Prognostic factors for supraclavicular relapse in N1 breast cancer patients. May that judge the need for supraclavicular irradiation?

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Abstract: Background: Post-mastectomy radiation therapy (PMRT) for patients with Stage II and III breast cancer has shown a significant benefit in locoregional control, disease free survival, and overall survival. However, the issue of those patients with 1-3 positive lymph nodes (LNs) should receive PMRT and, if so, to what volumes, remains a controversy among radiation oncologists. In the current study, we evaluated the prognostic factors for supraclavicular relapse in N1 breast cancer patients that may judge the need for supraclavicular radiation therapy (SCRT) **Methods:** This is a retrospective study conducted at Clinical Oncology department, Tanta University Hospital, between Jan. 2001 and December 2007. The study included 113 female breast cancer patients treated with breast conserving surgery (BCS) or modified radical mastectomy (MRM) and axillary evacuation. All patients had pathologically proved breast cancer with T1-T3 N1 M0 tumors. MRM was performed in 66.4% of patients and axillary LN dissection was performed in all patients. Chest wall irradiation after chemotherapy is given for patients who underwent BCS, patients with high risk T2 and T3 tumor size. Eighty-seven patients received adjuvant chemotherapy and patients with positive hormonal receptors received hormonal therapy for 5 years. **Results:** Overall locoregional relapse rate (LRR) was 16.8% and supraclavicular relapse (SCR) was 9.7%. The overall 5-year supraclavicular recurrence free survival (SCRFS) rate was 90.15%. In univariate analysis, SCRFS rate was significantly correlated to tumor size (p<0.0001), number of positive axillary LNs (p=0.0006), percentage of +ve axillary LN (p=0.002), extracapsular extension (ECE) (p=0.0001) and lymphovascular invasion (LVI) (p=0.003). Tumor size, percentage of +ve axillary LN and ECE were independent prognostic factors in multivariate analysis for SCRFS (p=0.011, 0.004 and 0.036 respectively). Accordingly, patients were classified into 2 groups; the low risk group (0-1 prognostic factor) and the high risk group (2-3 prognostic factors). Low risk group had a 5-year statistically significant benefit in SCRFS rate (97.6% and 68.97% respectively, p<0.0001). **Conclusion:** SCRT is recommended for patients with N1 who had ≥2 independent prognostic risk factors.
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Key words: Breast cancer, Supraclavicular recurrence, Prognostic factors**,** Supraclavicular radiation therapy.

1. Introduction

Breast carcinoma is the most common tumor among women. Multiple biological, pathological and clinical features correlated with outcome in patients with invasive breast cancer. Metastatic spread to regional lymph nodes (LNs) is one of the earliest event of tumor dissemination and presented an important significant factor for predicting survival in breast cancer.[1, 2]

The Danish and the British Columbia trials showed that postoperative radiation therapy (RT) improved locoregional control and overall survival in breast cancer patients. Locoregional recurrence (LRR) rates in N1 and N2 patients who were treated with mastectomy without adjuvant RT was ranged from 21% to 27% and from 41% to 51%, respectively, the LRR rate reduced to 7% to 10% when RT was considered.[3-5]

The National Comprehensive Cancer Network (NCCN) guidelines recommend that supraclavicular radiation therapy (SCRT) as a necessary treatment for patients with N2 breast cancer after surgery. However, SCRT is strongly considered for patients with N1 breast cancer if postoperative radiotherapy is indicated.[6]

Many authors studied patients with N0 and N1 breast cancer and did not receive SCRT, supraclavicular nodal recurrence rates was 1% to 8% [7-10]. National Institute for Health, recommended SCRT for N1 patients if they have poor prognostic factors (T3 or grade 3) and a good performance status [11]. There has been considerable debate and controversy regarding the use of SCRT for N1 breast cancer patients as some patients may get benefit.[12]

In the current study, we evaluated the prognostic factors for supraclavicular relapse in N1 breast cancer patients that may judge the need for SCRT

2. Patient and Methods

This is a retrospective study conducted at Clinical Oncology department, Tanta University Hospital, between Jan. 2001 and December 2007. The study included 113 breast cancer patients treated with breast conserving surgery (BCS) or modified radical mastectomy (MRM) and axillary evacuation. All patients had pathologically proved breast cancer with 1 to 3 positive axillary nodes (N1) and tumor size of T1-T3 with no evidence of

metastatic disease (M0). Patients received neoadjuvant therapy were excluded from the study. Modified radical mastectomy was performed in 75 patients (66.4%), and BCS was performed in 38 patients (33.6%). Axillary LN dissection was performed in all patients, with a median of 12 nodes (range, 2-31 nodes) dissected. Chest wall irradiation after chemotherapy was given for patients underwent BCS, patients with tumor size of T2 with high risk factors (lymphovascular invasion "LVI", extracapsular extension "ECE" and age <35 years) and T3 tumor size. Patients who received RT were planned through 2-D simulator-planning system and received irradiation to the breast and chest wall through two tangential fields without SCRT. Dose of 50 Gy was delivered in five weeks, 2 Gy daily for five days per week. Eighty-seven patients received adjuvant chemotherapy in the form of CMF (cyclophosphamide 600mg/m^2, methotrexate 40 mg/m^2, and 5-FU 600 mg/m^2), FAC (5-FU 500 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2) or FEC (5FU 500 mg/m^2, epirupcin 100 mg/m^2 and cyclophosphamide 500 mg/m^2). All the chemotherapy regimens were administrated intravenously for average 4-6 cycles. Patients with positive hormonal receptors received hormonal therapy for 5 years.

Statistical analysis

Supraclavicular recurrence–free survival (SCRFS) rate and distant metastasis–free survival (DMFS) rate were calculated from the date of pathological diagnosis to the date of event or the date of the last follow-up visit. Overall survival (OS) rate was measured from the date of pathological diagnosis to the date of death or to the date of the last follow-up visit. Survival rates were statistically analyzed by the use of log-rank test where the *p* value considered statistically significant if < 0.05. We estimated SCRFS, DMFS, and OS rates using the Kaplan-Meier method. A multivariate survival analysis was performed by use of a Cox proportional hazards model. All statistical analyses were performed with the SPSS System (version 17)

3. Results

The median age for all patients was 50 years with age ranged from 24 to 75 years. We had 10 patients (8.8%) ≤35 years while patient aged >35 years were 103 (91.2%). Thirty-four patients (30.1%) had tumors located in the inner quadrant and central location while 69.9% (79 patients) were in the outer quadrant. As regards the pathology, 91.2% of patients were invasive duct carcinoma (IDC, 103 patients) while only 10 patients (8.8%) presented with invasive lobular carcinoma (ILC). Tumor grade I&II presented in 78.8% of patients while grade III were 21.2%. We had 17.7% of patients presented with T1, 59.3% with T2 and 23% with T3. The median number of LNs retrieved was 12 (range 2 to 31). Thirty-nine patients (34.5%) presented with 10 or less retrieved LNs while 65.5% of patients presented with >10 retrieved LNs. Thirty-six patients (31.9%) had one pathologically positive LN, 39.8% (45 patients) had 2 +ve LNs and 28.3% (32 patients) had 3 +ve LNs. Extra-capsular extension was recorded in 23.9% of patients. As regard to LVI; 10.6% of patient were not reported (unknown) and 35.4% of patients were reported to have +ve LVI. Hormonal receptors status was not reported (unknown) in 7% of patient and 73.5% of patients reported to have +ve hormonal receptors, Table (1).

Eighty-two patients (72.6%) received adjuvant RT without SCRT while 27.4% of patients (31 patients) received no RT. Adjuvant chemotherapy was administrated in 77% of patients and 78.8% of patients received hormonal therapy.

Overall locoregional recurrence rate (LRR) in our study was 16.8% (19 patients) and supraclavicular relapse was 9.7% (11 patients). The overall 5-year SCRFS was 90.15%, Figure (1). In univariate analysis, SCRFS was significantly correlated to tumor size (p<0.0001), number of positive axillary LNs (p=0.0006), Percentage of +ve axillary LN (p=0.002), ECE (p=0.0001) and LVI (p=0.003). Tumor size, percentage of +ve axillary LN and ECE were independent prognostic factors in multivariate analysis of SCRFS (p= 0.011, 0.004 and 0.036 respectively), Table (2).

The 5-year DMFS rate among all patients was 80.46%. There was a statistically significant difference as regard 5-year DMFS rate between patients with SCR (22.73%) and patients without SCR (86.25%) (p<0.0001), Figure (2, 3).

The 5-year overall survival rate among all patients was 88.45%. There was a statistically significant difference as regard 5-year OS rate between patients with SCR (41.56%) and patients without SCR (93.14%) (p<0.0001), Figure (4, 5).

According to tumor size, percentage of +ve axillary LN and ECE, patients were classified into 2 groups; the low risk group (0-1 prognostic factor) and the high risk group (2-3 prognostic factors). There was a significant difference in SCRFS rate between the 2 groups (97.6% and 68.97% at 5-year respectively, p<0.0001), Table (3), Figure (6). There was also a statistical significant difference of the DMFS and OS rates according to risk score (p=0.0185 and p=0.0104 respectively), Figure (7 & 8).

Table (1): Patient and Treatment Characteristics

Factors		Patients (n, %)
Age *	≤35	10 (8.8)
	>35-60	78 (69)
	>60	25 (22.2)
Menestrual status	Menstruating	52 (46)
	Menopause	61 (54)
Location	Outer	79 (69.9)
	Inner	34 (30.1)
Pathology	IDC	103 (91.2)
	ILC	10 (8.8)
Pathological grade	I-II	89 (78.8)
	III	24 (21.2)
Tumor size (T)	1	20 (17.7)
	2	67 (59.3)
	3	26 (23)
Removed LN **	≤10	39 (34.5)
	>10	74 (65.5)
Positive LN	1	36 (31.9)
	2	45 (39.8)
	3	32 (28.3)
% of positive axillary LNs	≤20%	76 (67.3)
	>20%	37 (32.7)
Extracapsular extension	Yes	27 (23.9)
	No	86 (76.1)
Lymphovascular invasion	Yes	40 (35.4)
	No	61 (54)
	Unknown	12 (10.6)
Hormonal receptors status	+ve	83 (73.5)
	-ve	22 (19.5)
	Unknown	8 (7)
Surgical interference	Conservative	38 (33.6)
	MRM	75 (66.4)
Radiation therapy	Yes	82 (72.6)
	No	31 (27.4)
Chemotherapy	Yes	87 (77)
	No	26 (23)
Hormonal therapy	Yes	89 (78.8)
	No	24 (21.2)

* Median age 50 years, Mean age 50.35±11 years, range 24-75
**Median 12 LNs, range 2-31

Table (2): Factors affecting 5-year supraclavicular recurrence–free survival

		Univariate		Multivariate	
		5-year	p-value	p-value	HR (95% CI)
Age	≤35	76.19	0.2097	-	
	>35	91.24			
Menstrual status	Menstruating	90.06	0.9848	-	
	Menopause	90.16			
Location	Outer	92.27	0.2474	-	
	Inner	85.29			
Pathology	IDC	91.13	0.2232	-	
	Other	80.00			
Pathological grade	I-II	92.08	0.2506	-	
	III	83.33			
Tumor size (T)	1-2	96.50	**<0.0001**	**0.011**	5.48 (1.34-22.46)
	3	69.23			
Removed LN	≤10	84.30	0.1074	-	
	>10	93.20			
+ve LN	1-2	96.27	**0.0006**	0.279	
	3	74.64			
Percentage of +ve axillary LNs	≤20%	96.05	**0.0022**	**0.004**	6.28 (1.65-23.96)
	>20%	77.59			
ECE	Yes	70.37	**0.0001**	**0.036**	4.09 (1.00-16.68)
	No	96.50			
LVI	Yes	77.50	**0.0027**	0.349	
	No	98.36			
Surgery	Conservative	92.03	0.7077	-	
	MRM	89.28			
Hormonal receptors status	+	92.63	0.7875	-	
	-ve	90.91			

LN: Lymph node; ECE: extracapsular extension; LVI: lymphovascular invasion; HR (95%CI): Hazard ratio (95% confidence interval)

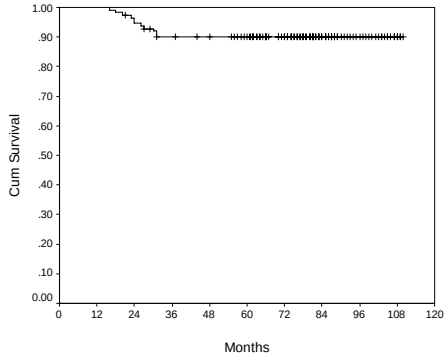

Fig. (1): SCRFS rate of all patients

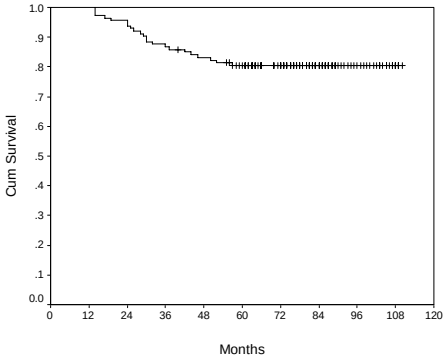

Fig. (2): DMFS rate of all patients

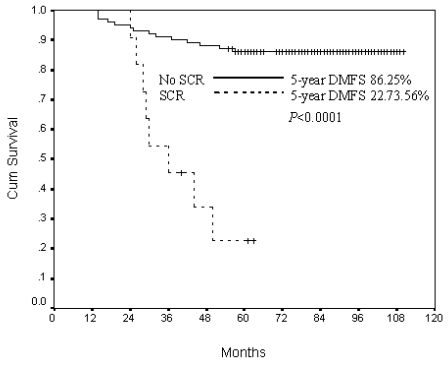

Fig. (3): DMFS rate according to SCR.

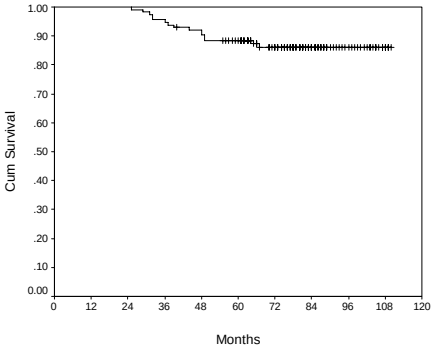

Fig. (4): OS rate of all patients.

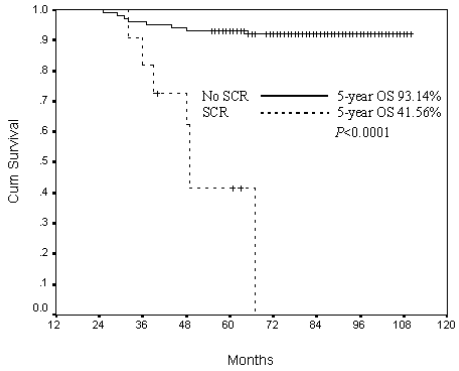

Fig. (5): OS rate according to SCR.

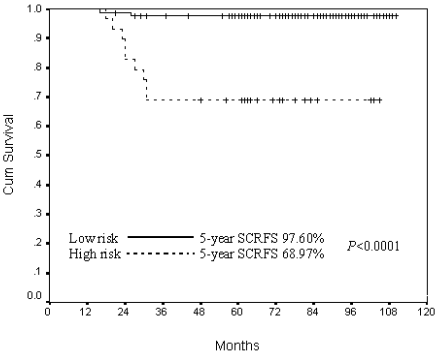

Fig. (6): SCRFS rate according to prognostic score.

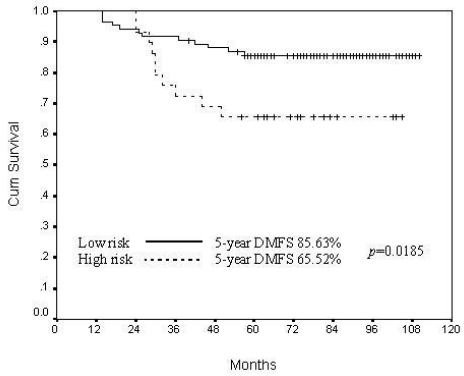

Fig. (7): DMFS rate according to prognostic score.

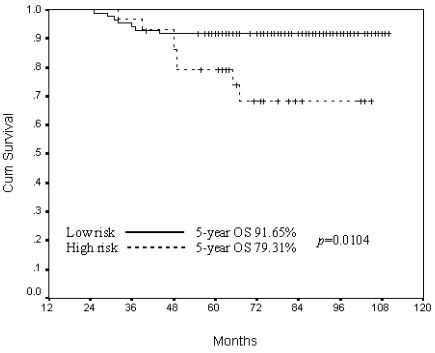

Fig. (8): OS rate according to prognostic score.

Table (3): 5-year supraclavicular recurrence–free survival according to prognostic score

Prognostic group	Score	No. of patients	5-year SCRFS	Median SCRFS (months)	*p*
Low risk	0-1	84 (74.3%)	97.60 %	77.8	<0.0001
High risk	2-3	29 (25.7%)	68.97 %	59.8	

4. Discussion

Post-mastectomy RT (PMRT) for patients with stage II and III breast cancer has shown a significant benefit in locoregional control, disease free survival (DFS), and OS [3-5]. However uncertainty exists regarding the selection of patients and RT volume [10]. PMRT for patients with ≥4 positive LNs with irradiated volumes include the chest wall (CW) and supraclavicular LN was advised for these patients [8, 13].

However, the issue of those patients with 1-3 positive LNs should receive PMRT and, if so, to what volumes, remains a controversy among radiation oncologists [14, 15]. The rationale of supraclavicular irradiation is that the addition of such adjuvant treatment would improve the survival of patients [16–18].

Overall LRR in current study was 16.8% with SCR encountered in (9.7%) of patients. The overall 5-year survival among all patients was 88.45%. There was a statistically significant difference as regard 5-year OS between patients with SCR (41.56%) and patients without SCR (93.14%) (p<0.0001). The overall 5-year SCRFS was 90.15%. In univariate analysis, SCRFS was significantly correlated to tumor stage (p< 0.0001), number of positive axillary LNs (p=0.0006), percent of positive axillary LNs (p=0.002), ECE (p=0.0001) and LVI (p=0.003). The 5-year DMFS among all patients was 80.46%. There was a statistically significant difference as regard 5-year DMFS between patients with SCR (22.73%) and patients without SCR (86.25%) (p<0.0001).

Yu et al [12] evaluated the prognostic factors for DMFS, OS and SCRFS rates among N1 breast cancer patients. They reported that the DMFS and OS rates were 85.7% and 94.4%, respectively, at 5 years and 79.6% and 86.2%, respectively, at 10 years. The DMFS and OS rates decreased significantly for those with LRR and supraclavicular recurrence (p<0.0001). The absolute decrements in the 5-year DMFS and OS rates were 44.7% and 7.4%, respectively, for patients with supraclavicular node recurrence. The SCRFS rates were 92.6% and 89.5% at 5 and 10 years, respectively. On multivariate analysis, lymphovascular invasion (LVI) (p<0.0001), number of involved axillary nodes (p=0.0003), level of involved axillary node (p=0.012), and ECE (p<0.0001) showed statistically significant effects on SCRFS.

Chen et al [19] reported the factors of significance for LRR in post-mastectomy patients with 1-3 positive axillary LNs without RT; which were age <40 years (p=0.006), tumor size >3 cm (p=0.002), negative ER status (p=0.02), presence of LVI (p=0.02), and no tamoxifen treatment (p=0.0006). In multivariate analysis, only tumor size remained statistically significant (p=0.006). On the basis of the 4 patient-related factors (age <40 years, tumor >3 cm, negative ER, and LVI), the high-risk group (with 3 or 4 factors) had a 4-year LRR rate of 66.7% compared with 7.8% for the low-risk group (with 0–2 factors; p<0.0001). For patients who received no adjuvant RT, LRR was associated with a 4-year distant metastasis rate of 49.0%. For patients without LRR, it was 13.3% (p<0.0001). The 4-year survival rate for patients with and without LRR was 75.1% and 88.7% (p=0.049), respectively.

In our study, tumor stage, percent of positive axillary LNs and ECE were independent prognostic factors in multivariate analysis of SCRFS (p= 0.011, 0.004 and 0.036 respectively). Patients were classified into 2 groups according to the number of prognostic factors; the low risk group (0-1 prognostic factor) and the high risk group (2-3 prognostic factors). There was a significant difference in SCRFS rate between the 2 groups (97.6% and 68.97% at 5-year respectively, p<0.0001).

Livi et al [20] reported that patients with >3 positive axillary nodes had a higher incidence of SCR compared with patients with ≤3 positive nodes. However, SCR is infrequent even in patients with N2 stage (5.5%). So, they suggested that SCR seems not to influence the outcome and distant metastasis was the only independent prognostic factor for breast cancer survival.

Macdonald et al [21] retrospectively analyzed 238 patients with 1-3 positive LNs treated with mastectomy. LRR and DFS were significantly improved by PMRT, with a 5- and 10-year LRR rate without PMRT of 6% and 11%, respectively and, with PMRT, of 0% at both 5 and 10 years (p=0.02). The 5- and 10-year DFS rate without PMRT was 85% and 75%, respectively, and, with PMRT, was 93% at both 5 and 10 years (p=0.03). A similar benefit was found for patients treated with RT to the CW alone. The LRR, DFS, and OS rate for patients treated to the CW only was 0%, 96%, and 95% at 10 years, respectively. They suggest that adjuvant PMRT to the CW alone provides excellent disease control for patients with breast cancer <5 cm with 1-3 positive LNs.

Stranzl et al [22] evaluated 274 patients with 1-3 positive axillary LNs, and concluded that LRR remains low in breast cancer patients (1-3 positive

axillary LNs +/- ECE) treated with surgery, adequate axillary dissection, and tangential field irradiation only. However, ECE is significantly linked to a considerable risk for subsequent distant failure.

In conclusion, tumor stage, percent of positive axillary LNs and ECE were independent prognostic factors for supraclavicular recurrence in breast cancer patients with 1-3 positive axillary LNs treated without SCRT. So, this study suggests that patients presented with ≥2 prognostic factors will gain statistical significant benefit from the addition of supraclavicular irradiation to chest wall irradiation as regard to SCRFS, DMFS & OS rates. However, further multicenter studies with a large number of patients still needed to judge the need for SCRT.

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