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Predicting Patients at Low Probability of Requiring Postmastectomy Radiation Therapy

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Background: Postmastectomy radiation therapy (PMRT) is recommended for patients with four or more positive lymph nodes (LN+). Given the ramifications of PMRT for immediate reconstruction, we sought to create a model using preoperative and intraoperative factors to predict which patients with a positive sentinel lymph node will have less than four LN+.

Methods: The database from a prospective multicenter study of 4,131 patients was used for this analysis. Patients with one to three positive sentinel lymph nodes (SLN) and tumors < 5 cm (n = 1,133) in size were randomly divided into a training set (n = 580) and a test set (n = 553). Multivariate logistic regression was used on the training set to create a prediction rule that was subsequently validated in the test set.

Results: Median patient age was 57 (range, 27–100) years, and median tumor size was 2.0 (range, 0.2–4.8) cm. In the training set, factors associated with having four or more LN+ on multivariate analysis were: tumor size [odds ratio (OR) = 2.087; 95% confidence interval (CI): 1.307–3.333, $P = 0.002$), number of positive SLN ($P < 0.0005$), and proportion of positive SLN (OR = 3.602; 95% CI: 2.100–6.179, $P < 0.005$). A predictive model was established with a point assigned to each positive SLN, T2 (vs. T1), and if proportion of positive SLN was > 50%, for a maximum of five points. In both the training and test sets, patients with one point had a low probability of having four or more LN+ (3.8% and 3.3%, respectively).

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Conclusion: Tumor size, number of positive SLN, and the proportion of positive SLN influence whether patients will have four or more LN+. A simple model can predict the probability of requiring PMRT.

Key Words: Lymph nodes—Breast cancer—Reconstruction—Radiation—Mastectomy.

Postmastectomy radiation therapy has been found in randomized controlled trials to decrease local recurrence and, in some studies, to improve survival in women with invasive breast cancer.[1–3] Although these results have been widely debated, the American Society of Clinical Oncology (ASCO)[4] and the American Society of Therapeutic Radiology and Oncology (ASTRO)[5] have issued guidelines advocating the use of PMRT in patients at high risk of chest-wall recurrence (primary tumors > 5 cm and/or those who have four or more positive axillary lymph nodes).

The finding of four or more positive nodes has substantial impact on decisions regarding immediate breast reconstruction, either with autologous tissue or tissue expanders. Although some centers do not alter their plan for immediate reconstruction regardless of the need for PMRT, many plastic surgeons[6–13] and radiation oncologists[14] prefer to delay reconstruction if PMRT is required. In the current era of SLN biopsy, intraoperative evaluation can often indicate as to whether patients will be node-negative. However, in patients with one to three positive SLN intraoperatively, it is currently not possible to predict whether patients will have four or more LN+ on final pathology, thus mandating PMRT. Patients with T3 tumors (>5 cm) usually receive PMRT regardless of nodal status. This creates a clinical dilemma in deciding whether or not to proceed with immediate reconstruction for patients with tumors < 5 cm who have one to three positive SLN.

Recently, there has been significant interest in the development of clinical prediction tools to estimate the risk of metastatic nonsentinel nodes in the setting of a positive sentinel node.[15] A clinical prediction rule to estimate the risk of having four or more positive nodes; however, has not yet been developed. The purpose of this study was to determine, based on multivariate analysis, the preoperative and intraoperative factors that predict the finding of four or more positive axillary lymph nodes and create a simple model to predict the likelihood of requiring PMRT.

METHODS

The University of Louisville Breast Sentinel Lymph Node Study is a multi-institutional prospective study of patients with clinical stage T1–2, node negative (N0) breast who had SLN biopsy followed by axillary node dissection. The study involved more than 300 surgeons from a variety of clinical practices (both community and academic) from across the United States and Canada. This study was approved by the Institutional Review Board at each site, and all patients were required to sign an informed consent prior to their participation.

Patients with T1 or T2 primary breast cancers who had one to three positive SLN formed the cohort of interest for this study. This is the population for whom the decision to perform immediate reconstruction is affected intraoperatively; SLN-negative patients do not need PMRT, and those with four or more positive SLN receive PMRT. Patient demographic information, clinicopathologic variables of the primary tumor, number of SLN excised, number of SLN positive, and number of LN+ on final pathology were all collected in a prospective fashion. Patients were randomly divided into two groups: a training set (n = 580) and a test set (n = 553). Factors predicting final lymph node status (four or more or less than four LN+) were evaluated using univariate analyses in the training set. Fisher's exact tests were used for bivariate categorical variables, likelihood ratio tests were used for discrete variables with greater than three categories, and Mann–Whitney *U* tests were used for continuous variables. A multivariate analysis was then performed using binary logistic regression to determine which factors were independent predictors of having four or more LN+ on final pathology. Statistical analyses were performed using SPSS Version 13.0 software (Chicago, IL, USA). An integer-based clinical prediction model was then created based on the beta coefficients of the multivariate analysis to predict which patients will have four or more LN+ on final pathology based on preoperative and intraoperative factors, and it was tested in the 553 patient test set.

RESULTS

From May 7, 1998 to August 2, 2004, 4,131 patients were enrolled in this study. Of these, 1,132 with T1 or T2 tumors on final pathology who had one to

three positive SLN were evaluated. The median patient age in this cohort was 57 (range, 27–100) years, and the median tumor size was 2.0 (range, 0.2–4.8) cm. Clinicopathologic features for this cohort of patients are shown in Table 1. The median number of SLN removed was two (range, 1–18). Only 227 (20.0%) had four or more SLN removed. The median total number of lymph nodes removed at the completion of lymphadenectomy was 13 (range, 3–45). Four or more LN+ were found on final pathology in 212 (18.7%) patients.

Patients were randomly divided into a training set (n = 580) and a test set (n = 553). In the training set, 113 (19.5%) patients had four or more LN+. In the test set, 99 (17.9%) had four or more LN+. Factors associated with having four or more LN+ on final pathology on univariate analyses in the training set are shown in Table 2. The number of positive SLN, the proportion of SLN positive (≤ 50% vs. > 50%), and tumor size (T1 vs. T2) were the only factors associated with having four or more LN+ on final pathology on univariate analyses. On multivariate analysis, all of these factors continued to be significant (Table 3).

Given the multivariate analysis, we sought to create a simple integer-based clinical model to predict whether individual patients will have four or more LN+ on final pathology given one to three positive SLN. Based on the beta coefficients of the logistic regression analysis, we established a clinical prediction rule based on which one point was given for each LN+, one point was given if the proportion of SLN positive was 50% or greater, and one point was given if the tumor was T2 (vs. T1). Although not a perfect match to the multivariate beta coefficients, it was felt that this represented the most simple, clinically usable model. The model had a total of five possible points. The probability of having four or more LN+ using this model in the training group ranged from a very low probability of 3.8% (one point) to a high probability of 81.8% (five points). This model was found to be highly correlated with the finding of four or more LN+ on final pathology (Table 4, $P < 0.001$). A receiver-operator curve (ROC) was generated using this predictive model (Fig. 1). The area under the ROC for the training set was 75.4% [95% confidence interval (CI): 70.5–80.4%).

The model was then validated on the test set of 553 patients. The model accurately predicted the probability of having four or more LN+, with only 3.3% of the patients with one point having greater than four LN+ and 46.2% of patients with five points having greater than four LN+ (Table 4, $P < 0.001$). Again, the area under the ROC for the test set was 76.5% (95% CI: 71.5–81.4%), suggesting that the model is robust in this population (Fig. 1).

TABLE 1. *Clinicopathologic variables*

Characteristic	Number of cases (%)
Number of positive SLN	
1	804 (71.0)
2	237 (20.9)
3	92 (8.1)
Proportion of positive SLN	
≤50%	544 (48.0)
>50%	589 (52.0)
Tumor size:	
≤2 cm	550 (48.5)
>2 cm–5 cm	583 (51.5)
Palpable primary tumor	
Yes	755 (66.6)
No	378 (33.4)
Histologic subtype	
Ductal	963 (85.0)
Lobular	98 (8.6)
Other	72 (6.4)
Method of detection[a]	
Hematoxylin-eosin	618 (54.5)
Immunohistochemistry	495 (43.7)

SLN, sentinel lymph node.
[a] Unspecified in 20 (1.8%) cases.

TABLE 2. *Factors associated with four or more positive lymph nodes in training set (n = 580)*

	Number of patients with ≥ 4 LN+ (%)	Significance (*P* value)
Patient age[a]		0.788
Number of SLN removed		0.458
Number of positive SLN		<0.001
1	55 (13.1)	
2	28 (24.8)	
3	30 (63.8)	
Proportion of SLN positive		
≤50%	21 (7.8)	<0.001
>50%	92 (29.6)	
Tumor size		<0.001
≤2 cm	40 (13.7)	
>2–5 cm	73 (25.4)	
Palpable tumor		0.441
Yes	35 (17.6)	
No	78 (20.5)	
Tumor location		0.332
Upper outer	36 (21.4)	
Upper inner	7 (21.2)	
Lower inner	2 (8.3)	
Lower outer	16 (15.0)	
Central	5 (12.2)	
Histologic subtype		0.266
Ductal	92 (18.4)	
Lobular	13 (28.3)	
Other	8 (22.9)	
Method of detection		<0.001
Hematoxylin-eosin	78 (25.2)	
Immunohistochemistry	31 (11.9)	

[a] Assessed as a continuous variable.

TABLE 3. *Multivariate analysis of factors predicting four or more positive lymph nodes in training set (n = 580), excluding detection method*

Factor	β	SE	Odds ratio (95% CI)	Significance (*P* value)
Number of positive SLN (vs. 1):				<0.0005
2	0.482	0.277	1.619 (0.941–2.784)	
3	2.171	0.355	8.766 (4.374–17.566)	
Proportion of positive SLN ≥ 50%	1.282	0.275	3.602 (2.100–6.179)	<0.0005
Tumor size (T2 vs T1)	0.736	0.239	2.087 (1.307–3.333)	0.002

SE, standard error; CI, confidence interval; SLN sentinel lymph node.

TABLE 4. *Clinical model predicting four or more positive lymph nodes on final pathology, excluding detection method*

	Number of patients with ≥ 4 positive lymph nodes (%)	
Points	Training set (n = 580)	Test set (n = 553)
1	5/132 (3.8)	4/122 (3.3)
2	24/199 (12.1)	17/198 (8.6)
3	41/163 (25.2)	35/135 (25.9)
4	25/64 (39.1)	31/72 (43.1)
5	18/22 (81.8)	12/26 (46.2)

Given the fact that most intraoperative evaluation techniques (either touch prep cytology or frozen section) utilize hematoxylin-eosin staining alone, we did not consider the use of immunohistochemistry (IHC) in the predictive model above. The finding of micrometastatic disease by immunohistochemistry is, however, associated with a lower finding of four or more positive nodes on final pathology (Table 2). When factoring the method of detection of sentinel node metastasis in a multivariate model, it is also found to be significant (Table 5).

Based on the beta coefficients of the multivariable logistic regression analysis, a new model can be developed to predict the presence of four or more positive nodes on completion axillary dissection. One point is given for each positive SLN, another point is given if the proportion of SLN positive was 50% or greater, another point is given if the tumor was T2 (vs. T1), and a final point is given if the SLN metastasis was found using hematoxylin-eosin staining (as opposed to IHC). With a maximum of six points, this clinical prediction rule again strongly correlated with the finding of four or more positive nodes on final pathology (Table 6, $P < 0.001$). In the training set (n = 569), patients with one point had a 2.7% probability of having four or more positive nodes on final pathology while those with six points had a 90% probability of having four or more positive nodes. An ROC was generated using this predictive model (Fig. 2). The area under the ROC for the training set was 88.2% (95% CI: 85.5–91.0%).

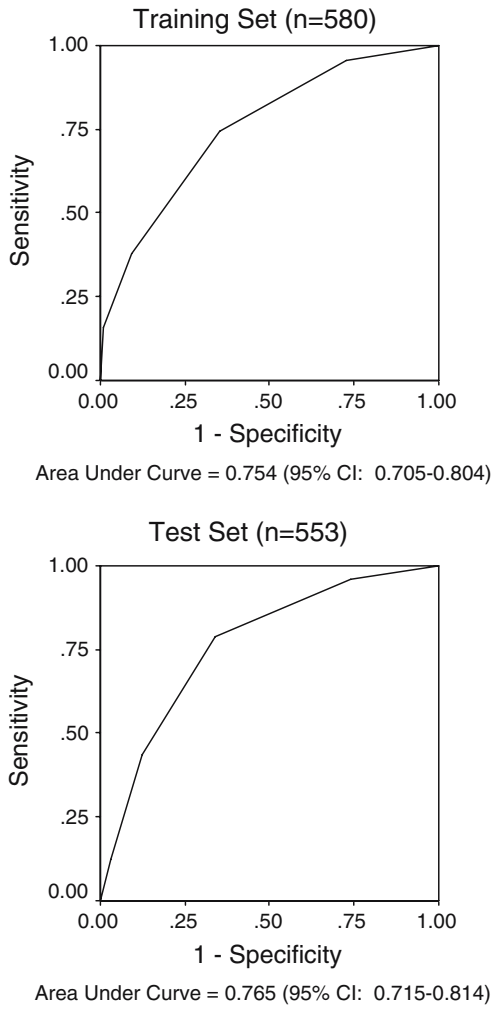

FIG. 1. Receiver-operator curve for model predicting four or more positive lymph nodes (excluding method of detection) in training set and test set.

This model was validated on an independent test set of 544 patients with similar findings (Table 6, $P < 0.001$). An ROC was generated in the test set (Fig. 2). The area under the ROC in the test set was 89.5% (95% CI: 86.9–92.1%).

TABLE 5. *Multivariate analysis of factors predicting four or more positive lymph nodes in training set (n = 580), including detection method*

Factor	β	SE	Odds ratio (95% CI)	Significance (p value)
Number of positive SLN (vs. 1):				<0.0005
2	0.468	0.285	1.597 (0.914–2.791)	
3	2.261	0.369	4.658–19.751)	
Proportion of positive SLN ≥ 50%	1.167	0.279	3.213 (1.858–5.554)	<0.0005
Tumor size (T2 vs T1)	0.683	0.244	1.979 (1.228–3.192)	0.005
Hematoxylin-eosin detection	0.951	0.260	2.588 (1.556–4.306)	<0.0005

SE, standard error; CI, confidence interval; SLN sentinel lymph node.

TABLE 6. *Clinical model predicting ≥ 4 positive lymph nodes on final pathology including method of detection*

	Number of patients with ≥ 4 positive lymph nodes (%)	
Points	Training set (n = 569)	Test set (n = 544)
1	2/74 (1.8)	1/69 (1.4)
2	10/149 (6.7)	7/138 (5.1)
3	24/154 (15.6)	23/154 (14.9)
4	42/140 (30.0)	32/111 (28.8)
5	22/42 (52.4)	29/59 (49.2)
6	9/10 (90.0)	6/13 (46.2)

DISCUSSION

This study develops a simple, clinically useful model to predict which patients with one to three positive sentinel nodes will have four or more sentinel nodes on final pathology. As clinical decision making regarding immediate reconstruction cannot wait for final pathology results, the model we created uses preoperative and intraoperative factors only and can identify a group of patients at a very low likelihood of requiring PMRT.

In general, if PMRT is anticipated, reconstruction is often delayed. Many radiation oncologists prefer to radiate a flat chest wall rather than a reconstructed breast, as the steep slopes associated with reconstruction (particularly if implant based) cause poor matching of tangential radiation fields and uneven dose distribution to the chest wall.[14] In addition, the growing trend among many plastic surgeons is to delay reconstruction if radiation is required, finding that PMRT following immediate reconstruction results in higher complication rates with flap shrinkage, capsular contracture, and increased reoperation rates.[6–13] Others, however, have found acceptable results of immediate reconstruction despite PMRT, particularly with autologous reconstruction.[16–21] Kronowitz et al. described the technique of "delayed immediate" reconstruction in which a tissue expander is placed and immediate reconstruction is delayed until the final pathology returns.[22] While certainly this technique would be useful in patients who would be at intermediate to high risk of having four or more LN+, a delayed-immediate procedure would man-

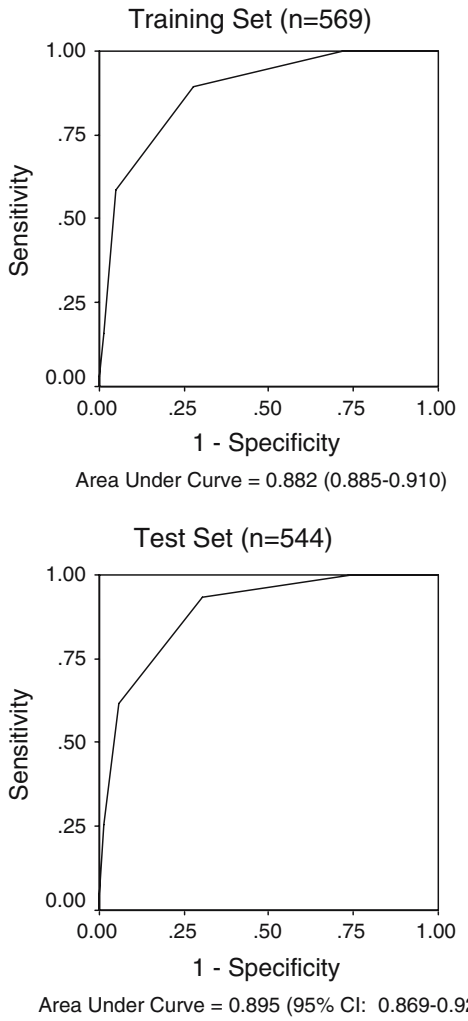

FIG. 2. Receiver-operator curve for model predicting four or more positive lymph nodes (including method of detection) in training set and test set.

date a second operation to complete the immediate reconstruction. It would be ideal to predict intraoperatively which patients will not require postmastectomy radiation therapy, as this may obviate the need to delay the immediate reconstruction in patients at low risk. Most patients with tumors less than 5 cm and one to three LN+ will not have four or more positive nodes. To subject all such patients to a second procedure to await final pathology may therefore be unwarranted. Our model allows clinicians to reliably predict which patients are at very low risk of needing postmastectomy radiation.

A number of studies have evaluated clinicopathologic variables associated with the finding of four or more LN+ on final pathology. Shahar et al., in a retrospective study of 265 consecutive patients with one to three positive SLN who underwent completion axillary node dissection, found that 28 patients (10.6%) had four or more positive nodes on final pathology.[23] They found that lack of drainage on lymphoscintigraphy, lymphovascular invasion, and the finding of more than one positive SLN were independent predictors of finding four or more LN+. Our study of 1,138 patients similarly found that the number of positive SLN was a significant independent predictor of the finding of four or more LN+ on final pathology. Lymphoscintigraphic drainage patterns, however, were not included in our model, as many surgeons opt not to use lymphoscintigraphy preoperatively given that this does not seem to improve SLN identification rates.[24] In addition, while lymphovascular invasion is certainly an important factor predicting which patients will have four or more LN+, this information is often not available preoperatively on core needle biopsy and was not recorded in the University of Louisville Breast Sentinel Lymph Node Study.

A follow-up study by Rivers et al.[25] combining the University of Michigan data to the University of Texas M. D. Anderson experience found that tumor size > 2 cm, extranodal extension, lymphovascular invasion, number of LN+, and the ratio of positive SLN to total number of SLN removed were significant predictors of having four or more LN+ on multivariate analysis. Our study also found T2 tumors, number of LN+, and proportion of SLN positive were significant predictors. Our model did not include extranodal extension as a parameter, as this is often not available preoperatively or intraoperatively. In addition, many radiation oncologists would treat patients who had one to three LN+ demonstrating extranodal extension with postmastectomy radiation therapy.[26] Therefore, even if information regarding extranodal extension were available preoperatively or intraoperatively, the inclusion of this factor, while certainly important in predicting four or more LN+, would not alter management.

Another consideration is that, in our study, we included not only patients who actually underwent mastectomy but those who underwent breast conservation. Because the clinicopathologic factors that predict four or more LN+ should be independent of the type of operation performed for treatment of the primary tumor, we reason that this is a valid approach. Certainly, this approach has been used by others in their models, as well.[23,25]

The strengths of our model are that it predicts the likelihood of having four or more LN+ based on common factors available preoperatively and intraoperatively and that it is based on patients in whom decisions regarding potential PMRT would not be clear cut (i.e., patients with tumors less than 5 cm and with one to three LN+). Our model, which is simple and easy to compute, may therefore have significant clinical impact in decision making, particularly in the setting of immediate reconstruction. However, because of this focus, our study also has a number of limitations. It does not include factors that may be important predictors of extensive nodal disease if those factors are not generally available preoperatively or intraoperatively; but this more closely mimics actual clinical practice.

Our initial model does not account for the method of detection of SLN metastasis, as, in general, intraoperative evaluation is performed using hematoxylin-eosin staining alone. However, for those who wish to incorporate the method of detection (hematoxylin-eosin vs. IHC), we found that the model can be extended to incorporate this factor, yielding a highly predictive model.

Given commonly available preoperative and intraoperative factors, our model will predict the likelihood of having four or more LN+ as a percent probability, but it does not advise clinicians as to when to delay immediate reconstruction due to a "high" likelihood of PMRT and when to proceed with immediate reconstruction due to a "low" likelihood of PMRT. To define what constitutes a "high" versus "low" risk, a formal decision analysis is currently being planned. It is notable, however, that in both our training set and test set, we were able to predict a group of patients whose risk of needing PMRT on the basis of having four or more LN+, given a positive SLN, was < 5%.

Currently no recommendations exist regarding PMRT for the group of patients with tumors less

than 5 cm with one to three LN+. Truong et al. evaluated locoregional recurrence rates in 821 patients with T1–2 breast cancers who had one to three positive lymph nodes.[27] They found that women who were younger than 45 years of age who had more than 25% positive nodes, medial primary tumor location, and estrogen-receptor (ER)-negative cancers had a higher rate of locoregional recurrence with a median follow-up of 7.7 years. While all of these patients had an axillary node dissection, the median number of nodes removed in their study was ten (range, 1–39). Unfortunately, the North American Intergroup Trial designed to answer the question of whether or not postmastectomy radiation is beneficial in this group of patients closed prematurely due to poor accrual. A similar European study is being planned.[28]

While a recent survey of ASTRO and the European Society for Therapeutic Radiology and Oncology members suggested that the majority of radiation oncologists would not to offer PMRT to patients with T1–2 tumors and one to three positive nodes,[29] this viewpoint may change with the recent publication of the 20-year follow-up data from the British Columbia Postmastectomy Radiation Trial, which demonstrated a survival benefit associated with PMRT for all node-positive patients, including those with only one to three positive nodes.[1] The practice of treating all node-positive patients with PMRT has not been ratified by a change in the ASCO/ASTRO guidelines, but for those who adopt such a policy, our model predicting the likelihood of having four or more LN+ on final pathology would be needless.

Decision making regarding immediate reconstruction in the setting of one to three positive sentinel lymph nodes must be done in a multidisciplinary context. For physicians who would prefer to delay reconstruction if PMRT is planned and who would offer PMRT only if a patient has four or more LN+, the clinical prediction model described here may be useful in preoperative patient counseling and may guide intraoperative management. While our model predicts the likelihood of having four or more LN+ on axillary dissection, further work is needed to validate this model and to determine the probability at which a change in management would ensue.

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