RESEARCH ARTICLE

Predictive Factors for Supraclavicular Lymph Node Recurrence in N1 Breast Cancer Patients

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Abstract

Background: The purpose of this study was to identify predictive factors for supraclavicular lymph node recurrence (SCLR) in N1 breast cancer patients and define a high-risk subgroup who might benefit from supraclavicular nodal radiotherapy (RT). Materials and Methods: From January 1995 to December 2009, 113 breast cancer patients with 1 to 3 positive axillary lymph nodes were enrolled in this study. All patients underwent breast-conserving surgery (BCS) or modified radical mastectomy (MRM). RT was given to all patients who received BCS. Among the patients given MRM, those with breast tumors >5 cm in size received RT. Regional nodal irradiation was not applied. Systemic chemotherapy was given to 105 patients (92.9%). Patient data were retrospectively reviewed and analyzed to identify predictive factors for SCLR. Results: The median follow-up duration was 6.5 years, with 5- and 10-year actuarial SCLR rates of 9.3% and 11.2%, respectively. Factors associated with SCLR on univariate analysis included histologic grade, number of dissected axillary lymph nodes, lymphovascular invasion, extracapsular extension (ECE), and adjuvant chemotherapy. On multivariate analysis, histologic grade and ECE remained significant. The patient group with grade 3 and ECE had a significantly higher rate of SCLR compared with the remainder (5-year SCLR rate; 71.4% vs. 4.0%, p<0.001). Conclusions: Histologic grade and ECE status are significant predictive factors for SCLR. Supraclavicular nodal RT is necessary in N1 breast cancer patients featuring histologic grade 3 and ECE.

Keywords: Breast cancer - predictive factor - radiotherapy - supraclavicular lymph node recurrence

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Introduction

Supraclavicular lymph node recurrence (SCLR) in breast cancer is usually considered an unfavorable sign of subsequent distant metastasis (Fentiman et al., 1986; Kiricuta et al., 1994; Harris et al., 2003). A variety of treatments are used for SCLR including surgical resection, radiotherapy (RT), and chemotherapy. However, despite these treatments, SCLR usually results in significantly reduced survival (Fentiman et al., 1986; McKinna et al., 1999; Harris et al., 2003), and prevention of SCLR is therefore very important.

To prevent SCLR, supraclavicular nodal RT is routinely implemented in N2-3 breast cancer patients after breast-conserving surgery (BCS) or modified radical mastectomy (MRM) (Overgaard et al., 1997; Overgaard et al., 1999; Clarke et al., 2005; Goldhirsch et al., 2005; Ragaz et al., 2005). However, because the reported SCLR rate in N1 breast cancer patients is very low (0.9-10%) (Vicini et al., 1997; Fodor et al., 1999; Grills et al., 2003; Truong et al., 2009; Yu et al., 2010; Yates et al., 2012), and supraclavicular nodal RT increases the risk of treatment complications such as lymphedema and pneumonitis (Halverson et al., 1993; Kahan et al., 2007), the role of supraclavicular nodal RT for N1 breast cancer patients is controversial, and it's use varies greatly between clinicians (Ceilley et al., 2005). A few studies have reported a subgroup of N1 breast cancer patients who may be at particularly high risk of SCLR and might benefit from supraclavicular nodal RT (Chen et al., 2002; Grills et al., 2003; Reddy and Kiel, 2007; Truong et al., 2009; Yu et al., 2010). However, there is a lack of consensus between these studies.

The purpose of this study was to identify the predictive factors for SCLR in N1 breast cancer patients and define a high-risk subgroup of patients who might benefit from supraclavicular nodal RT.

Materials and Methods

The eligibility criteria included: 1) breast cancer with 1 to 3 positive axillary lymph nodes confirmed by surgical resection, 2) no supraclavicular nodal RT, 3) no neoadjuvant chemotherapy, 4) no evidence of distant metastasis at diagnosis of breast cancer, 5) no previous breast cancer, and 6) follow-up period greater than 2 years

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after breast cancer surgery. At our institution, 113 breast cancer patients met the eligibility criteria between January 1995 and December 2009 and were enrolled in this study. Institutional Review Board approval was obtained for the retrospective review and analysis of patient data.

All patients underwent BCS or MRM. If the surgical margins were not free from disease, re-excision was performed to acquire negative surgical margins. Axillary lymph node dissection was performed in all patients. The extent of axillary lymph node dissection was usually confined to level I and II nodes. In the case of suspected level II or III nodal involvement, dissection was extended to level III.

RT was given to all patients who received BCS. Among the patients who received MRM, patients with breast tumors >5 cm received RT. RT was delivered using a 6-MV photon beam to the whole breast or chest wall. With a schedule of 2 Gy per fraction and 5 fractions weekly, the whole breast or chest wall was treated with tangential fields to 46 Gy. All patients also received an electron boost to the tumor bed, with a median dose of 10 Gy (range, 10-16 Gy). Regional nodal irradiation was not used.

Systemic chemotherapy was given to 105 patients (92.9%). Decisions regarding the chemotherapy regimen were individualized by the treating physician. The regimens consisted of doxorubicin, cyclophosphamide (AC); fluorouracil, doxorubicin, cyclophosphamide (FAC); docetaxel, doxorubicin, cyclophosphamide (TAC); cyclophosphamide, methotrexate, fluorouracil (CMF); and cyclophosphamide, epirubicin, fluorouracil (CEF). All patients with positive estrogen receptor (ER) or progesterone receptor (PR) received adjuvant hormone therapy for 5 years.

ER and PR status was determined by immunohistochemistry (IHC) staining. Positive human epidermal growth factor receptor-2 (HER2) status was determined using either IHC 3+ staining or amplification on fluorescence in situ hybridization. Patients were classified according to receptor status: luminal (ER- or PR-positive), triple negative (ER-, PR-, HER2-negative), and HER2-positive (ER-, PR-negative, and HER2-positive).

SCLR was defined as any recurrence of tumor in the ipsilateral supraclavicular lymph nodes with or without local recurrence and/or distant metastases. Local recurrence was defined as any recurrence of tumor in the ipsilateral breast or chest wall. Distant metastasis was defined as evidence of tumor in any area other than the ipsilateral breast and/or regional nodes. All recurrences were diagnosed by either clinical or radiologic examination. When possible, histologic confirmation was also implemented.

To identify potential predictive factors for SCLR, the following parameters were included in the analysis: age, tumor location, histologic grade, tumor size, hormone receptor status (ER or PR), HER2 status, molecular subtypes, number of positive axillary lymph nodes, number of dissected axillary lymph nodes, percentage of positive axillary lymph nodes, lymphovascular invasion (LVI), extracapsular extension (ECE), surgical resection margin, type of surgery, adjuvant chemotherapy, regimen of chemotherapy, and post-surgery cancer antigen 15-3 (CA15-3) and carcinoembryogenic antigen (CEA) levels. Post-surgery CA15-3 and CEA levels were measured within 2 weeks after BCS or MRM.

Actuarial recurrence and survival rates were estimated using the Kaplan-Meier method, and comparisons among groups were performed using log-rank tests. Parameters with a P value <0.10 in univariate analysis were further assessed by multivariate analysis. Multivariate analysis was performed using the Cox proportional hazard regression model. Elapsed time was calculated from the date of surgery to the date of recurrence recognition, death, or the final follow-up visit. All tests were two-sided and P values <0.05 were considered statistically significant. All analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Patient and tumor characteristics are summarized in Table 1. One hundred eight patients (95.6%) had invasive ductal carcinoma and the other five had invasive lobular carcinoma, mucinous carcinoma, metaplastic carcinoma, and medullary carcinoma, respectively. The tumor grade was 1 in 18 patients (15.9%), 2 in 68 patients (60.2%), and 3 in 25 patients (22.1%). The most commonly used adjuvant chemotherapy regimen was AC (doxorubicin 60 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1, cycled every 21 days for 4 cycles). AC chemotherapy was given to 69 patients (61.1%), CMF chemotherapy to 19 patients (16.8%), CEF chemotherapy to 6 patients (5.3%), FAC chemotherapy to 6 patients (5.3%), and TAC chemotherapy to 5 patients (4.4%). The median follow-up duration was 6.5 years (range, 1.8-19.5).

Recurrence and survival

Eleven patients (9.7%) experienced SCLR. The median duration from surgery to SCLR was 2.7 years (range, 0.6-7.9). The 5- and 10-year actuarial SCLR rates were 9.3% and 11.2%, respectively. Of the patients who experienced SCLR, five patients experienced concurrent distant metastasis; five experienced concurrent local recurrence, ipsilateral axillary lymph node recurrence, and distant metastasis; and one experienced concurrent ipsilateral axillary lymph node recurrence. There was no isolated SCLR. Six patients (5.3%) experienced local recurrence. The median duration from surgery to local recurrence was 2.2 years (range, 0.6-3.5), and the 5- and 10-year actuarial local recurrence rates were both 5.4%.

Overall survival and distant metastasis-free survival for all patients were 91.0% and 88.2% at 5 years, and 83.2% and 82.9% at 10 years. Patients who experienced SCLR had a significantly decreased overall survival compared with patients who did not (5-year overall survival rate; 50.5% vs. 95.5%, P<0.001) (Figure 1). Of the 11 patients who experienced SCLR, eight died during the follow-up period. Distant metastasis-free survival was also significantly decreased in patients who experienced SCLR compared with those did not (5-year distant metastasis-free survival rate; 27.3% vs. 94.9%, P<0.001) (Figure 2). Only 1 of the 11 patients who experienced

Table 1. Patient Characteristics

Characteristics		n (%)
Age (years)	Median	49.0 (range, 32.1-75.6)
	≤50	65 (57.5)
	>50	48 (42.5)
Tumor location	Right	56 (49.6)
	Left	57 (50.4)
	Upper	79 (69.9)
	Lower	19 (16.8)
	Center	15 (13.3)
Grade	1-2	86 (76.1)
	3	25 (22.1)
	Unknown	2 (1.8)
Histology	Invasive ductal	108 (95.6)
	Others	5 (4.4)
Tumor size (cm)	Median	2.1 (range, 0.5-7)
	≤2	45 (39.8)
	>2	67 (59.3)
	Unknown	1 (0.9)
Hormone receptor status	Positive	89 (78.8)
	Negative	24 (21.2)
HER2 status	Positive	31 (27.4)
	Negative	72 (63.7)
	Unknown	10 (8.9)
Molecular subtype	Luminal	89 (78.8)
	Triple negative	14 (12.4)
	HER2-positive	10 (8.8)
No. of positive nodes	1	57 (50.4)
	2	39 (34.5)
	3	17 (15.1)
No. of dissected nodes	Median	16 (range, 4-38)
	≤15	53 (46.9)
	>15	60 (53.1)
Percentage of positive nodes (%)	Median	10 (range, 2.6-50)
	≤10	59 (52.2)
	>10	54 (47.8)
Lymphovascular invasion	Yes	31 (27.4)
	No	79 (69.9)
	Unknown	3 (2.7)
Extracapsular extension	Yes	13 (11.5)
	No	97 (85.8)
	Unknown	3 (2.7)
Resection margin (mm)	>5	80 (70.8)
	≤5	31 (27.4)
	Positive	2 (1.8)
Type of surgery	MRM	85 (75.2)
	BCS	28 (24.8)
Adjuvant chemotherapy	Yes	105 (92.9)
	No	8 (7.1)
Regimen of chemotherapy	Adriamycin-based	80 (76.2)
	Non-adriamycin-based	25 (23.8)
Post-surgery CA15-3 level (U/mL)	Median	7 (range, 1.5-23)
	≤6.5	46 (40.7)
	>6.5	58 (51.3)
	Unknown	9 (8.0)
Post-surgery CEA level (ng/mL)	Median	1.52 (range, 0.2-4.7)
	≤1.5	40 (35.4)
	>1	48 (42.5)
	Unknown	25 (22.1)

*HER2, human epidermal growth factor receptor-2; MRM, modified radical mastectomy; BCS, breast-conserving surgery; CA15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen

SCLR did not experience distant metastasis.

Predictive factors for supraclavicular lymph node recurrence

Predictive factors for SCLR were analyzed. Factors associated with SCLR on univariate analysis included histologic grade, number of dissected axillary lymph nodes, LVI, ECE, and adjuvant chemotherapy. On multivariate analysis, histologic grade (hazard ratio=7.568, 95% confidence interval 1.534-37.334), and ECE (hazard ratio=13.253, 95% confidence interval 3.303-53.173) remained significant factors for SCLR (Table 2).

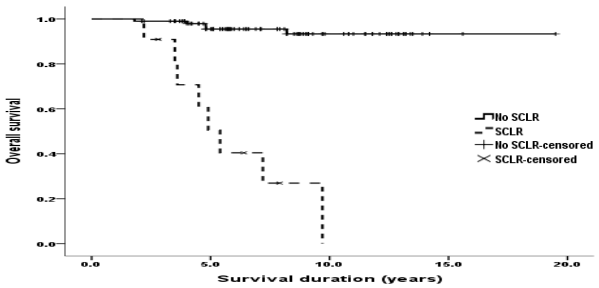

Figure 1. Overall Survival According to Status of Supraclavicular Lymph Node Recurrence (SCLR). Patients who experienced SCLR had significantly decreased overall survival compared with patients who did not (5-year overall survival rate; 50.5% vs. 95.5%, P<0.001)

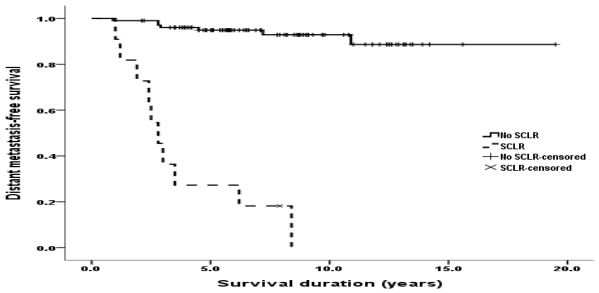

Figure 2. Distant Metastasis-free Survival According to Status of Supraclavicular Lymph Node Recurrence (SCLR). Patients who experienced SCLR had significantly decreased distant metastasis-free survival compared with patients who did not (5-year distant metastasis-free survival rate; 27.3% vs. 94.9%, P<0.001)

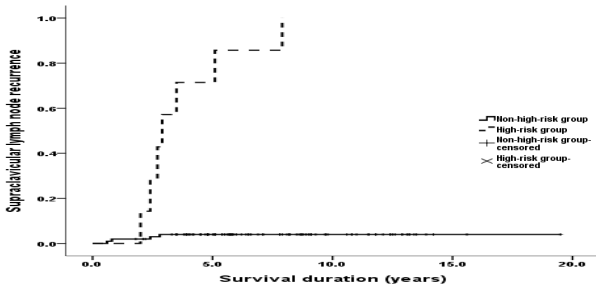

Figure 3. Supraclavicular Lymph Node Recurrence (SCLR) According to Risk Groups. The high-risk group had significantly higher SCLR rate compared with the non-high-risk group (5-year SCLR rate; 71.4% vs. 4.0%, P<0.001)

Based on predictive factors for SCLR that remained significant on multivariate analysis, we divided the patients into four groups. The first group of patients (78 patients), with tumor grade 1-2 and no ECE, had a very low SCLR rate with a 5-year SCLR of 1.3%. The second group of patients (18 patients), with grade 3 and no ECE, had a 5-year SCLR rate of 11.1%. The third group of patients (6 patients), with grade 1-2 and ECE, had a 5-year SCLR rate of 11.7%. The fourth group of patients (7 patients), with grade 3 and ECE, had a very high SCLR rate with a 5-year SCLR rate of 85.7% (Table 3). Because the fourth group of patients had a much higher SCLR rate than the other groups, we defined this group as the high-risk group. The high-risk group had a significantly higher rate of SCLR

Table 2. Analysis of Predictive Factors for Supraclavicular Lymph Node Recurrence

Variables		5-year SCLR rate(%)	P value	
			Univariate analysis	Multivariate analysis
Age (years)	≤50 vs. >50	11.4 vs. 6.3	0.289	
Tumor location	Right vs. left	9.5 vs. 9.0	0.750	
	Upper vs. lower or center	11.8 vs. 3.1	0.093	0.400
Histologic grade	1-2 vs. 3	2.3 vs. 33.5	<0.001	0.005
Tumor size (cm)	≤2 vs. >2	4.5 vs 12.7	0.098	0.149
Hormone receptor status	Positive vs. negative	6.9 vs. 19.4	0.093	0.061
HER2 status	Positive vs. negative	9.8 vs. 10.5	0.685	
Molecular subtype	Luminal vs. triple negative vs. HER2-positive	6.9 vs. 14.3 vs. 10.0	0.214	
Number of positive nodes	1 vs. 2-3	5.3 vs. 13.5	0.091	0.747
Number of dissected nodes	≤15 vs. >15	15.5 vs. 3.4	0.021	0.205
Percentage of positive nodes (%)	≤10 vs. >10	5.2 vs. 13.7	0.093	0.687
Lymphovascular invasion	Yes vs. No	24.7 vs. 3.9	<0.001	0.261
Extracapsular extension	Yes vs. No	59.6 vs. 3.2	<0.001	<0.001
Resection margin (mm)	≤5 vs. >5	15.2 vs. 7.7	0.475	
Type of surgery	MRM vs. BCS	9.9 vs. 7.3	0.632	
Adjuvant chemotherapy	Yes vs. No	7.1 vs. 37.5	0.002	0.070
Regimen of chemotherapy	Adriamycin-based vs. non-adriamycin-based	5.1 vs. 12.2	0.136	
Post-surgery CA15-3 level (U/mL)	≤6.5 vs. >6.5	4.4 vs. 14.8	0.057	0.242
Post-surgery CEA level (ng/mL)	≤1.5 vs. >1.5	5.3 vs. 12.4	0.174	

*SCLR, supraclavicular lymph node recurrence; HER2, human epidermal growth factor receptor-2; MRM, modified radical mastectomy; BCS, breast-conserving surgery; CA15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen

Table 3. 5-year Supraclavicular Lymph Node Recurrence Rates According to Extracapsular Extension and Histologic Grade

Histologic grade	Extracapsular extension	
	No	Yes
1-2	1.3%	11.7%
3	11.1%	85.7%

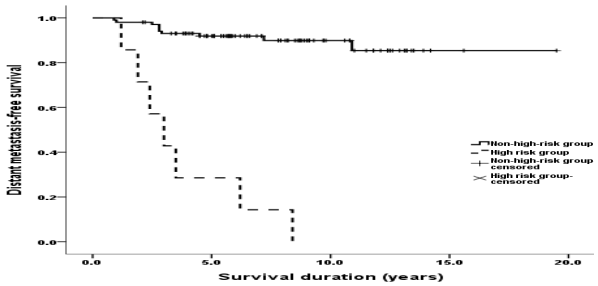

Figure 4. Overall Survival According to Risk Groups. The high-risk group had significantly lower overall survival rate compared with the non-high-risk group (5-year overall survival rate; 42.9% vs. 92.9%, P<0.001)

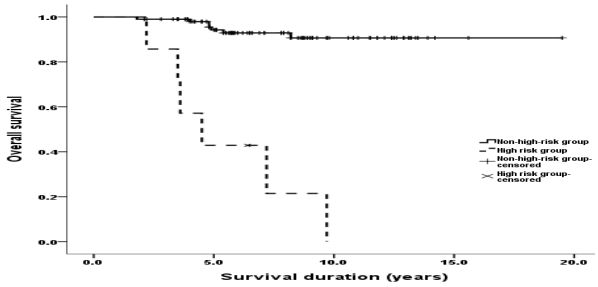

Figure 5. Distant Metastasis-free Survival According to Risk Groups. The high-risk group had significantly lower distant metastasis-free survival rate compared with the non-high-risk group (5-year distant metastasis-free survival rate; 28.6% vs. 91.9%, P<0.001)

compared with the non-high-risk group (5-year SCLR rate; 71.4% vs. 4.0%, P<0.001) (Figure 3). Moreover, the high-risk group had significantly decreased overall survival (5-year overall survival rate; 42.9% vs. 92.9%, P<0.001) and distant metastasis-free survival (5-year distant metastasis-free survival rate; 28.6% vs. 91.9%, P<0.000) than the non-high-risk group (Figure 4, 5).

Discussion

The reported SCLR rate in N1 breast cancer ranges from 0.9-10% (Vicini et al., 1997; Fodor et al., 1999; Grills et al., 2003; Truong et al., 2009; Yu et al., 2010; Yates et al., 2012). In our study, the median duration from surgery to SCLR was 2.7 years. The crude SCLR rate was 9.7%, and the actuarial SCLR rate was 9.3% at 5 years and 11.2% at 10 years. The results of our study are similar to those of Yates et al. (2012) who performed a retrospective analysis of the pathologic features of 1,065 N1 breast cancer patients. In their study, patients underwent MRM or BCS, and no patient received supraclavicular nodal RT. The median duration from primary diagnosis to SCLR was 3.4 years, and the crude, 5-year and 10-year actuarial SCLR rates were 9.2%, 7%, and 10%, respectively. Inconsistencies in the reported SCLR rate may be mainly attributable to the different number of dissected axillary lymph nodes; the reported number of dissected axillary lymph nodes in previous studies ranges from less than 10 to 24 (Vicini et al., 1997; Fodor et al., 1999; Grills et al., 2003; Truong et al., 2009; Yu et al., 2010; Yates et al., 2012). Other possible reasons for inconsistent SCLR rates include different indications for post-operative RT, inconsistent RT field and fractionation schedule, and different indications and regimens for adjuvant chemotherapy.

Several retrospective studies have reported predictive

Table 4. Reported Predictive Factors for Supraclavicular Lymph Node Recurrence in N1 Breast Dancer Patients

Authors	Sample size (n)	Significant predictive factor for SCLR	
		Univariate analysis	Multivariate analysis
Reddy et al.	202	Histologic grade, hormone receptor status	Not reported
Yates et al.	1,065	Number of positive axillary lymph nodes, percentage of positive axillary lymph nodes, maximum size of positive axillary lymph node, histologic grade, hormone receptor status	Number of positive axillary lymph nodes, histologic grade
Yu et al.	448	LVI, ECE, number of positive axillary lymph nodes, level of involved axillary lymph nodes	LVI, ECE, number of positive axillary lymph nodes, level of involved axillary lymph nodes
Truong et al.	1,255	Age, histologic grade, hormone receptor status, number of positive axillary lymph nodes, percentage of positive axillary lymph nodes	Not reported
Our study	113	Histologic grade, number of dissected axillary lymph nodes, LVI, ECE, adjuvant chemotherapy	Histologic grade, ECE

*SCLR, supraclavicular lymph node recurrence; LVI, lymphovascular invasion; ECE, extracapsular extension

factors for SCLR in N1 breast cancer patients. Reddy and Kiel (2007) included 202 N1 breast cancer patients in their analysis and reported histologic grade and hormone receptor status as significant predictors for SCLR. Yates et al. (2012) performed a retrospective review of 1,065 N1 breast cancer patients and reported that the number of positive axillary lymph nodes, percentage of positive axillary lymph nodes, maximum size of positive axillary lymph node, histologic grade, and hormone receptor status were associated with SCLR on univariate analysis. On multivariate analysis, only histologic grade and number of positive axillary lymph nodes remained significant. Yu et al. (2010) included 448 N1 breast cancer patients in their retrospective review, and reported LVI, ECE, number of positive axillary lymph nodes, and level of involved axillary lymph nodes as significant predictors for SCLR on both univariate and multivariate analysis. Truong et al. (2009) included 1,255 N1 breast cancer patients in their retrospective study, and reported age, histologic grade, hormone receptor status, number of positive axillary lymph nodes, and percentage of positive axillary lymph nodes as significant predictive factors for SCLR. In our study, factors associated with SCLR on univariate analysis included histologic grade, number of dissected axillary lymph nodes, LVI, ECE, and adjuvant chemotherapy. On multivariate analysis, histologic grade and ECE remained significant factors for SCLR (Table 4). Because there is some inconsistency between published studies, prospective multicenter trials with large sample sizes will be required to define definitive predictive factors for SCLR in N1 breast cancer patients.

Some of the above studies divided their patients into subgroups according to predictive factors for SCLR and proposed specific subgroups who had a high SCLR rate and would benefit from supraclavicular nodal RT. Yu et al. (2010) divided patients into low-, intermediate-, and high-risk groups according to the number of predictive factors. Patients with no or one predictive factor were defined as the low-risk group and had a 3.2% SCLR rate at 5 years. On the other hand, the intermediate-risk group, with two predictive factors, and high-risk group, with three or four predictive factors, had relatively high 5-year SCLR rates of 21.3% and 48.8%, respectively. Consequently, the authors proposed that supraclavicular nodal RT would be necessary in intermediate- and high-risk groups. Likewise, Yates et al. (2012) divided their patients into low-, intermediate- and high-risk groups based on histologic grade and number of positive axillary lymph nodes. Patients with histologic grade 1 cancer were defined as the low-risk group and had very low 5-year SCLR rates of 0-1.4%. The intermediate-risk group, with either histologic grade 2 cancer and 1-2 positive axillary lymph nodes or histologic grade 3 cancer and 1 positive axillary lymph node, had 5-year SCLR rates of 4.9-7.6%. The high-risk group, with histologic grade 3 cancer and 2-3 positive axillary lymph nodes or histologic grade 2 cancer and 3 positive axillary lymph nodes, had 5-year SCLR rates of 10.9-21.1%. Consequently, these authors proposed that high-risk and possibly also intermediate-risk groups would gain significant benefit from supraclavicular nodal RT. In our study, we divided the patients into four groups according to histologic grade and ECE status. Compared with other patient groups, patients with histologic grade 3 cancer and ECE had a very high 5-year SCLR rate (85.7%), and were defined as the high-risk group. In addition, the high-risk group had significantly decreased overall and distant metastasis-free survival rate compared with the non-high-risk group (Figure 4, 5). Therefore, we propose that supraclavicular nodal RT would be necessary in N1 breast cancer patients with histologic grade 3 and ECE. We believe that supraclavicular nodal RT might reduce SCLR and also improve survival in this patient group.

There were some limitations in this study. First, this study was retrospective and therefore may have inherent bias. For example, adjuvant chemotherapy was provided according to the attending physician's discretion rather than a predetermined protocol. Thus, the regimens of adjuvant chemotherapy varied widely. In addition, because of incomplete patient medical records, we could not analyze some potential predictive factors for SCLR, such as maximum size of positive axillary lymph node and level of involved axillary lymph nodes. Second, the sample size was relatively small. Third, the follow-up durations were not sufficiently long in some cases and consequently this study may underestimate the recurrence rate. Despite these limitations, we believe that our study contributes to the definition of high-risk subgroup of patients who might

benefit from supraclavicular nodal RT.

In conclusion, our results indicated that histologic grade and ECE status are significant predictive factors for SCLR. When patients are divided into subgroups according to predictive factors for SCLR, supraclavicular nodal RT would be necessary in N1 breast cancer patients with histologic grade 3 and ECE.

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