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
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/m² on day 1, cyclophosphamide 600 mg/m² 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...
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).

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 compared with the non-high-risk group (5-year SCLR rate; 71.4% vs. 4.0%, P<0.001)
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              |                       |
| Histologic grade                       | Upper vs. lower or center | 11.8 vs. 3.1 | 0.093              | 0.400                |
| Tumor size (cm)                        | ≤2 vs. >2           | 2.3 vs. 33.5 | <0.001             | 0.005                |
| Hormone receptor status                | Positive vs. negative | 4.5 vs 12.7 | 0.098              | 0.149                |
| HER2 status                            | Positive vs. negative | 6.9 vs. 19.4 | 0.093              | 0.061                |
| Molecular subtype                      | Luminal vs. triple negative vs. HER2-positive | 9.8 vs. 10.5 | 0.865              |                       |
| 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% |

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...
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. 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 in 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.

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

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

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

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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