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Long-Term Outcome for Patients with Isolated Supraclavicular Nodal Recurrence After Mastectomy and Doxorubicin-Based Chemotherapy for Breast Cancer

Jay P. Reddy, BS¹, Larry Levy, MS², Julia L. Oh, M.D.², Eric A. Strom, M.D.², George H. Perkins, M.D.², Thomas A. Buchholz, M.D.², and Wendy A. Woodward, M.D., Ph.D.²

¹Department of Molecular & Cellular Biology, Baylor College of Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, TX

²Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

Purpose—To examine the outcome of patients who developed an isolated locoregional recurrence (LRR) involving the supraclavicular fossa (SCV) after initial treatment with modified radical mastectomy and chemotherapy.

Methods—Records from 140 breast cancer patients treated on 5 prospective trials with mastectomy and doxorubicin-based chemotherapy +/- radiation who developed a LRR were reviewed. Kaplan-Meier survival times were calculated using date of LRR as time zero.

Results—The median follow-up following LRR was 2.9 years (N = 140; interquartile range [IR] 1.3–6.6 years). 47/140 patients (34%) had a SCV component to their LRR. These patients had lower 3 yr DMFS (40% vs. 54%, P = 0.003) and OS (49% vs. 69%, P = 0.04) than patients without a SCV component. Multivariate analysis revealed that LRR involving a SCV component (hazard ratio [HR] 1.96, P=0.004) and patients with lymphovascular space invasion in their primary tumors (HR 1.65, P = 0.029) were independently associated with a poor DMFS. However, among 23 patients with isolated SCV recurrence OS was not statistically different between isolated chest wall recurrence and isolated SCV recurrence. Patients with isolated SCV recurrence displayed a median follow-up of 3.3 years (IR 1.2–5.2). Only 6 LRR of 23 patients were treated with aggressive local therapy, including surgery, chemotherapy, and radiation (alone or in combination).

Conclusions—Although breast cancer recurrence with SCV involvement carries a high risk of DM and death, among women with recurrence limited to the SCV alone, overall survival after isolated SCV recurrence can be long (25% > 5 years).

Keywords

Breast cancer; locoregional recurrence; supraclavicular fossa; radiation

INTRODUCTION

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has demonstrated a direct relationship between prevention of locoregional recurrence (LRR) and overall survival for breast cancer (1). However, patients who present with LRR are potentially curable and as such, additional data are needed to determine which subsets of patients warrant attempts at salvage therapy. A recent report demonstrated that among patients with an isolated chest wall recurrence, time to recurrence (greater than 24 months) and node negative status at presentation were strong predictors of longer survival (2). Such findings confirm that a subset of patients with LRR can be salvaged.

One manifestation of LRR, the recurrence of positive lymph nodes in the supraclavicular fossa (SCV), has been considered to foretell an especially poor outcome; however, the outcome for patients with recurrence in the SCV has not been explicitly reported. Until recently nodal involvement of the SCV fossa at presentation was considered to be distant metastatic disease (M1) and subsequently treated with palliative intent. However, data show that aggressively treating patients with SCV disease at the time of original diagnosis have an improved overall survival to rates comparable to patients without metastatic disease (Stage IIb) (3), and in 2002 the staging system was revised to classify primary SCV disease as Stage III. Data from our institution suggest that such patients have a 32% overall survival (OS) at 10 years with this presentation (4). In this study we examined the outcomes and treatment strategies of patients who developed a LRR with a SCV component when treated with modified radical mastectomy and a doxorubicin-based chemotherapeutic treatment regimen and we similarly found that a subset of patients can have long overall survival.

PATIENTS AND METHODS

Patient, Tumor, and Treatment Characteristics

Between 1975 and 1994, 1805 patients were treated with doxorubicin-based adjuvant systemic therapy with or without tamoxifen in five prospective clinical trials at The University of Texas M. D. Anderson Cancer Center (5–10). Each protocol was reviewed and approved by the institutional review board, and participants gave written informed consent. For this study, we reviewed the records of 462 patients (including 8 cases of bilateral breast cancer for a total of 470 cases) who received post-mastectomy radiation therapy and 1,031 patients who did not receive radiation. In this group, 140 patients developed isolated LRR, which represent the cohort for this study. In prior analysis of the British Columbia Cancer Agency randomized data from the post-mastectomy radiation versus none trial (11), we compared outcomes among patients who experienced a LRR after post-mastectomy radiation to those who experienced a LRR after mastectomy alone and demonstrated no difference in overall survival based on prior post-mastectomy radiation (12). The same was observed for isolated LRR in the patient cohort being examined herein in spite of the non-randomized use of post-mastectomy being associated with higher risk characteristics of the presenting disease in these data (12). For this reason, the patients who had prior post-mastectomy radiation and those who did not were combined for this analysis. Of this total group, 47 cases involved a SCV component of their LRR, and 23 of which developed isolated SCV LRR. These 47 cases were further reviewed for treatment details after the local

recurrence. The remaining 312 patients treated on these trials were treated with breast conserving surgery and were not analyzed in this report.

Details regarding the patients and treatments on the trials have been previously reported (13–16). Briefly, patients over the age of 75 years, those with evidence of distant dissemination at diagnosis, and those with a prior or concurrent malignancy were excluded. Pathology information for this study was obtained from report from the review at our institution, which was done prior to treatment for all patients. Pathology materials were not specifically reexamined for the purpose of this study. Pathologic tumor size was determined from the report of the surgical specimen. All patients underwent mastectomy prior to adjuvant systemic therapy and no patient received neoadjuvant chemotherapy. Patients were then randomly assigned to one of several chemotherapy regimens. Each protocol stipulated a minimum of 6 cycles of a doxorubicin-containing regimen and a minimum doxorubicin dose of 40–50 mg/m² per cycle. For the patients who received radiation at the time of original diagnosis, the median radiation dose to the chest wall was 50 Gy, delivered with Co60 or electrons, except 13 cases that were treated with 6 MV photons. The post-mastectomy irradiation typically targeted the chest wall, internal mammary lymph nodes, and supraclavicular lymph nodes. Techniques used to target the chest wall often provided coverage of the level I and level II axilla, although this is not a specified target. Additionally, patients routinely receive a chest wall boost, which included the mastectomy scar with generous margins. The median dose to the chest wall including the chest wall boost was 55 Gy (interquartile range 50–60 Gy). The median dose to both the internal mammary lymph nodes and supraclavicular lymph nodes was 50 Gy (interquartile range 50 – 50 Gy). Dose information was available for 351 cases. Radiation treatment was delivered at an outside institution in 167 cases.

Follow-up

Patient follow-up consisted of physical examination, routine laboratory studies, chest radiographs, mammogram of the remaining breast, and bone scans, according to protocol guidelines. Ultrasound and computerized tomography (CT) were not routinely ordered during the follow-up period but were performed when indicated to further evaluate clinical findings consistent with possible recurrence. CT technology was not available for routine clinical use at M. D. Anderson Cancer Center before the early 1980s and was not used systematically for some time after this.

Endpoints and Statistical Analysis

LRR was defined as recurrence on the ipsilateral chest wall, or in axillary, supraclavicular, infraclavicular, or internal mammary nodes. Recurrence at any other site was considered distant metastasis. Three-year actuarial rates of overall survival, disease-free survival, and isolated LRR were calculated according to the Kaplan-Meier method, with comparisons among groups performed using two-sided log-rank tests (17, 18). Isolated LRR was defined as any LRR without prior or simultaneous distant metastases. Isolated SCV recurrence explicitly excluded LRR on the chest wall or other draining lymphatics in addition to the SCV recurrence. Multivariate analysis was performed using the Cox proportional hazards

model. Outcomes were calculated using the date of LRR as time zero. All P values were two-tailed, with values of 0.05 considered to be significant (18).

RESULTS

Of 1500 patient records examined, 140 patients developed isolated LRR. The median age at the time of diagnosis was 51 years (range 25–74 years). 87 patients (62.1%) were white, 21 (15%) were Hispanic, 13 (9.3%) were black, and the remaining 19 patients (13.6%) were of unknown ethnic origin. Primary tumor characteristics are described in Table 1. The median follow-up time following diagnosis of LRR was 2.9 years (interquartile range [IR] 1.3–6.6 years, maximum 16 years). Overall survival (OS) and distant metastasis-free survival (DMFS) from the time of recurrence for patients with any LRR (N = 140) at 3 years were 62% and 47.5%. Of the 140 patients who developed a LRR, 47 (34%) had a SCV component. These patients had a lower 3 yr DMFS (40% vs. 54%, $P = 0.003$) and OS (49% vs. 69%, $P = 0.04$) compared to the patients without a SCV component (Figure 1). In multivariate analysis that considered factors related to the primary tumor and LRR, patients with LRR involving a SCV component (hazard ratio [HR] 1.96, $P = 0.004$) and patients with LVSI+ primary tumors (HR 1.65, $P = 0.029$) were independently associated with a poor DMFS, confirming that LRR with SCV involvement often indicates a poor prognosis. Similar results were seen for OS (Table 2). Time to LRR and use of post-mastectomy radiation did not predict for worse outcome after LRR. Grade was not included in the model due to the large number of unknowns in this variable.

The 23 patients with an isolated SCV recurrence had a lower 3-year DMFS as compared to patients with LRR involving only the chest wall (Table 3). The 3 -year DMFS survival rates were 56% for chest wall only recurrence, 41% for SCV only, and 30% for LRR involving multiple sites (24/31 of these cases also involved the SCV, $P = 0.021$ between chest wall and SCV, 0.0025 between chest wall and multiple sites, and 0.5299 between isolated SCV and multiple sites; Figure 2). However, OS was not statistically different between the patients with isolated chest wall recurrence and those with isolated SCV recurrence (Figure 2). Patients with isolated LRR involving multiple sites had lower OS with 3-year rates of 73%, 60%, and 30%, for chest wall, SCV and multiple site recurrences respectively ($P = 0.0002$ between chest wall and multiple sites, else NS, Figure 2). Excluding the cohort who received post-mastectomy radiation as a component of their primary cancer treatment yields similar results for DMFS and OS (data not shown), although the difference in the 3 year DMFS for isolated chest wall vs. isolated SCV is smaller and not statistically significant (57% vs. 50%, $p = .099$). LRR isolated to the axilla, infraclavicular nodes or internal mammary nodes only occurred in 9 patients. There was no observed difference in ethnicity, hormone therapy, LVSI, grade, ER status, stage, or nodal status between the 23 cases with isolated SCV recurrence and the remaining 24 patients with LRR with some SCV component ($P = \text{NS}$). Patients with isolated SCV recurrence displayed a median follow-up time of 3.3 years [Interquartile range, 1.2–5.2 years]. Therefore, 25% of patients with isolated SCV recurrence lived longer than 5 years after SCV recurrence.

Treatment of patients with isolated SCV LRR was individualized and varied considerably based on physician preference and prior therapy. Only three patients with SCV LRR had

received radiation to the SCV fossa as a component of their primary therapy, and only 6 of 23 patients were treated with aggressive local therapy at the time of their LRR. These treatments included surgery, chemotherapy, and radiation (alone or in combination, Table 4). Of the patients who received no local salvage therapy, 18% (3/17), were DM-free at last follow-up and 41% (7/17) were alive (median follow up 82 months). 33% (2/6) of patients receiving either surgery or radiotherapy were DM-free at last follow-up and 50% (3/6) were alive (median follow-up was 68 months).

DISCUSSION

In this study, we report that patients with isolated SCV recurrence can exhibit a long OS even though SCV recurrence is classically considered to predict a poor outcome. Indeed, we demonstrate that LRR with a SCV component has a significantly lower DMFS and OS than LRR at other sites, confirming prior observations that SCV involvement carries a poor prognosis. Despite this finding, recurrence in the SCV does not always lead to immediate death and as such these patients should be considered candidates for aggressive local therapy with curative intent.

The largest study of LRR after breast cancer reported the outcome of 2,669 women treated with lumpectomy on five randomized trials of node positive patients reported a 5-year OS of 24% for patients who experienced a LRR outside of the breast (19); however, this study did not examine distinct subsites of locoregional failure. A recent study by Chagpar and colleagues demonstrated that, when stratified on several criteria, a subset of patients with LRR of the chest wall after mastectomy do exhibit relatively long DMFS and OS (2). These criteria include initial node negativity at presentation, greater than 24 months to initial recurrence (of the chest wall), and treatment with radiotherapy. A similar report of patients with isolated axillary recurrence after breast conserving therapy reported good salvage with a 5-year OS of 70% (20). The most recent study of prognosis after breast conserving therapy and LRR reported 5-year OS of 68% for 29 patients with regional nodal failures including 5 isolated supraclavicular recurrences (21). The current study is the largest series to report specifically on the cohort of patients with regional recurrence in the SCV after mastectomy. Although recurrence including the SCV as a component does portend a poor prognosis, consistent with reports regarding curability of patients with SCV nodes at presentation, we found that patients 25% of patients with isolated SCV recurrence (n=23) were still alive at 5 years. Despite this, only six patients received local salvage therapy in some form, 3 of which received radiation. The cohort in this study was treated before the era of positron emission tomography (PET) scanning, a sensitive study for detecting occult macrometastases, which may help to select patients who truly have isolated local disease from those with disease not detected with CT and bone scan alone.

The small number of patients who received local therapy as well as numerous confounding factors do not allow for comparisons of outcome in this group by treatment. In addition, although prior analysis suggests the use of post-mastectomy radiation does not lead to more aggressive LRR (12), the small number of isolated SCV LRR after post-mastectomy radiation make it difficult to generalize to this setting. Indeed, all patients who experience an isolated SCV recurrence after PMRT developed distant disease in less than three years.

Nevertheless, the above findings suggest the use of curative local therapeutic modalities, such as surgery or radiotherapy, in patients with isolated SCV recurrence should be considered for selected patients. This is especially true for patients who have not previously received radiation, in that radiation use has been previously shown to be associated with favorable outcome in patients with isolated chest wall recurrence (2).

In conclusion, LRR of multiple sites including a SCV component generally forecasts a poor outcome in breast cancer patients with the eventual appearance of distance metastases (DM) and death. However, some patients that present with isolated SCV recurrence may have biologically indolent disease and survive over 5 years. Such patients are often not treated aggressively with early radiotherapy or surgery at presentation but may benefit from such an approach. In the current treatment era, PET/CT may prove a useful imaging modality to identify patients with isolated recurrence who may be considered for more aggressive local therapy.

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Figure 1.
DMFS after LRR including or not including a supraclavicular (SCV) component.

Figure 2.
Distant metastasis-free survival (DMFS) and overall survival (OS) by site of LRR

Table 1

Patient and tumor characteristics.

Patients with LRR at any site (140)			Patients with LRR including SCV component (47)		
Characteristic	No.	%	Characteristic	No.	%
T stage ^a			T stage		
T1	26	18.6%	T1	13	27.7%
T2	65	46.4%	T2	21	44.7%
T3	26	18.6%	T3	5	10.6%
T4	1	0.7%	T4	1	2.1%
TX	20	14.3%	TX	7	14.9%
N stage			N stage		
N0	7	5.0%	N0	1	2.1%
N1	127	90.7%	N1	44	93.6%
N2	4	2.9%	N2	2	4.3%
Recurrent	2	1.4%	Recurrent	0	0%
Grade ^b			Grade		
1	7	5.0%	1	2	4.3%
2	46	32.9%	2	15	31.9%
3	39	27.9%	3	14	29.8%
None	89	63.6%	None	30	63.8%
Tamoxifen	43	30.7%	Tamoxifen	14	29.8%
ER status			ER status ^c		
			Negative	20	42.6%
			Positive	21	44.7%
			Lymphovascular invasion ^e		
			Absent	19	40.4%
			Present	24	51.1%

^aDoes not include 2 patients (1.4%) with recurrent disease.

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- ^b Nuclear grade was not specified in 48 patients (34%).
- ^c ER status was not known for 6 patients (12.8%).
- ^d Information was not available for 10 patients (7%).
- ^e Information was not available for 4 patients (8.5%).

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Table 2

Factors governing poor outcome.

		HR	P	95% CI
DMFS				
OS	LVI	1.65	0.029	1.05–2.59
	SCV	1.96	0.004	1.24–3.09
	LVI	1.82	0.011	0.045
	SCV	1.62	0.045	1.01–2.60

Table 3

Outcome of patients with LRR (by site).

Site	3 years		5 years		10 years	
	OS	DMFS	OS	DMFS	OS	DMFS
Chest wall only	73%	56%	57%	52%	37%	40%
SCV only	60%	41%	46%	30%	18%	12%
Multiple sites	30%	30%	22%	23%	0%	0%

Table 4

Treatment for Isolated SCV Recurrence

Treatment	No.
Observation	2
Hormonal therapy	8
Chemotherapy	2
Hormonal therapy + Chemotherapy or Surgery	2
Surgery + Chemotherapy	2
Surgery + Chemotherapy + Radiotherapy	2
Radiotherapy	1