

Supraclavicular Nodal Failure after Surgery in N1 Breast Cancer Patients without Supraclavicular Irradiation

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Abstract

Background: We conducted a retrospective analysis to evaluate the impact of omission of supraclavicular radiotherapy on supraclavicular failure rate and treatment outcomes in N1 breast cancer patients with evaluation of prognostic factors that affected supraclavicular recurrence free survival.

Methods: This study analyzed the medical records of 109 patients with N1 breast cancer. All patients underwent surgery and received adjuvant chemotherapy without supraclavicular radiotherapy. Supraclavicular recurrence free survival, distant metastasis free survival, disease free survival, and overall survival were estimated using the Kaplan-Meier method and compared using log-rank analysis.

Results: After a median follow up period of 58 months, treatment failed in 31 patients (28.4%); patterns of failure consisted of locoregional (n=21, 19.3%), isolated supraclavicular (n=7, 6.4%), and distant metastasis (n=14, 12.8%). Survival rates at 5 years were as follows: supraclavicular recurrence free survival (84.9%), distant metastasis free survival (87.6%), and overall survival (86.4%). Univariate analysis revealed that the type of chemotherapeutic regimen was the only significant prognostic factor affected supraclavicular recurrence free survival; patients who received the cyclophosphamide, methotrexate, 5-fluorouracil chemotherapy regimen experienced lower supraclavicular recurrence free survival than those who received doxorubicin based and taxane based chemotherapy. Development of supraclavicular recurrence significantly lowered the 5-year overall survival (57.1%) and distant metastasis free survival (50%) rates compared to patients without supraclavicular recurrence who had an overall survival rate of 88.5% ($P<0.0001$) and distant metastasis free survival rate of 90% ($P<0.0001$).

Conclusion: Patients with N1 breast cancer had an overall supraclavicular recurrence of 6.4% which denoted that additional supraclavicular radiotherapy was unnecessary and could be given in N1 patients after surgery and an adjuvant CMF regimen. A prospective randomized trial would be needed to clarify the impact of supraclavicular radiotherapy on treatment outcome.

Keywords: Breast cancer, N1 disease, Prognostic factors, Supraclavicular recurrence

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Introduction

Supraclavicular node radiotherapy (S/C RT) is used routinely in N2-3 breast cancer patients after modified radical mastectomy (MRM) or breast conserving surgery (BCS).¹⁻⁵ Regarding the role of S/C RT in N1 breast cancer patients, the Danish Breast Cancer Cooperative Group 82b and c have analyzed the failure pattern among this cohort. The results showed an overall supraclavicular node recurrence (SCR) rate of 6.8%, and isolated SCR rate of 2% in high-risk patients (involvement of axillary nodes, tumor size >5 cm, pathologic stages II or III) without radiation therapy.⁶ Other studies reported SCR rates of 1% to 8% in patients with fewer than 4 positive axillary nodes without radiation therapy.⁷⁻¹⁰ Owing to the low rate of SCR reported by these series together with the increased toxicity associated with S/C RT, the routine use of S/C RT for N1 breast cancer patients has remained controversial.¹¹⁻¹³

Several trials have intended to detect the subset of N1 breast cancer patients who might benefit from postoperative S/C RT in order to prevent subsequent recurrence which is difficult to manage and associated with high morbidity. The current study sought to determine the supraclavicular nodal failure (SCF) rate, supraclavicular recurrence free survival (SCRFS), distant metastasis free survival (DMFS), disease free survival (DFS), overall survival (OS), and evaluate the risk factors associated with SCF in patients with one to three positive axillary nodes treated with MRM or BCS and axillary dissection without S/C RT.

Patients and Methods

This retrospective study analyzed the medical records of histologically confirmed non metastatic breast cancer patients who presented to the Radiotherapy Department of South Egypt Cancer Institute during the period of April 2001 and March 2013 after MRM or BCS, adjuvant systemic therapy and adjuvant radiation therapy to the breast and/or chest wall without S/C RT.

Eligibility criteria for this study included breast cancer patients with histologically involved 1-3

axillary lymph nodes treated with either MRM or BCS who did not receive adjuvant S/C RT. Microscopically involved resection margin, evidence of distant metastasis at diagnosis, those who received neoadjuvant chemotherapy, and those with a prior or concurrent malignancy were not eligible for inclusion in this study. The Institutional Review Board of the South Egypt Cancer Institute approved this study.

Between July 2001 and March 2013, there were 2047 breast cancer patients treated at South Egypt Cancer Institute. Of those patients, we excluded 680 metastatic cases from the current study. The remaining 1367 patients were treated with adjuvant therapy (breast and/or chest wall radiotherapy and chemotherapy with or without tamoxifen) after MRM or BCS. Of those patients, we excluded 907 who received postoperative breast and/or chest wall with supraclavicular irradiation (163 patients had N1 disease, 334 had N2 disease, 280 had N3 disease, and 130 patient were Nx). A total of 460 patients did not receive supraclavicular irradiation (351 patients were N0 and 109 patients were N1). There were 109 out of 460 patients with N1 disease that did not receive supraclavicular irradiation. These patients underwent analysis for clinicopathological characteristics, patterns of failure and survival rates.

Treatment

All patients underwent MRM or BCS. Re-excision was performed if margins were positive. Surgical margins were negative for all patients. Levels I and II axillary lymph nodes were dissected. In case of suspected level II or III nodal involvement, dissection was extended to level III. Following MRM or BCS, all 109 patients received systemic chemotherapy. The choice of administration of these chemotherapeutic regimens depended upon the time of administration. Until 2002, six cycles of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) were used; after that time, six cycles of 5-fluorouracil, adriamycin, cyclophosphamide (FAC) or 5-fluorouracil, epirubicin, cyclophosphamide (FEC) were given. Since late 2004, taxane based chemotherapy (adriamycin, cyclophosphamide,

Taxol) was administered. Those patients that underwent BCS and whose tumor was ≥ 4 cm received postoperative radiotherapy delivered to the breast and/or chest wall using tangential fields to a dose of 50 Gy (2.0 Gy/fraction) or a dose of 42.5 Gy (2.65 Gy/fraction) by 6-megavolt photon beams. A boost dose of 14 Gy in 7 fractions to the tumor site using 12 Mev electrons was given to patients ≤ 50 years of age who underwent BCS.

Follow up

All patients were followed up by physical examinations and laboratory studies every three months for the first three years, every six months for the fourth and fifth years, and after five years patients were followed up annually. Chest X-ray and abdominal ultrasonography were done every six months for the first three years and annually for the fourth and fifth years. Bone scans were requested annually and when indicated. Computerized tomography (CT) scans were performed when indicated and not routinely requested. The median follow-up time was 58 months (range: 12–144) calculated from the date of surgery.

Treatment end points

All recurrences were diagnosed by either clinical or radiologic examination. Local recurrence was defined as any relapse in the breast and/or chest wall. Any relapse in the axillary lymph nodes, and/or other nodes in the infra- or supraclavicular fossa or in the internal mammary chain was considered regional recurrence. We defined SCF as any recurrence of tumor in the ipsilateral supraclavicular lymph nodes. Locoregional recurrence (LRR) was identified as local recurrence (breast and/or chest wall) and peripheral lymphatic recurrence (axillary, supraclavicular and internal mammary lymph nodes alone). Any recurrence outside these areas was considered distant metastasis. Supraclavicular recurrence free survival and DMFS were calculated either from the date of surgery to the date of event recognition, date of the last follow-up visit, or death. Disease free survival was defined as the interval from surgery to the date of

Table 1. Characteristics of 109 patients with N1 breast cancer.

| Variable | Patients (N) | Percentage |
|--------------------------------|--------------|------------|
| Age (years) | | |
| Median | 49 | |
| Range | 24-70 | |
| ≤ 40 | 20 | 18.3 |
| 41-50 | 33 | 30.3 |
| 51-60 | 33 | 30.3 |
| Grade | | |
| 1 | 21 | 19.3 |
| 2 | 64 | 58.7 |
| 3 | 24 | 22.0 |
| Tumor | | |
| T1 | 15 | 13.8 |
| T2 | 53 | 48.6 |
| T3 | 41 | 37.6 |
| No. of involved nodes | | |
| 1 | 52 | 47.7 |
| 2 | 33 | 30.3 |
| 3 | 24 | 22.0 |
| No. of nodes examined | | |
| Median | 14 | |
| Range | 6-27 | |
| < 10 | 26 | 23.9 |
| ≥ 10 | 83 | 76.1 |
| Extracapsular extension | | |
| No | 92 | 84.4 |
| Yes | 17 | 15.6 |
| Lymphovascular invasion | | |
| No | 81 | 28 |
| Yes | 74.3 | 25.7 |
| Hormone receptor status | | |
| Positive | 55 | 50.5 |
| Negative | 39 | 35.8 |
| Unknown | 15 | 13.8 |
| HER2 status | | |
| Positive | 16 | 14.7 |
| Negative | 31 | 28.4 |
| Unknown | 62 | 56.9 |
| Chemotherapy regimens | | |
| CMF | 20 | 18.3 |
| FAC | 48 | 44.0 |
| FEC | 16 | 14.7 |
| AC/Taxol | 25 | 22.9 |

CMF: Cyclophosphamide, methotrexate, 5-fluorouracil; FAC: 5-fluorouracil, adriamycin, cyclophosphamide; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; AC/Taxol, Adriamycin, cyclophosphamide, taxol.

relapse or death from any cause or last follow up. Overall survival was measured from the date of surgery to the date of death or to the date of the final follow-up visit.

Table 2. Characteristics of seven patients with supraclavicular nodal failure (SCF).

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|--------------------|---------|----------|----------|-----------|---------|---------|---------|
| Age (years) | 39 | 51 | 53 | 33 | 29 | 53 | 49 |
| Grade | 3 | 1 | 2 | 1 | 2 | 3 | 2 |
| Tumor | T2 | T3 | T1 | T2 | T1 | T1 | T3 |
| Node | 1 | 1 | 1 | 2 | 1 | 2 | 1 |
| Nodes examined | 6 | 17 | 17 | 24 | 18 | 25 | 11 |
| LN dissection | <10 | ≥10 | ≥10 | ≥10 | ≥10 | ≥10 | ≥10 |
| ECE | No | No | Yes | No | No | No | No |
| LVI | No | No | Yes | No | No | No | Yes |
| HR | +ve | +ve | +ve | -ve | +ve | -ve | +ve |
| HER2 status | Unknown | Negative | Positive | Unknown | Unknown | Unknown | Unknown |
| Cth regimens | CMF | CMF | FEC | FEC | FAC | CMF | CMF |
| Associated failure | No | No | LR+ DM | LR + DMDM | | DM | LR |
| Outcome | Dead | Dead | Dead | Dead | Live | Dead | Dead |

Abbreviations: LN: lymph nodes; ECE: extracapsular extension; LVI: lymphovascular invasion; HR: hormone receptor: +ve, positive; -ve, negative; Cth: chemotherapy; CMF: Cyclophosphamide, methotrexate, 5-fluorouracil; FAC: 5-fluorouracil, epirubicine, cyclophosphamide; FEC: 5-fluorouracil, epirubicine, cyclophosphamide; LR: local recurrence; LR+DM: local recurrence plus distant metastasis; DM: distant metastasis.

Statistical analysis

Supraclavicular recurrence free survival, DMFS, DFS and OS were estimated using the Kaplan-Meier method.¹⁴ Survival rates were compared by use of log-rank analysis. The level of significance was set at $P < 0.05$. All analyses were conducted using SPSS software (version 16.0.1; SPSS Inc., Chicago, IL).

Results

Patients, and tumor characteristics

Patients and tumor related characteristics (age, histologic grade, tumor stage, number of involved and examined lymph nodes, estrogen/progesterone receptor status, extracapsular extension, lymphovascular invasion and chemotherapeutic regimens) are listed in Table 1. There were 55 (50.5%) who were hormone receptor positive and received adjuvant endocrine therapy (tamoxifen in most cases) for five years. Positive HER2 receptor was detected in 16 (14.7%) patients.

Patterns of treatment failure

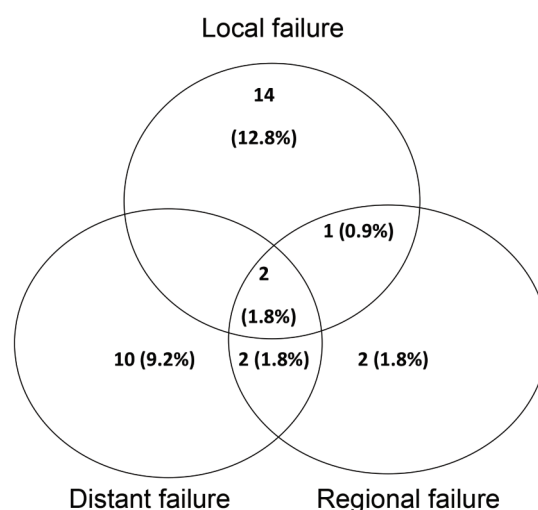
After a median follow up period of 58 months, treatment failed in 31 (28.4%) patients. Locoregional recurrence occurred in 21 (19.3%) with a median time of 21 months (Graph 1). Distribution of LRR was the breast/chest wall in 14 (66.7%), supraclavicular lymph node in 4 (19.0%), and breast/chest wall with supraclavic-

ular lymph node in 3 (14.3%) patients. All patients with SCR were salvaged with chemotherapy and radiation. The clinicopathological characteristics of 7 patients who developed SCR are presented in Table 2.

Distant metastasis occurred in 14 (12.8%) with median time of 48 months. In the 14 patients with distant metastasis, metastatic sites included the bones in 7 patients, lungs in 4 patients, the brain in 2 patients and the liver in 1 patient (Graph 1).

Survival

At 5 years, the OS rate was 86.4% and DFS rate was 80.9%. The SCRFS rate was 84.9% at 5



Graph 1. Patterns of failure of 109 patients with N1 breast cancer.

years and DMFS rate was 87.6% at 5 years. Patients with SCR had significantly lower OS (57.1%) compared to patients without SCR (88.5%, $P < 0.0001$, Figure 1). Patients with SCR also had significantly lower DMFS (50.0%) compared to those without SCR (90.0%, $P < 0.0001$, Figure 2).

Prognostic factors for supraclavicular recurrence free survival (SCRFS)

Univariate analysis revealed that age, pathologic tumor stage, number of involved nodes, number of nodes examined, the presence of extracapsular nodal extension, lymphovascular invasion, hormone receptor status and HER2 status were not significant prognostic factors for SCRFS (Table 2). The type of chemotherapeutic regimens significantly affected SCRFS. The 5-year SCRFS according to chemotherapy regimen were: CMF (56.7%), FAC (93.4%), AC/Taxol (91.7%) and FEC (81.3%) with a P -value of < 0.0001 (Figure 3).

Discussion

Our retrospective study included 109 N1 breast cancer patients, all of whom were treated with MRM or BCS and adjuvant chemotherapy without postoperative supraclavicular radiotherapy.

The overall LRR rate was 19.3% which matched results reported by several series. The average rate of LRR for patients with one to three positive lymph nodes in these series was approximately 12% (range 5-20%).^{2,15-17} The Danish group observed an LRR rate of 30%, which was greater than that reported by our study. The reason for this might be due to the fact that in the Danish 82b trial many patients did not undergo level I/II axillary dissection; the median number of dissected axillary lymph nodes was 7, with 76% of the patients having less than 10 lymph nodes removed and 15% having 3 or fewer lymph nodes removed.¹ In contrast, the median numbers of lymph nodes removed in our study was 14, whereas the median number of lymph nodes removed in the ECOG and M.D. Anderson Cancer Center series were 15 and 17, respectively.^{15,16}

Our study showed that the most common site for locoregional failure was breast and/or chest wall which was detected in 17 (15.6%) patients, followed by the supraclavicular fossa in 7 (6.4%) patients. Our figures agreed with most series which reported the chest wall as the site at greatest risk for LRR followed by the supraclavicular fossa.^{6,15,18} The incidence of SCR in most series ranged from 1% to 8% in patients with fewer

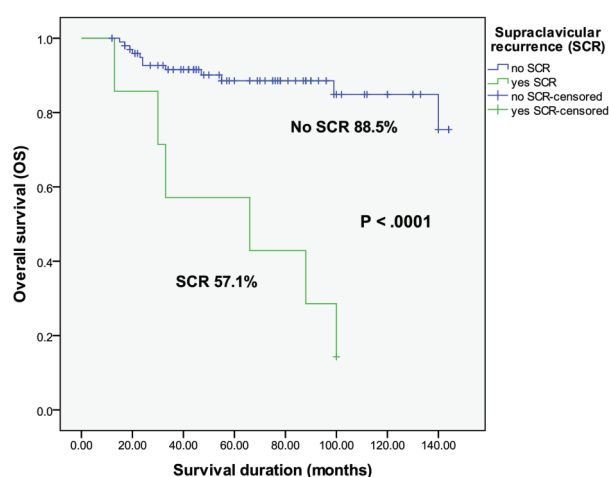


Figure 1. The five-year overall survival (OS) in relation to supraclavicular recurrence (SCR) of 109 patients with N1 breast cancer after modified radical mastectomy (MRM) or breast conserving surgery (BCS) and adjuvant chemotherapy without supraclavicular radiotherapy (S/C RT).

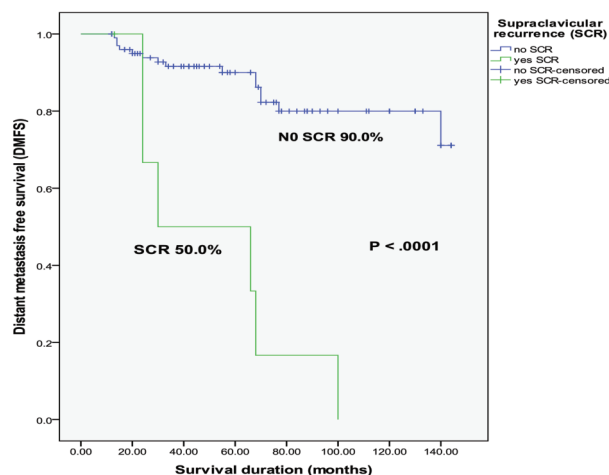


Figure 2. Distant metastasis free survival (DMFS) in relation to supraclavicular recurrence (SCR) of 109 patients with N1 breast cancer after modified radical mastectomy (MRM) or breast conserving surgery (BCS) and adjuvant chemotherapy without supraclavicular radiotherapy (S/C RT).

than 4 positive axillary nodes without the use of radiation therapy.⁷⁻¹⁰ Yu et al.¹⁹ detected a supraclavicular recurrence rate of 7.2% which was the most common LRR site followed by the breast/chest wall which constituted 2% among 18 patients who experienced LRR and did not receive SCRT. In our study there was no regional failure other than the supraclavicular fossa. Katz et al.¹⁶ reported low rates of regional failure other than the supraclavicular fossa (10% axillary failure and 10% internal mammary nodal failure). The Danish trial reported an axillary failure of 45%, which might be due to inadequate axillary dissection performed in this trial (the median number of nodes removed was 7 compared with the median number of 14 in the current study).¹

The 5-year SCRFS was 84.9%, for DMFS it was 87.6% and 86.4% for OS. Yu et al.²⁰ reported similar DMFS (85.7%), but higher 5-year SCRFS (92.6%) and OS (94.4%). This difference might be due to the higher percentage of pT3 tumors in the current study (37.6%) compared to the study by Yu et al. (2.9%). In our study SCF resulted in statistically significant decreased OS at five-year (57.1% vs. 88.5%, $P < 0.0001$) and decreased DMFS at five-year (50.0% vs. 90.0%, $P < 0.0001$) compared to patients without SCF. Yu et al.²⁰ have reported significantly decreased five-year DMFS (43.9%) and OS (7.9%) rates for patients with SCR ($P < 0.0001$). It is not known whether the addition of S/C RT can prevent subsequent development of distant metastasis and subsequently translation into better OS or not.

Several retrospective studies have identified prognostic factors for SCLR in breast cancer patients with 1-3 positive lymph nodes. Some of these studies consequently divided their patients into risk groups and suggested that patients with high risk might benefit from SCRT regarding locoregional control and survival.^{9,20-23} A univariate analysis of our study revealed that age, tumor stage, number of involved nodes, number of dissected nodes, hormone receptor status, presence of extracapsular extension, and lymphovascular invasion were not significant prognostic factors of SCRFS. The type of

chemotherapeutic regimens, however, was the only significant prognostic factor of SCRFS in our cohort; patients who received CMF experienced lower SCRFS than those who received doxorubicin based and taxane based chemotherapy ($P < 0.0001$). The impact of chemotherapy on locoregional failure rates has varied among randomized trials involving patients with positive nodes. Some have shown reductions in failure rates of one-third to one-half lower than the incidence in the control arms,²⁴⁻²⁷ whereas other trials detected minimal to no reduction.^{28,29} Yu et al.¹⁹ reported by multivariate analysis that taxol, adriamycin, cyclophosphamide TAC chemotherapy regimen was an independent factor for better locoregional recurrence free survival, distant metastasis free survival and overall survival. However, most published retrospective studies reported several prognostic factors other than type of chemotherapy regimens. Yu et al.²⁰ included 448 N1 breast cancer patients in their retrospective review and reported that LVI, ECE, the number of positive axillary lymph nodes, and level of involved axillary lymph nodes were significant factors for SCLR by univariate and

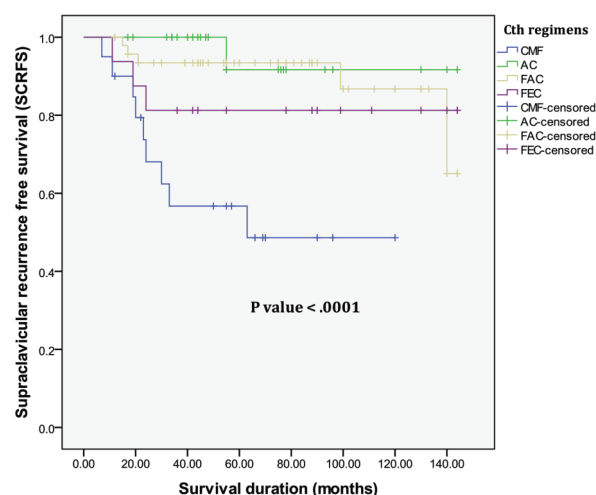


Figure 3. The five-year supraclavicular recurrence free survival (SCRFS) according to types of chemotherapeutic regimens of 109 patients with N1 breast cancer after modified radical mastectomy (MRM) or breast conserving surgery (BCS) and adjuvant chemotherapy without supraclavicular radiotherapy (S/C RT). CMF: cyclophosphamide, methotrexate, 5-fluorouracil; AC: / Taxol, adriamycin, cyclophosphamide, taxol; FAC: 5-fluorouracil, adriamycin, cyclophosphamide; FEC: 5-fluorouracil, epirubicine, cyclophosphamide.

multivariate analysis. Yates et al.²² performed a retrospective review of 1065 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 nodes, histologic grade, and hormone receptor status were associated with SCLR on univariate analysis. On multivariate analysis, histologic grade and number of positive axillary lymph nodes were the only significant prognostic factors. Kong and Hong²³ found that histologic grade, number of dissected axillary lymph nodes, LVI, ECE, and adjuvant chemotherapy were significant prognostic factors associated with SCLR on univariate analysis. On multivariate analysis, histologic grade and ECE remained significant factors for SCLR. Our results were inconsistent with most published retrospective studies that analyzed the predictive factors of SCR in N1 breast cancer patients. The reason that we had only the type of chemotherapeutic regimen as a significant prognostic factor for SCRFS compared to other studies might be the small sample size, a relatively short follow up time, and retrospective nature of the study.

The first limitation of our study was the fact that information about some patients was incomplete in view of the retrospective nature of the study. This required omission of these patients and led to a relatively small number of patients that were included in the current study. Second, we could not analyze some predictive factors for SCR such as the involved level of axillary lymph nodes because their detection rates in our institute were low. Third, this study included only patients who were evaluated and treated at South Egypt Cancer Institute (SECI), which might not reflect the entire population in Egypt. Fourth, the follow up duration might have been too short and consequently this study might have underestimated the rate of treatment failure. However the data collected in our setting would need to be addressed in order to deliver the optimal treatment for breast cancer patients with pathologic N1 after MRM or BCS and adjuvant systemic therapy in our local setting.

Our analysis of recurrence patterns and survival in 109 breast cancer patients treated with MRM or BCS and adjuvant systemic therapy without postoperative supraclavicular radiotherapy revealed an isolated supraclavicular failure rate of 1.8% along with the following rates: OS (86.4%), SCRFS (84.9%), and DMFS (87.6%). Supraclavicular node recurrence had a significant association with poor OS and DMFS which suggested the need for prevention of SCR. Although the role of S/C RT in patients with N1 disease has not been clearly defined, S/C RT may be necessary and worth the risk of treatment morbidity regarding patients in whom adjuvant CMF regimen is administered as it is a significant prognostic factor for treatment failure. Whether S/C RT offers an advantage in patients that receive optimal systemic adjuvant therapy is unclear. A prospective randomized trial is needed to clarify the effect of S/C RT on OS and whether or not S/C RT can reduce the rate of distant metastasis.

Conflict of Interest

No conflict of interest is declared.

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