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ORIGINAL ARTICLE

Predictors of 4 or More Positive Axillary Nodes in Patients with Node-positive T1-2 Breast Carcinoma: The Indications for Adjuvant Irradiation of the Level III Axilla and Supraclavicular Fossa

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Purpose: We evaluate the predictors of 4 or more involved axillary nodes in patients with node-positive T1-2 breast carcinoma to select a group of patients who are indicated for adjuvant irradiation of the level III axilla and supraclavicular fossa (SCF). **Methods**: We analyzed 286 patients with positive axillary nodes and who were without distant metastases and who underwent breast conserving surgery and axillary lymph node dissection or modified radical mastectomy. We investigated the relationship between the patients and the tumor factors and 4 or more positive axillary nodes. **Results**: On the multivariate logistic-regression analysis, an increased tumor size (p=0.002), the presence of lymphovascular space invasion (LVSI) (p<0.001) and a palpable mass p<0.001) were positively associated with involvement of 4 or more axillary lymph nodes. In our study, 86.1% of the patients with all the unfavorable factors had involvement of 4 or more nodal metastases. **Conclusion**: Our data suggest that for patients with node-positive T1-2 breast cancer, the presence of 4 or more involved nodes is frequently observed for the patients with an increased tumor size, the presence of LVSI and a palpable mass at the time of diagnosis, and we recommend that they undergo irradiation of the high axilla and SCF for adjuvant care, if they do not undergo complete axillary dissection.

Key Words: *Axillary lymph node, Breast neoplasms, Predictor*

INTRODUCTION

Administering adjuvant irradiation to the level III axilla and supraclavicular fossa (SCF) is indicated for those patients who undergo the standard level I-II axillary dissection and who have four or more positive axillary nodes or T3-4 primary disease.*(1-3)* The risk of failure in the axillary apex or SCF is less than 5% for the patients who have T1-2 primary tumors and fewer than 4 involved axillary nodes, and these regions are generally not included in the radiation field.*(4-6)*

The standard treatment for patients with a positive sentinel lymph node (SLN) is complete level I-II axillary lymph node dissection (ALND). However, for various reasons, some node-positive patients are referred for adjuvant radiotherapy without undergoing axillary dissection. The appropriate treatment for these patients is currently unclear. In these circumstances, some radiation oncologists include a portion of levels I and II of the axilla in the standard tangential fields and they treat the breast after lumpectomy or local excision by extending the cranial border of these fields to near the humeral head. This technique can include >80% of the axillary level I and II lymph nodes.*(7)* Alternatively, others comprehensively treat these patients with a third anterior field to encompass the axillary apex and SCF, with or without a posterior boost field at the mid-axilla. Yet irradiating the high axilla and SCF has been shown to increase the treatment morbidity, including causing pneumonitis, lymphedema, brachial plexopathy and significant shoulder-joint dysfunction.*(8-10)* Radiation oncologists are faced with the

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challenge of designing radiation fields that treat the nodal area at risk, while minimizing the volume of the irradiated normal tissue. The purpose of this study was to evaluate the predictors of 4 or more involved axillary nodes in patients with node-positive T1-2 breast carcinoma to select a group of patients who require adjuvant irradiation of the level III axilla and SCF.

METHODS

Patient and tumor characteristics

We have reviewed the database of all the patients who were diagnosed with node-positive T1-2 breast carcinomas and who underwent surgery at St. Vincent's Hospital, Suwon, Korea between January 1999 and June 2009. Institutional review board approval was obtained before the record review. A population of 412 patients was identified, and their pathology records and treatment charts were retrospectively reviewed to obtain information on the patient and tumor characteristics. From this group of patients, 286 patients without distant metastases and who underwent breast conserving surgery and ALND (level I and II) or modified radical mastectomy (MRM) were identified, and these patients were evaluated in this study. None of these patients received neoadjuvant chemotherapy or hormonal therapy.

The clinical information included age and the tumors' palpability. A lesion was recorded as palpable if it could be felt by at least one examiner prior to radiographic identification, and it was scored as nonpalpable if it was not palpated on the physical examination and so it was recorded as negative, and it was ultimately discovered by mammography. The histopathologic characteristics that were evaluated included the tumor size, the histologic grade (1-3), lymphovascular space invasion (LVSI), the estrogen receptor (ER) and progesterone receptor (PR) statuses, the epidermal growth factor receptor 1 (EGFR) and human epidermal growth factor receptor 2 (HER2) expressions and the presence of tumor calcification. The tumor size was determined using the largest dimension of the invasive component, as measured from the gross pathologic specimen, and this was categorized using the tumor-node-metastasis system of the American Joint Committee on Cancer *(11)* as T1mic: 1 mm or less, T1a: 1.1 mm to 5.0 mm, T1b: 5.1 to 10.0 mm, T1c: 10.1 to 20.0 mm and T2: 20.1 to 50.0 mm. In this study there were only 3 T1mic lesions. Thus, the T1mic lesions were grouped together with the T1a lesions. Immunohistochemistry (IHC) analysis was performed on the formalin-fixed, paraffin-embedded breast cancer tissue. The ER and PR analyses were based on an IHC assay, in which a report of 10% or greater of the cells that had nuclear staining for either ER or PR was defined as positive. IHC was performed with anti-ER (Thermo, clone: SP1, dilution: 1:100, Fermont, USA) and anti-PR (Thermo, clone: SP2, dilution: 1:100, Fermont, USA) by using an autostaining system. Breast cancer tumors were classified as HER2-positive if they demonstrated HER2 gene amplification with using the fluorescence in-situ hybridization (FISH) method, or they were scored as 3+ by the IHC method. The intensity of the membrane staining was defined by a semiquantitative score (0 to 3+). The tumor staining was compared to the staining of the normal breast epithelium from the same patient as a negative control. For clinical purposes, 3+ staining was defined as uniform, intense membrane staining in more than 30% of the invasive breast cancer cells, and this was considered as overexpression.

Statistical analyses

Univariate analysis using Pearson's chi-square test was used to evaluate the likelihood of having four or more involved nodes according to the patient- and tumor-related factors. Unadjusted odds ratios (OR), the 95% confidence intervals (CI) and p-values were calculated. Multivariate logistic regression was performed to evaluate the independent relationship between the clinical and pathologic variables and four or more axillary lymph nodes after adjusting for all the other factors. The adjusted ORs, 95% CIs and p-values are presented. All the p values were two-sided, and a p-value of 0.05 or less was considered to be significant. The data analysis was performed with commercial statistical software (SPSS 12.0; SPSS Inc., Chicago, USA).

RESULTS

The patient and tumor characteristics are listed in Table 1. The median age of the included patients who were treated with surgery was 48 yr (range, 29–75 yr). The majority of the patients included in this study were Koreans (94%). Most of the tumors were T2 tumors (62.9 %), and most of the patients had palpable masses at the time of diagnosis (79%).

The predominant tumor type was invasive ductal carcinoma (87%), followed by medullary carcinoma (6%). Positive LVSI was identified in 37.1% of the tumors. Of the patients included in this study, 59.1% were ER-positive, 59.5% were PR-positive and 72.0% were HER2-negative.

Table 1. Patient and tumor characteristics (n=286)

Characteristic	No.	%
Age groups (yr)		
0-50	158	55.2
>50	128	44.8
Tumor size (mm)		
T1a (0-5.0)	14	4.9
T1b (5.1-10)	19	6.6
T1c (10.1-20.0)	73	25.6
T2 (20.1-50.0)	180	62.9
Histologic grade		
1	20	7.0
2	67	23.4
3	83	29.0
Unknown	116	40.6
Lymphovascular invasion		
Negative	138	48.2
Positive	106	37.1
Unknown	42	14.7
ER status		
Negative	112	39.2
Positive	169	59.1
Unknown	5	1.7
PR status		
Negative	111	38.8
Positive	170	59.5
Unknown	5	1.7
HER2 status		
Negative	156	54.6
Positive	125	43.7
Unknown	5	1.7
EGFR status		
Negative	140	49.0
Positive	23	8.0
Unknown	123	43.0
Tumor calcification		
Negative	86	30.1
Positive	109	38.1
Unknown	91	31.8
Palpable mass		
Negative	60	21.0
Positive	226	79.0

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; EGFR=epidermal growth factor receptor 1.

Potential predictors of 4 or more involved nodes

Of the 286 patients, 130 had 4 or more involved axillary

Table 2. Involvement of 4 or more axillary nodes with regard to the patient and tumor characteristics

Characteristic	Four or more involved nodes	%	*p*-value
Age groups (yr)			0.140
0-50	78/158	49.4	
>50	52/128	40.6	
Tumor size (cm)			<0.001
T1 (≤2)	22/106	20.8	
T2 (>2, ≤5)	108/180	60.0	
Histologic grade			0.404
1	8/20	40.0	
2	38/67	56.7	
3	42/83	50.6	
Lymphovascular invasion			<0.001
Negative	44/138	31.9	
Positive	78/106	73.6	
ER status			0.663
Negative	52/112	46.4	
Positive	74/169	43.8	
PR status			0.044
Negative	58/111	52.3	
Positive	68/170	40.0	
HER2 status			0.144
Negative	76/156	47.7	
Positive	50/125	40.0	
EGFR status			0.752
Negative	78/140	55.7	
Positive	12/23	52.2	
Tumor calcification			0.102
Negative	48/86	55.8	
Positive	48/109	44.0	
Palpable mass			<0.001
Negative	12/60	20.0	
Positive	118/226	52.2	

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; EGFR=epidermal growth factor receptor 1.

lymph nodes. Table 2 lists the proportion of patients who had 4 or more involved nodes with regard to the patient and tumor characteristics for the 286 patients who underwent complete ALND. In this study, there were no involvement of 4 or more axillary lymph nodes for the T1a-1b lesions (n=33). Thus, the T1a-b and T1c lesions were grouped together in the analysis of the relationship between the tumor size and the involvement of four or more axillary nodes. The proportion of patients who had 4 or more involved nodes increased with the tumor size. The presence of LVSI, a palpable mass on diagnosis and PR-negativity were also positively associated with the presence of 4 or more axillary lymph nodes.

Table 3. Univariate logistic-regression analysis for factors associated with involvement of 4 or more axillary nodes

Variable	Unadjusted odds ratio (95% of confidence interval)	*p*-value
Tumor size (cm)		
T1 (≤2)	1.00 (referent)	
T2 (>2, ≤5)	5.72 (3.28-9.98)	<0.001
Lymphovascular invasion		
Negative	1.00 (referent)	
Positive	5.95 (3.39-10.42)	<0.001
PR status		
Negative	1.00 (referent)	
Positive	0.60 (0.37-0.98)	0.037
Palpable mass		
Negative	1.00 (referent)	
Positive	4.37 (2.20-8.66)	<0.001

ER=estrogen receptor; PR=progesterone receptor.

Table 4. Multivariate logistic-regression analysis for factors associated with involvement of 4 or more axillary nodes

Variable	Adjuated odds ratio (95% of confidence interval)	*p*-value
Tumor size (cm)		
T1 (≤2)	1.00 (referent)	
T2 (>2, ≤5)	2.91 (1.52-5.57)	0.001
LVSI		
Negative	1.00 (referent)	
Positive	4.70 (2.58-8.57)	<0.001
Palpable mass		
Negative	1.00 (referent)	
Positive	5.01 (2.19-11.45)	<0.001

LVSI=lymphovascular space invasion.

Univariate and multivariate analyses using the logistic-regression model

On the univariate logistic-regression analysis, an increased tumor size ($p<0.001$), the presence of LVSI ($p<0.001$), a palpable mass ($p<0.001$) and PR-negativity ($p=0.044$) were positively associated with involvement of 4 or more axillary lymph nodes (Table 3). Additional multivariate logistic-regression analysis was performed on those variables that were found to be statistically significant on the univariate analysis. Again, an increased tumor size ($p=0.002$), the presence of LVSI ($p<0.001$) and a palpable mass ($p<0.001$) were positively associated with

Table 5. Involvement of 4 or more axillary nodes with regard to the combinations of the significant factors identified on the multivariate analysis

Characteristic	Four or more involved nodes	%
No LVSI, nonpalpable, T1 mass	2/20	10.0
No LVSI, nonpalpable, T2 mass	4/23	21.1
No LVSI, palpable, T1 mass	13/49	17.4
No LVSI, palpable, T2 mass	14/33	42.4
LVSI, nonpalpable, T1 mass	0/3	0
LVSI, nonpalpable, T2 mass	5/19	26.3
LVSI, palpable, T1 mass	9/18	50.0
LVSI, palpable, T2 mass	68/79	86.1

LVSI=lymphovascular space invasion.

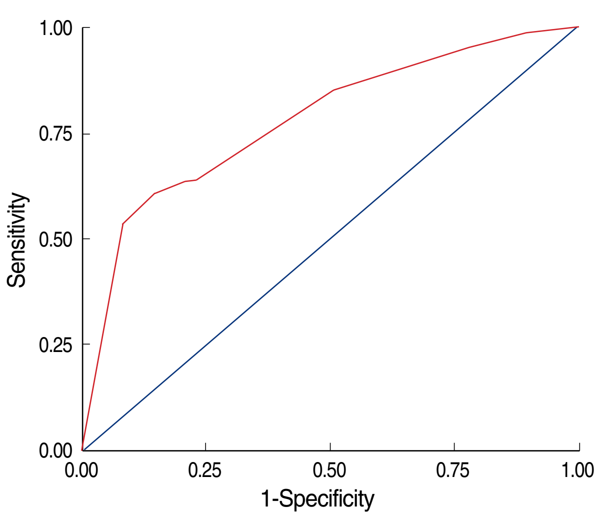

Figure 1. It shows the receiver operating curve (ROC) that corresponds to the multiple logistic model we applied to our data set of 286 patients. The area under the ROC is 0.80 ($p<0.001$; 95% CI, 0.742-0.858), which indicates the potentially promising predictive power of the multivariate logistic-regression model.

involvement of 4 or more axillary lymph nodes on the multivariate logistic-regression model (Table 4). Table 5 lists the proportion of patients who had 4 or more involved nodes for the patients who had some combinations of the potential prognostic factors identified on the multivariate analysis. When all the unfavorable factors such as T2 tumor, the presence of LVSI and a palpable mass at the time of diagnosis were taken into account, a total of 79 patients were identified, and 68 of the 79 patients (86.1%) had involvement of 4 or more axillary lymph nodes. On the contrary, when all the favorable factors were taken into account, only one patient (10%) had involvement of 4 or more axillary lymph nodes. Figure 1 shows the receiver operating curve (ROC) that corresponds to the multiple logistic model that was applied to our data set of 286 patients. The area under the ROC curve is 0.80 ($p<0.001$; 95% CI of 0.742-0.858), which indicates the potentially promising predictive power of the multivariate logistic-regression model.

DISCUSSION

In our study, involvement of 4 or more axillary lymph node was associated with an increased tumor size, the presence of LVSI and a palpable mass at the time of diagnosis on the multivariate analysis. The axillary nodal station is a common route of spread of breast cancer. Previous reports have demonstrated the strong relationship between the primary tumor size and axillary lymph node metastasis,*(12,13)* and the incidence of four or more axillary nodes is likely to be increased with larger tumors in the same manner. Similarly, the presence of lymphovascular invasion is a well known risk factor for axillary lymph node metastases, in accordance with a number of published studies.*(14,15)* Nonpalpable lesions lack the bulk that would make them palpable, so the number of tumor cells they contain may be less than that in a palpable tumor of equivalent diameter. Thus, there may be significant volume differences between equally sized palpable and nonpalpable tumors. The patients who undergo routine screening mammography are more likely to have their tumors diagnosed as nonpalpable lesions, and these nonpalpable tumors are more likely to be smaller and lower in their nodal positivity. Silverstein et al. *(16)* demonstrated that tumor palpability was an independent predictor of axillary lymph node metastasis on the multivariate analysis of more than 2,000 patients with breast carcinoma.

Level I-II axillary dissection remains the standard care for patients with positive SLNs. However, for a variety of reasons, many patients with positive SLNs do not undergo complete axillary dissection. Some radiation oncologists irradiate these patients with a wide field technique, with including the high axilla and SCF if the patients had no surgical evaluation of the axilla at all. Perhaps they are overtreating many of these patients and they are trading one set of risk factors and morbidities for another. Shahar et al.*(17)* from the M.D. Anderson Cancer Center analyzed 265 patients who were treated with mastectomy, SLNB and complete axillary dissection, and they found that no drainage seen on lymphoscintigraphy, involvement of more than 1 SLN and LVSI were the independent predictors of an increased risk of 4 or more involved axillary nodes. In their patient population, 106 patients of the 265 patients (40%) who lacked these 3 features had less than a 2% risk for involvement of 4 or more axillary nodes, according to their hypothesis. Katz et al.*(18)* from Massachusetts General Hospital analyzed 224 patients with breast cancer and who had 1 to 3 involved SLNs and who underwent complete axillary dissection without neoadjuvant chemotherapy or hormonal therapy. On the multivariate analysis, the presence of 4 or more involved axillary nodes was associated with positive LVSI, an increased number of involved SLNs, an increased size of the SLN metastasis and a lobular histology. They suggested that patients with 1 or more involved SLN, LVSI or SLN macrometastasis should have their axillary apex and SCF treated via irradiation if they do not undergo complete axillary dissection. Katz et al. recently reported a nomogram that consisted of the tumor histology, the primary tumor size, LVSI, extranodal extension, the number of involved SLNs and the size of the largest SLN metastasis for predicting having four or more involved nodes for the patients with sentinel lymph node-positive breast cancer.*(19)*

In our institution, the patients with early breast carcinomas do not routinely undergo a SLNB procedure since this involves a prolonged operative time and a multidisciplinary team with the surgeon, a nuclear medicine specialist, a radiologist and a pathologist. It is also a time-consuming procedure, and the frozen section evaluation has a 15-20% false negative rate that leads patients to a second surgery and a significant increase in cost. Thus, we did not collect information on the pathologic features of the SLNs, and this is one weak point of our study. Another weak point of our study is that we have reported that 40.6% of the patients' histologic grade and 43.0% of the patients' EGFR status were unavailable for analysis.

However, we found a preoperative clinical factor, that is, tumor palpability, to be a prognostic factor for 4 or more involved axillary nodes, and our study is still worthy. For the patients with all the favorable factors such as a lack of LVSI, a nonpalpable mass and T1 tumor, and only a small percentage of these patients (10%) have 4 or more nodal metastases, irradiation of the high axilla and SCF would be overtreating almost 90% of these patients. However, for the patients who have all the unfavorable factors, and 86.1% of these patients have 4 or more nodal metastases, adjuvant irradiation of the high axilla and SCF is strongly justified and it should be carried out if they do not undergo complete ALND.

CONCLUSION

Our data suggests that for the patients with node-positive T1-2 breast cancer, the presence of 4 or more involved nodes is frequently seen for the patients with an increased tumor size, the presence of LVSI and a palpable mass at the time of diagnosis, and we recommend that these patients receive irradiation of the high axilla and SCF for adjuvant care, if they do not undergo complete axillary dissection.

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