Lymph Node Status and Breast Cancer-related Lymphedema

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Objective: This study examines the association between nodal positivity and risk of developing breast cancer-related lymphedema (BCRL) in patients who underwent axillary lymph node dissection (ALND).

Summary Background Data: The pathophysiology of BCRL is poorly understood. It has been assumed that one of the factors predisposing to the development of BCRL is nodal positivity, although retrospective series have produced contradictory findings. As these studies have included treatment regimens known to cause BCRL, such as axillary radiotherapy, any relationship between nodal positivity and the development of BCRL remains speculative.

Methods: A total of 212 patients who had undergone ALND for invasive breast cancer had arm volume measurements preoperatively, and at intervals postoperatively. No patient received axillary radiotherapy. Arm volumes were obtained by measuring serial arm circumferences every 4 cm up the arm and then calculated by using the formula for the volume of a truncated cone. Robust regression techniques were used to analyze the effects of node positivity, age, preoperative body mass index, and wound infection on arm volume excess.

Results: In all, 64 of 212 (30%) patients were node positive. Contrary to previous assumptions, positive node status was significantly inversely associated with arm volume after adjusting for tumor size, time since operation, and allowing for correlated observations within subjects. Furthermore, the number of positive nodes also correlated inversely with arm volume.

Conclusion: These results are counterintuitive to the conventional understanding of the pathophysiology of BCRL. A possible explanation is that patients who develop disease in axillary lymph nodes and subsequently undergo ALND have more time and ability to develop lymphatic collaterals, which may provide adequate lymphatic drainage following surgery, thereby reducing the risk of developing BCRL.

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Breast cancer-related lymphedema (BCRL) occurs as a consequence of surgery and/or radiotherapy to axillary lymph nodes. However, its pathophysiology is poorly understood and likely to be complex and multifactorial. The conventional view of the pathophysiology of BCRL is that axillary lymphatic obstruction resulting from surgical or radiotherapy treatment impairs lymph drainage from the ipsilateral arm. However, this model fails to explain a number of intriguing observations in BCRL. First, only a minority of women develop BCRL despite similar treatment. Second, the swelling is often regional and does not involve the whole arm. Lastly, BCRL may not become clinically manifest until years after surgery or radiotherapy.

Several studies have attempted to correlate clinicopathologic and treatment factors with the development of BCRL.[1–9] These have largely been retrospective with contradictory findings. It has been suggested that nodal positivity is a risk factor for the development of BCRL,[1–4] although published data are conflicting and have included confounding variables, so that any relationship between nodal positivity and the development of BCRL remains speculative is largely unproven.[5–9]

The aim of this study was to examine the association between nodal positivity and the risk of developing BCRL in patients who underwent axillary lymph node dissection (ALND).

PATIENTS AND METHODS

For the analysis, data from 2 separate studies on the relationship between ALND and BCRL were pooled. The first study was a prospective randomized controlled study (study 1) comparing morbidity following sentinel lymph node biopsy and ALND in primary breast cancer.[10] The second study was a prospective assessment of the axillary vein by Doppler ultrasound examination in patients undergoing ALND correlating venous changes with the development of BCRL.[11] Both studies were approved by the Local Ethics Research Committee, and all patients gave written, informed consent prior to participation.

In all, the data on 212 patients who had undergone ALND as part of treatment of primary breast cancer were analyzed (142 patients in study 1 and 70 patients in study 2). No patient underwent axillary radiotherapy following ALND. Objective assessment of arm swelling was performed by circumferential arm measurements at 4-cm intervals from the wrist. This yielded around 10 measurements (5 each for

forearm and upper arm, respectively), which were then used to calculate the limb volume using the formula for the volume of a truncated cone. This technique has previously been validated against the water displacement method to assess lymphedema and has been shown to have good correlation.[12–16] Changes in volume in the ipsilateral arm were corrected for changes in the contralateral arm. Measurements were undertaken preoperatively and 1, 3, 6, and 12 months postoperatively in patients in study 1, and preoperatively and 3 and 12 months postoperatively in patients in study 2.

Statistical Analysis

The arm volume excess was defined as the change in arm volume since preoperative measurement for the ipsilateral side, minus the same change on the contralateral side. Data were analyzed by linear regression and analysis of variance, adjusting for time since operation and taking into account the repeated measures on the same individuals. For the latter, linear regression analyses were performed, which allowed for correlations between observations on the same individual but which assumed observations on different individuals were independent.[17] Average arm volume changes were first compared between node-positive and node-negative subjects. We also estimated trends in arm volume changes with number of positive nodes. We first analyzed each study separately, so that the node-positive patients in study 1 were never directly compared with the node-negative patients in study 2, and vice versa, and so that in each study results were adjusted for the relevant number of repeat determinations (4 in study 1 and 2 in study 2). Because the tumors in the ultrasound study were significantly larger on average than those in the sentinel node study, we performed the analyses separately for tumors of size 20 mm or smaller and for tumors of size greater than 20 mm, then analyzed for all sizes combined, but adjusting for size in the regression models. The results were then combined by taking an inverse-variance weighted average of the difference (or trend) in each study.[18] In addition, we estimated the effects of age at operation, preoperative body mass index (BMI) and infection on arm volume excess.

TABLE 1. Patients' Age, Tumor Size, and Adjuvant Treatment Received

	Study 1	Study 2
No. cases	142	70
Average age (yr)		
Mean (SD)	58.5 (10.4)	60.7 (12.7)
Median	57.7	58.2
Average tumor size (mm)		
Mean (SD)	10.8 (8.3)	20.1 (9.0)
Median	11	119.5
No. node pos./neg. (%)		
Pos.	37 (26)	27 (39)
Neg.	105 (74)	43 (61)
No. receiving chemotherapy (%)	33 (23)	23 (33)
No. receiving radiotherapy (%)	129 (91)	55 (79)
No. receiving Tamoxifen (%)	111 (78)	56 (80)
Average BMI		
Mean (SD)	26.3 (4.6)	26.2 (3.2)
Median	26.0	25.7
No. wound infection (%)	23 (16)	11 (16)

TABLE 2. Arm Volume Excess by Node Status and Time Since Operation Corrected for Change in Contralateral Arm

		Study 1		Study 2	
Time (mo)	Node Status	Excess (mL) [mean (SE)]	n	Excess (mL) [mean (SE)]	n
1	Neg.	59.0 (10.9)	94	—	0
	Pos.	16.0 (17.7)	27	—	0
3	Neg.	67.8 (15.8)	97	71.6 (15.6)	43
	Pos.	35.4 (16.7)	32	61.4 (15.0)	27
6	Neg.	57.7 (14.0)	76	—	0
	Pos.	13.3 (14.6)	27	—	0
12	Neg.	59.7 (12.7)	85	67.0 (16.1)	43
	Pos.	46.3 (22.3)	29	51.3 (14.8)	27

RESULTS

Table 1 shows patient age, tumor size, and adjuvant therapy received. Table 2 shows the arm volume changes by node status and time since operation in both studies, corrected for changes in the contralateral arm.

Positive node status was associated with lower arm volume excess. This was significant in the case of study 1 ($P = 0.05$) and for both studies combined ($P = 0.03$), adjusting for tumor size, time since operation, and allowing for correlated observations within subjects. Adjusting for size, time since operation, and repeated measures, the average arm volume excess in the node-positive subjects was 30.8 mL lower in study 1, 20.3 mL lower in study 2, and 26.8 mL lower when both studies were combined (Table 3). No significant heterogeneity between the studies was observed with respect to the difference in arm volume changes between node-positive and node-negative patients. Within the 2 tumor size groups, the difference was suggestive but did not reach statistical significance.

More strongly significant results were obtained when we estimated the trends in arm volume excess by number of positive nodes. Adjusted for tumor size, time since operation, and repeated measures, the arm volume excess was reduced with increasing number of positive nodes, significantly in study 1 ($P = 0.001$) and in both studies combined ($P < 0.001$). When both studies were combined, the results of the regression analysis indicated a reduction in arm volume excess of 9.2 mL per positive node found, again with no significant heterogeneity between the 2 studies. For tumors of size 20 mm or less, the trend was significant in study 1 ($P = 0.002$), study 2 ($P = 0.02$), and both studies combined ($P < 0.001$). For tumors of size greater than 20 mm, the result was significant in study 1 only ($P = 0.04$) (Table 3).

The arm volume excess was higher in those with higher BMI, but this was not statistically significant ($P = 0.1$). For those with BMI of 25 or more, the excess was 9 mL higher on average than in those with BMI of less than 25. The excess was 12 mL higher on average in those who had wound

TABLE 3. Arm Volume Excess Adjusted for Tumor Size, Time Since Operation, and Repeated Measures

		Node-Pos./-Neg. Comparison		Trend With No. Pos. Nodes	
Tumor Size (mm)	Study	Estimate (mL) [mean (SE)]	*P*	Estimate (mL) [mean (SE)]	P
≤20	Sentinel node	−28.5 (17.4)	0.1	−13.1 (4.12)	0.002
	Ultrasound	−6.5 (23.7)	0.8	−9.7 (4.0)	0.02
	Combined	−20.8 (14.0)	0.1	−11.3 (2.9)	<0.001
>20	Sentinel node	−69.3 (34.2)	0.06	−11.2 (5.1)	0.04
	Ultrasound	−22.8 (34.6)	0.5	4.8 (7.6)	0.5
	Combined	−46.3 (24.3)	0.06	−6.2 (4.2)	0.1
All, size-adjusted	Sentinel node	−30.8 (15.4)	0.05	−11.5 (3.4)	0.001
	Ultrasound	−20.3 (19.7)	0.3	−4.5 (4.9)	0.4
	Combined	−26.8 (12.1)	0.03	−9.2 (2.8)	<0.001

infection, but again this was not significant ($P = 0.2$). There was a highly significant increase in arm volume excess for patients at older ages ($P = 0.001$). Table 4 shows the excesses by age, study, and time since operation. The significant effects related to node status shown in Table 3 remained significant (indeed, they became slightly more significant) when adjusted for age.

DISCUSSION

A number of retrospective studies have suggested that lymph node positivity correlates with the development of BCRL,[1–4] but other studies have failed to demonstrate this association.[5–9] A confounding factor contributing to the contradictory reports has been the administration of axillary radiotherapy to lymph node-positive patients in all of these studies, which has previously been shown to be independently associated with the development of BCRL.[1,19–22] To investigate the relationship between lymph node status and the development of BCRL, we analyzed data from 2 separate prospective studies on patients who underwent ALND. It is worth emphasizing that none of the patients in either study received radiotherapy to the axilla, eliminating it as a possible confounding factor. The results showed lower arm volume excesses in node-positive cases, which were significant in study 1 and when both studies were combined. This finding was further strengthened by the observation that arm volume inversely correlated with the number of positive nodes, again significant in study 1 and when both studies were combined. These results remained the same after adjusting for the other significant factor, age.

These results are counterintuitive to the conventional understanding of the pathophysiology of BCRL. Current understanding of the etiology of BCRL has given primacy to the initiating event of surgery or radiotherapy. Our results suggest that, while BCRL is indeed initiated by these treatments, the determining factors in the development of BCRL may depend on factors that preexist these interventions. Therefore, it may be possible to identify patients at risk for developing BCRL before surgical intervention, for example, by preoperative ultrasound-guided axillary lymph node core biopsy.[23]

A possible explanation for our findings is that patients who develop metastatic disease in the axillary lymph nodes and who then subsequently undergo ALND have more time and ability to develop collateral lymphatic drainage. These collaterals function adequately postsurgery and thereby reduce the risk of developing BCRL. This explanation is further supported by the observation that the number of involved nodes inversely correlated with the development of BCRL. Alternatively, there may be host factors that are associated with both predisposition to lymphatic spread and with a lesser tendency to edema. Further studies are required to determine whether other genetic, molecular, and physiologic characteristics exist that may predispose to the development of BCRL.

TABLE 4. Arm Volume Excess by Age and Time Since Operation, Corrected for Change in the Contralateral Arm

		Study 1		Study 2	
Time (mo)	Age Group (yr)	Excess (mL) [mean (SE)]	n	Excess (mL) [mean (SE)]	n
1	<60	47.9 (11.6)	72	—	0
	60+	51.7 (16.2)	49	—	0
3	<60	56.0 (14.0)	76	39.0 (9.2)	39
	60+	65.2 (23.4)	53	99.3 (20.6)	32
6	<60	35.4 (12.8)	60	—	0
	60+	61.0 (19.7)	43	—	0
12	<60	55.1 (14.4)	63	34.6 (11.3)	38
	60+	57.7 (17.2)	51	88.2 (20.0)	32

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