph node metastasis in this population.

Summary Background Data: Nodal evaluation in elderly women with breast cancer remains controversial. The ability to predict which elderly patients may be node-negative may spare them the morbidity of lymph node evaluation.

Methods: Hormone-receptor positive breast cancer patients ≥ 70 years old who participated in a prospective multicenter trial were divided into a training set ($n = 554$) and a test set ($n = 146$). Univariate and multivariate analyses were conducted to determine factors predictive of final nodal status. A clinical prediction rule was developed on the training set, and validated in the independent test set.

Results: Median patient age was 76; median tumor size was 1.4 cm. 15.9% and 16.2% were LN+ in the training and test sets, respectively. On univariate analysis, patient age, tumor size, palpability, grade, and lymphovascular invasion predicted lymph node status. On multivariate analysis, patient age, tumor size, and lymphovascular invasion remained significant. A prediction rule was created; patients were categorized into quartiles by predicted risk. 5.4% and 0% of patients in the lowest quartile were node positive in the training and test sets, respectively.

Conclusion: Some elderly breast cancer patients at low likelihood of lymph node metastasis may be spared lymph node evaluation.

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Breast cancer is the leading malignancy affecting women in the United States, accounting for 1 in 3 cancers diagnosed in American women.¹ The probability of developing this disease increases with age, with women between 75–79 years of age having the highest incidence of breast cancer.¹ Appropriate treatment of elderly women with breast cancer, however, remains controversial, as many clinical trials have excluded women over the age of 70. While it has been demonstrated that lymph node status is an important predictor of early distant metastasis in elderly patients,² the question of whether older patients require lymph node evaluation is still often debated. In an elderly population, often facing multiple comorbidities, the risk of lymph node evaluation must be balanced with the benefit of staging and local control. Whether all elderly patients, particularly those who have hormonally-responsive tumors, require lymph node evaluation is therefore unclear.

A number of nomograms and clinical prediction rules have been developed to elucidate the risk of having non-SLN metastases in patients with a positive SLN.^{3–7} None of these, however, specifically focus on the elderly population treated with hormonal therapy. Furthermore, in this population, it may be more relevant to ask the question of which elderly patients are likely to have any lymph node metastasis, so as to identify a subpopulation in which lymph node evaluation may be omitted. The purpose of this study, therefore, was to (1) determine factors associated with lymph node metastasis among hormonally-responsive breast cancer patients ≥ 70 years old, (2) develop a clinical prediction rule to predict the risk of lymph node metastasis, and (3) to validate this rule in an independent test set.

METHODS

The North American Fareston and Tamoxifen Adjuvant (NAFTA) trial is an investigator-initiated prospective multicenter study in which patients with hormonally sensitive invasive breast cancer were randomized to receive either tamoxifen 20 mg or toremifene (Fareston) 60 mg orally daily for 5 years as adjuvant therapy. While the primary end point of the NAFTA trial was to evaluate differences in long-term outcome between these 2 selective estrogen receptor modulators, we chose to study patients who participated in this trial to determine factors related to lymph node metastasis in elderly breast cancer patients. Patients who were 70 years of age or greater at the time of diagnosis who participated in this trial formed the cohort of interest. All participants had hormone receptor positive invasive breast cancer defined as estrogen receptor positive (ER+), progesterone receptor positive (PR+), or both, without evidence of distant metastases. Data regarding clinicopathologic factors were prospectively collected. Decisions regarding definitive surgical management, lymph node evaluation, adjuvant chemotherapy, and adjuvant radiation therapy were left to the discretion of the individual treating physicians. This study was approved by the Institutional Review Board of each of the 127 participating sites, and informed consent was signed by each of the patients prior to enrolling in the study.

Patients were divided into a training set comprising $\sim 75\%$ of patients to be used for statistical analysis and creation of the clinical prediction rule, and a test set of the remaining $\sim 25\%$ of patients to be used as an independent cohort for validation of the clinical prediction rule. Factors associated with the finding of positive lymph nodes were evaluated using univariate and multivariate analyses in the training set only. The multivariate analysis was then used to develop a clinical prediction rule to estimate risk of having positive lymph node disease. This risk stratification was then categorized into quartiles, and validated in the independent test set. All statistical analyses were performed using SPSS Version 14.0 (Chicago, Illinois). Fisher exact test tests were used for univariate comparison of dichotomous variables, likelihood ratio tests were used for discrete variables of 3 or more categories, and Mann-Whitney U tests were used for continuous variables. Multivariate analysis was performed using binary logistic regression. Beta coefficients from the multivariate analysis were used to create a continuous prediction rule, which was then categorized by quartiles. Receiver operator curves

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(ROC) were used to evaluate the prediction rule created in the training and test sets. While ROC analysis gives an overall impression of the performance of these clinical prediction rules, the ability of these rules to predict which patients are at low risk of lymph node metastasis is of paramount importance as these patients may potentially be spared the morbidity of lymph node evaluation. In patients at high risk of lymph node positivity, standard operative lymph node staging would be recommended.

RESULTS

Between July 1998 and December 2002, 1812 patients were enrolled in the NAFTA trial. Of these, 752 patients (41.5%) were 70 years of age or older. Fifty-two of these patients (6.9%) did not have any lymph node evaluation. The remaining 700 patients formed the cohort of interest for this analysis. The median patient age was 76

(range; 70–100) years, with a median tumor size of 1.4 cm (range; 0.1–12.0). Clinicopathologic tumor features are shown in Table 1.

Of these patients, 352 (50.3%) underwent an axillary node dissection as their initial nodal evaluation procedure, 224 (32.0%) underwent sentinel lymph node biopsy (SLNB) alone, and 124 (17.7%) had a sentinel lymph node biopsy with completion axillary node dissection. The median number of lymph nodes removed was 9 (range; 1–34). Sixteen percent of patients ($n = 112$) had lymph node metastases. Of these, the median number of positive nodes was 1 (mean = 2.24; range: 1–30).

The patients in this study were divided randomly into a training set, constituting approximately 75% of the total population ($n = 554$) and an independent test set of the remaining patients ($n = 146$). In the training set, 88 patients (15.9%) were node positive. In the test set, 24 patients (16.4%) were node positive. Only the training set was used for statistical analyses leading to the clinical prediction rule development. Factors correlating with lymph node positivity in the training set on univariate analyses are shown in Table 2. All factors with a significance of $P < 0.1$ were incorporated

TABLE 1. Clinicopathologic Features

Clinicopathologic Characteristic	Number of Patients (%)
Race	
Caucasian	638 (91.1)
Black	40 (5.7)
Hispanic	9 (1.3)
Other	13 (1.9)
Tumor size*	
T1	537 (76.7)
T2	142 (20.3)
T3	4 (0.6)
Palpable tumor	
No	266 (38.0)
Yes	434 (62.0)
Tumor grade†	
1	185 (26.4)
2	319 (45.6)
3	110 (15.7)
Histologic subtype‡	
Ductal	544 (77.7)
Lobular	106 (15.1)
Other	43 (6.1)
Estrogen receptor status	
Positive	696 (99.4)
Negative	4 (0.6)
Progesterone receptor status§	
Positive	574 (82.0)
Negative	120 (17.1)
Lymphovascular invasion¶	
Positive	48 (6.9)
Negative	433 (61.9)
Tumor location	
Upper outer quadrant	302 (43.1)
Upper inner quadrant	76 (10.9)
Lower outer quadrant	60 (8.6)
Lower inner quadrant	55 (7.9)
Central	93 (13.3)

*Tumor size not specified in 17 patients (2.4%).

†Grade not specified in 86 patients (12.3%).

‡Histologic subtype not specified in 7 patients (1.0%).

§PR status not specified in 6 patients (0.9%).

¶Lymphovascular invasion not specified in 219 patients (31.3%).

||Tumor location not specified in 114 patients (16.3%).

TABLE 2. Factors Correlating With Lymph Node Positivity on Univariate Analysis in Training Set

Factor	No. Patients With Positive Lymph Nodes (%)	Significance
Patient age*		0.001
Race		0.533
Caucasian	79 (15.5)	
Black	5 (20.0)	
Hispanic	3 (33.3)	
Other	1 (11.1)	
Tumor size*		<0.001
Palpable tumor		<0.001
No	38 (11.0)	
Yes	50 (24.0)	
Tumor grade		0.006
1	15 (9.7)	
2	46 (18.8)	
3	21 (24.4)	
Histologic subtype		0.063
Ductal	74 (17.4)	
Lobular	11 (12.8)	
Other	2 (5.3)	
Lymphovascular invasion		<0.001
No	43 (12.5)	
Yes	13 (38.2)	
Estrogen receptor positive		0.456
No	1 (33.3%)	
Yes	87 (15.8%)	
Progesterone receptor status		0.453
Positive	17 (18.7)	
Negative	71 (15.5)	
Tumor location		0.907
Upper outer quadrant	39 (16.5)	
Upper inner quadrant	8 (12.9)	
Lower outer quadrant	10 (20.8)	
Lower inner quadrant	7 (16.3)	
Central	11 (15.3)	

*Analyzed as a continuous variable.

TABLE 3. Multivariate Analysis of Lymph Node Positivity on Univariate Analysis in Training Set

Factor	β	SE	Odds Ratio (95% CI)	Significance (P Value)
Patient age	0.073	0.033	1.076 (1.008–1.148)	0.028
Tumor size	0.467	0.178	1.596 (1.126–2.260)	0.009
Lymphovascular invasion	1.271	0.454	3.563 (1.464–8.675)	0.005

into a multivariable binary logistic regression analysis for lymph node positivity. The results of this analysis are shown in Table 3. Patient age, tumor size, and lymphovascular invasion were independent predictors of lymph node positivity in the training set. Using the beta coefficients of these factors from the multivariate analysis, a linear model for predicting lymph node positivity was created. The log odds of the probability of having lymph node metastasis is given by: $\text{logit} [P(\text{positive node})] = \beta_0 + 0.073(\text{age}) + 0.4670(\text{tumor size}) + 1.271(\text{LVI}) + \epsilon$, where β_0 is a constant and ϵ is an error term. When stratified by quartile, it was demonstrated that only 5.4% of patients with the lowest quartile of predicted probability of lymph node positivity in the training set were node positive (Table 4). This model was then applied to the test set, using the same cutoffs for quartiles as in the training set. All patients in the lowest quartile of predicted probability of lymph node metastasis were node negative in the test set (Table 4). In other words, if $Q = 0.073 \times (\text{age in years}) + 0.467 \times (\text{tumor size in cm}) + 1.271 \times (1 \text{ if LVI is present, or } 0 \text{ if LVI is absent}) < 5.8835$, then the likelihood of having positive lymph nodes is low, and therefore the utility of lymph node evaluation may be questionable.

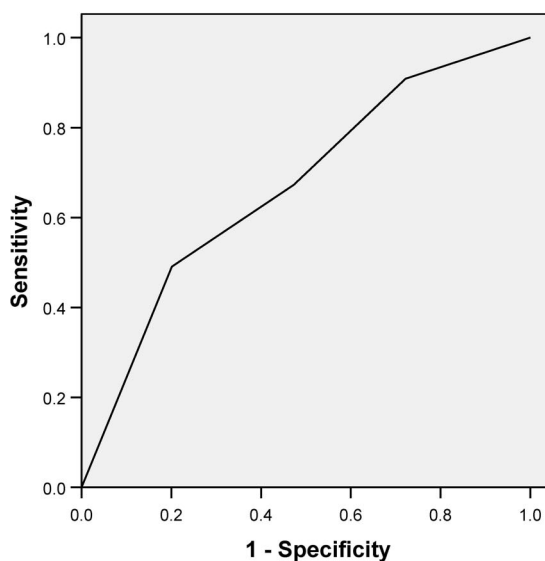
The model performed well in predicting lymph node metastasis in both the training and test sets ($P < 0.001$ and $P = 0.007$, respectively). Receiver operator curves were then evaluated for both the training and test sets (Fig. 1). The area under the curves by predicted quartile for the training set was 67.0% (95% CI: 59.2–74.7) and that for the test set was 72.9% (95% CI: 60.5–85.3).

Lymphovascular invasion is frequently not available preoperatively, and was missing in 175 patients (31.6%) in the training set and 44 patients (30.1%) in the test set. Therefore, using the training set, a second multivariate analysis was performed without lymphovascular invasion. In this model, patient age, tumor size and palpability were found to be independent predictors of lymph node status (Table 5). The log odds of the probability of having lymph node metastasis in this model is given by: $\text{logit} [P(\text{positive node})] = \beta_0 + 0.064(\text{age}) + 0.623(\text{tumor size}) + 0.560(\text{palpability}) + \epsilon$. When predicted probability in this model was stratified by quartile, 5.2% of patients in the training set with predicted

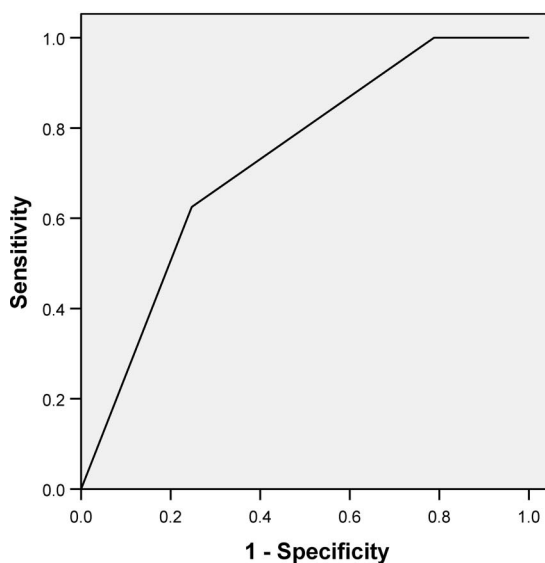
TABLE 4. Predicted Probability of Lymph Node Positivity in Training and Test Sets (Model Including Patient Age, Tumor Size, and Lymphovascular Invasion)

Quartile*	Number of Node Positive Patients (%)	
	Training Set ($P < 0.001$)	Test Set ($P = 0.007$)
1	5/92 (5.4)	0/18 (0)
2	13/91 (14.3)	3/26 (11.5)
3	10/95 (10.5)	3/26 (11.5)
4	27/90 (30.0)	10/31 (32.3)

*Based on $\text{logit} [P(\text{positive node})] = \beta_0 + Q + \epsilon$; $Q = 0.073(\text{age}) + 0.467(\text{tumor size}) + 1.271(\text{LVI})$; 1st quartile: $Q < 5.8835$, 2nd quartile: $5.8835 \leq Q < 6.2485$, 3rd quartile: $6.2485 \leq Q < 6.7885$, 4th quartile: $Q \geq 6.7885$.

Training Set

AUC=0.670 (95% CI: 0.592-0.747); $p < 0.001$

Test Set

AUC=0.729 (95% CI: 0.605-0.853), $p = 0.004$

FIGURE 1. Receiver-operator curve for model predicting lymph node positivity (including lymphovascular invasion) in training set and test set.**TABLE 5.** Multivariate Analysis of Lymph Node Positivity in Training and Test Sets (Excluding Lymphovascular Invasion)

Factor	$>\beta$	SE	Odds Ratio (95% CI)	Significance (P Value)
Patient age	0.064	0.027	1.066 (1.011–1.124)	0.019
Tumor size	0.623	0.141	1.865 (1.414–2.462)	< 0.001
Palpability	0.560	0.270	1.751 (1.032–2.973)	0.038

TABLE 6. Predicted Probability of Lymph Node Positivity in Training and Test Sets (Model Including Patient Age, Tumor Size, and Palpability, Excluding Lymphovascular Invasion)

Quartile*	Number of Node Positive Patients (%)	
	Training Set (<i>P</i> < 0.001)	Test Set (<i>P</i> < 0.001)
1	7/135 (5.2)	1/36 (2.8)
2	15/134 (11.2)	1/32 (3.1)
3	19/137 (13.9)	5/34 (14.7)
4	47/135 (34.8)	16/40 (40.0)

*Based on logit [$P(\text{positive node}) = \beta_0 + Q + \epsilon; Q = 0.064(\text{age}) + 0.623(\text{tumor size}) + 0.560(\text{palpability}); 1\text{st quartile: } Q < 2.6792, 2\text{nd quartile: } 2.6792 \leq Q < 3.1270, 3\text{rd quartile: } 3.1270 \leq Q < 3.6414, 4\text{th quartile: } Q \geq 3.6414.$

probability in the lowest quartile were node positive (Table 6). In the test set, only 1 patient (2.8%) in the lowest quartile of predicted probability of lymph node metastasis was node positive (Table 6). In other words, if $Q = 0.064 \times (\text{age in years}) + 0.623 \times (\text{tumor size in cm}) + 0.560 \times (1 \text{ if palpable tumor, or } 0 \text{ if nonpalpable}) < 2.6792$, then the likelihood of positive lymph node metastasis is low, and therefore the utility of lymph node evaluation is questionable.

Receiver operator curves for this model in both the training and test sets are shown in Figures 2. The area under the curve using quartiles of predicted probability of lymph node metastasis for the training and test sets were 67.8% (95% CI: 61.7–73.8) and 84.1% (95% CI: 76.7–91.5), respectively.

DISCUSSION

As our population ages, the incidence of breast cancer in patients older than 70 continues to increase.⁸ Older breast cancer patients pose unique challenges to clinicians who must balance the risks and benefits of therapy. These patients often have multiple comorbidities, and tend to be frailer. In addition, older breast cancer patients often present with less aggressive disease,^{9,10} and are less likely to have lymph node involvement than their younger counterparts.¹¹ On the other hand, undertreatment of this population may lead to suboptimal outcomes.¹² This population has been understudied, and therefore, often leaves clinicians in a conundrum as to optimal management.

The issue of lymph node staging in this population has been hotly debated in the literature. While it has been well-established that lymph node status is a key predictor of early distant metastatic spread,² many elderly patients will not have lymph node evaluation. In our study, we found that 6.9% of patients 70 years of age or older did not have lymph node evaluation. Indeed, Edge et al found that increasing age was associated with decreased odds of having lymph node evaluation independent of health status, patient preferences, clinical factors and provider variables.¹³ This echoes Giordano et al's finding that increased age was also associated with decreased adherence with breast cancer treatment guidelines independent of comorbidity score, clinical stage, and tumor characteristics.¹⁴

A number of authors have found that lymph node evaluation significantly influences subsequent treatment decisions in the elderly population and therefore have advocated routine sentinel node biopsy and possible axillary node dissection in this population.^{15–17} Others, however, have elucidated the fact that lymph node staging in the elderly is not without morbidity. While the technique of performing sentinel node biopsy under local anesthesia has been reported,¹⁸ many surgeons use general anesthesia for this procedure. In addition, sentinel node biopsy using blue dye is associated with potential morbidity including anaphylaxis.¹⁹ Mandelblatt et al demonstrated that patients 67 years or older who underwent lymph node

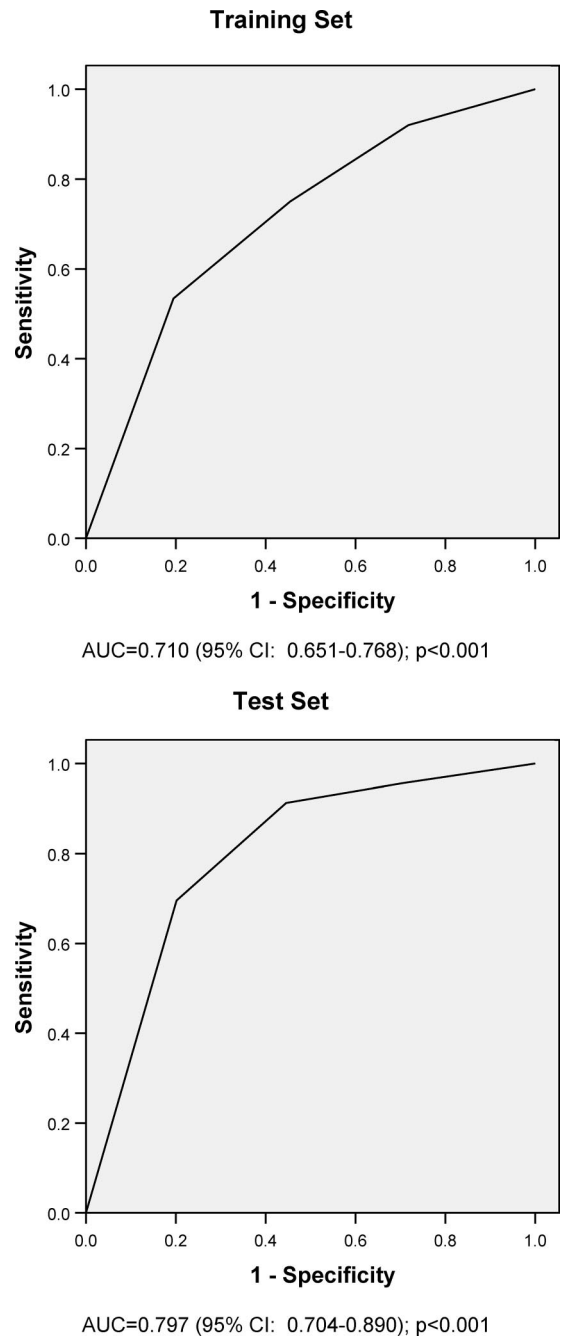


FIGURE 2. Receiver-operator curve for model predicting lymph node positivity (excluding lymphovascular invasion) in training set and test set.

evaluation with sentinel node biopsy and/or axillary node dissection had 3 times the rate of arm complications 2 years post-treatment than those who did not have any axillary surgery.²⁰ In addition, these arm sequelae resulted in lower physical and mental functioning.²⁰ Therefore, the balance of risk and benefit for lymph node evaluation in some elderly breast cancer patients remains nebulous.

While several studies have found that older breast cancer patients are less likely to have lymph node evaluation, undertreatment does not necessarily result in worse outcomes.²¹ Some have

suggested that there is a subpopulation of elderly patients with small tumors for whom lymph node evaluation may not be needed. Several small nonrandomized studies found low rates of locoregional failure and no adverse effect on survival in elderly patients in whom lymph node evaluation was omitted, particularly in those with small hormone-responsive tumors and clinically negative axillae.^{22,23} These preliminary studies set the groundwork for a randomized controlled trial comparing axillary dissection to no axillary dissection in patients 65–80 years of age with clinical T1N0 breast cancer.²⁴ In this study, 23% of the 109 patients who underwent an axillary node dissection in this study were node positive; with 72% of these patients having disease only in one lymph node and 24% having disease in 4 or more nodes. Of the 110 patients who did not have an axillary dissection, 2 patients (1.8%) developed clinically apparent axillary disease during follow-up. With a median follow-up of 60 months, no significant differences were found between the 2 groups in terms of overall mortality, breast cancer mortality and breast cancer events (including ipsilateral breast cancer recurrence, contralateral breast cancer and distant metastasis).

While these results suggest that some elderly patients, particularly those with small hormone-responsive breast cancers, may be spared lymph node evaluation, some patients may still develop overt axillary disease. Therefore, the ability to predict which elderly patients are at low likelihood of having lymph node metastases may obviate axillary surgery in this subpopulation. Clearly, the benefit of removing negative lymph nodes is minimal.²⁵ In our study, we found that the population of patients 70 years of age or older with hormone-responsive tumors is a heterogeneous one. Lymph node status is determined by patient age, tumor size, and lymphovascular invasion. By creating a linear prediction rule, we were able to stratify this elderly breast cancer population to define a subpopulation in whom the risk of lymph node metastasis was ~5%. Recognizing that lymphovascular invasion is frequently not available preoperatively, our second clinical prediction rule including patient age, tumor size, and tumor palpability, which also defines a subpopulation of elderly patients at low risk of lymph node metastasis, may be more clinically useful. Both of these prediction rules were validated in an independent test set, and while further validation is needed, by stratifying elderly patients by risk of lymph node metastasis they may potentially spare some elderly patients the morbidity of lymph node evaluation. While these linear prediction rules are somewhat complex, a web-based calculator can be easily created which would allow clinicians to counsel their elderly patients preoperatively; allowing patients to make informed decisions regarding whether they wish to undergo a surgical lymph node staging procedure.

Our prediction model was based on the outcome of nodal status based either on sentinel node biopsy or on axillary node dissection. Axillary dissection has long been accepted as the gold standard for the evaluation of axillary lymph node status. Some may argue that the inclusion of patients with sentinel node biopsy alone ignores the false negative rate of this minimally invasive procedure. Others, however, will point to the fact that sentinel node biopsy has allowed for increased pathologic scrutiny of the sentinel nodes, which often results in upstaging of patients who would otherwise be classified as node-negative with standard axillary node dissection. Given that sentinel node biopsy and axillary node dissection are both commonly accepted techniques of staging the axilla, we based our model on the outcome of either of these techniques.

One of the potential limitations of our model is that less than 10% of the patients in our study were noncaucasian. However, we found that race did not significantly affect lymph node status. Others have similarly found that race is not an independent factor influencing lymph node status.²⁶ Therefore, race was not incorporated into our model.

However, further validation of this model in racially diverse populations will shed more light into its applicability in these groups.

With the advent of sentinel node biopsy, the majority of patients will have lymph node evaluation with a procedure that carries with it minimal morbidity. However, in some elderly patients with significant other comorbidities in whom risk of lymph node evaluation is significant, the ability to predict the likelihood of lymph node metastasis may aid surgeons in weighing the risks and benefits of this procedure.

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