ORIGINAL ARTICLE

Lymphedema of the Arm and Breast in Irradiated Breast Cancer Patients: Risks in an Era of Dramatically Changing Axillary Surgery

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■ **Abstract:** The purpose of this study was to assess risk for lymphedema of the breast and arm in radiotherapy patients in an era of less extensive axillary surgery. Breast cancer patients treated for cure were reviewed, with a minimum follow-up of 1.5 years from the end of treatment. Clinical, surgical, and radiation-related variables were tested for statistical association with arm and breast lymphedema using regression analyses, *t*-tests, and chi-squared analyses. Between January 1998 and June 2001, 240 women received radiation for localized breast cancer in our center. The incidence of lymphedema of the ipsilateral breast, arm, and combined (breast and arm) was 9.6%, 7.6%, and 1.8%, respectively, with a median follow-up of 27 months. For breast edema, *t*-test and multivariate analysis showed body mass index (BMI) to be significant ($p = 0.043$, $p = 0.0038$), as was chi-squared and multivariate testing for site of tumor in the breast ($p = 0.0043$, $p = 0.0035$). For arm edema, *t*-test and multivariate analyses showed the number of nodes removed to be significant ($p = 0.0040$, $p = 0.0458$); the size of the tumor was also significant by multivariate analyses ($p = 0.0027$). Tumor size appeared significant because a number of very large cancers failed locally and caused cancer-related obstructive lymphedema. In our center, even modern, limited level 1–2 axillary dissection and tangential irradiation carries the risk of arm lymphedema that would argue in favor of sentinel node biopsy. For breast edema, disruption of draining lymphatics by surgery and radiation with boost to the upper outer quadrant increased risk, especially for the obese. Fortunately both breast and arm edema benefited from manual lymphatic drainage. ■

Key Words: axillary surgery, breast edema, breast irradiation, lymphedema

Lymphedema of the arm following breast cancer treatment has severe psychological and physical morbidity (1–3). The cumulative incidence of lymphedema appears to increase with each year after surgery (4) and is a source of problems as diverse as job disability and sexual dysfunction (5–7). Unfortunately confusion is added to the diagnosis and treatment of lymphedema by scant randomized data, conflicting results and therapies, and varying definitions (8–10).

With the evolution toward more conservative surgical breast cancer treatment, there has been considerable progress in the reduction in the incidence of lymphedema. Institutions have tended to measure and stratify lymphedema in a variety of ways, but within an institution, the change from modified radical mastectomy with aggressive level 1–3 nodal dissection to lumpectomy with level 1 and 2 dissection and radiation has resulted in at least a halving in the lymphedema rate (2,11). However, just as modified radical mastectomy has been documented to produce frequent arm lymphedema (12), so too has radiation been blamed for increasing the incidence after both mastectomy (13,14) and to a lesser extent after conservative surgery (15). As for radiation technique, hypofractionation appears particularly disposed to increasing the risk of lymphedema (16), as has full axillary irradiation after nodal dissection (3).

In the era of complete axillary dissection and frequent complete axillary irradiation in conservative breast treatment, the extent of nodal surgery and the number of nodes taken appeared to correlate directly with lymphedema risk (17). The move toward less aggressive nodal dissection is a direct result of increased awareness of arm lymphedema risk. Furthermore, early follow-up strongly suggests that assessment of the axilla solely with sentinel node biopsy combined with simple mastectomy (18) or combined with conservative breast surgery followed by radiation results in reduced risk of arm lymphedema

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Table 1. All Patients: Invasive and Noninvasive Cancer

Tumor characteristic	No. of patients	Percent
Age, years		
Mean	56.5	
Range	26–90	
Race		
White	155	64.6
Black	83	34.6
Asian	2	0.83
BMI		
Mean	29.26	
Range	17–62	
Underweight	0	0.0
Normal	80	33.3
Overweight	72	30.0
Obese	63	26.3
Extremely obese	25	10.4
Tumor location		
Left or right upper outer quadrant	100	41.7
Left or right other	140	58.3
Surgery performed		
Lumpectomy alone	40	16.7
Lumpectomy and SLND	12	5.0
Lumpectomy, SLND, and AND	49	20.5
Lumpectomy and AND	105	43.8
Total mastectomy	4	1.7
Total mastectomy, SLND, and AND	1	0.4
Modified radical mastectomy	29	12.1
Radiation		
Tangential fields only	184	76.7
Tangents and SC field	56	23.3
Dose (cGy)		
Mean	6112	
Range	4600–6500	

AND, axillary node dissection; SC, supraclavicular; SLND, sentinel lymph node dissection.

Table 2. Invasive Cancer Characteristics

	No. of patients	Percent
No. of cases	208	
Percent of total cohort	87.5	
Size (cm)		
Mean	2.2	
Range	0.3–13.0	
T stage		
Tx	1	0.48
T1a	5	2.38
T1b	51	24.29
T1c	77	36.67
T2	52	24.76
T3	14	6.67
T4	10	4.76
N stage		
Nx	11	5.24
N0	131	62.38
N1	67	31.90
N2	1	0.48
N3	0	0.00
No. of nodes removed		
Mean	11.2	
Range	0–31	
No. of positive nodes		
Mean	1.3	
Range	0–21	
Histology		
Ductal	187	89.90
Lobular	19	9.13
Other	2	0.96
Estrogen receptor status		
Negative	58	27.6
Positive	150	71.4
Unknown	2	1.0
Progesterone receptor status		
Negative	79	37.6
Positive	129	61.4
Unknown	2	1.0
HER-2/*neu* status		
Negative	137	65.6
Positive	24	11.5
Unknown	48	23.0
Noninvasive tumor characteristics		
No. of cases	32	
Percent of total cases	12.5	
Size		
Mean	1.0 cm	
Range	0.2–3.0 cm	

(19,20). In patients who for various reasons had lumpectomy with five or fewer nodes sampled and prophylactic radiation treatment of the axilla, lymphedema occurred in only 1.2% of patients (21). The transition to sentinel node biopsy as the sole axillary assessment is highly variable, especially in our community. Over the last few years an increasing number of cases were performed with sentinel lymph node dissection (SLND) followed by simultaneous completion axillary dissections in which fewer than 10 nodes total were removed. During the study period, only 5% of patients received SLND alone. Our cohort permitted evaluation of a spectrum of changing aggressiveness in axillary surgery.

METHODS

We reviewed all radiation oncology charts of breast cancer patients treated with intent to cure during the period of January 1998 to June 2001. Data extracted from the charts regarding the general characteristics of the cohort are shown in Table 1. Pathologic data are presented in Table 2.

Those patients were defined for study purposes as having lymphedema of the arm or breast if (a) the physician or the oncology nurse in follow-up visually noted swelling of the ipsilateral arm or breast, which included hyperemia and changes similar to peau d'orange of the breast, (b) the patient raised concerns over persistent or intermittent swelling, heaviness, redness, and pain in the ipsilateral arm, or (c) the patient complained of similar signs and symptoms in the treated breast. This breast condition was quite distinct from the minor swelling often seen during irradiation, especially in women of larger breast size. All patients with symptomatic arm or breast complaints or visible swelling were first evaluated for other etiologies, such as deep vein thrombosis or infection. If the work-up revealed no other explanation except lymphedema, the patient was referred for manual lymphatic drainage (MLD).

Patients received uniform radiation technique in virtually all cases by the same physician. Patients were routinely treated to a dose of approximately 6000 to 6500 cGy with 4500 to 5040 cGy to the whole breast at 180 cGy/day followed by a tumor bed boost defined by clips or planning computed tomography (CT) scan at 180 to 200 cGy/day, to bring the total dose to 6000 to 6500 cGy. A third field was added for patients with more than three positive axillary nodes, T3 or T4 tumors, or in cases in which fewer than seven axillary nodes were removed. Field depth for the third field was determined from the chest CT. The routine third field ended laterally between the coracoid process and the humeral head, covering the subclavian, supraclavicular, and level III axillary nodes. This field was extended laterally to encompass two-thirds of the humeral head ("full axillary field") in rare cases of inadequate or limited sampling with an overwhelming number of positive nodes.

All identified cases of lymphedema of the breast or arm triggered a physical therapy consultation with one of two therapists who practiced complex decongestive physiotherapy and who had specific training in MLD. Patients were not routinely screened for minimal lymphedema with tape measured arm circumferences or water displacement. Thus our system of edema evaluation would underestimate lymphedema rates compared to clinics that routinely perform follow-up arm measurements.

RESULTS

From January 1998 to June 2001, 240 female patients received radiation therapy in our department as part of their breast cancer treatment with intent to cure. Patients had a minimum of 1.5 years of follow-up after radiation treatment. The majority of the patients had invasive carcinoma ($n = 208$; 87.5%) with a small portion having ductal carcinoma in situ (DCIS) only ($n = 32$; 12.5%). Breast conservation was performed on 206 patients (86%), with the remainder (34; 14%) having a mastectomy. Axillary assessment was performed in 82% of patients. Of this 82%, 5% had sentinel lymph node (SLN) biopsy alone, 20% had both SLN and axillary node dissection, and 56% had standard level 1 and 2 axillary dissection. General characteristics of the study cohort are seen in Table 1. Pathologic data for all patients are shown in Table 2. All analyses were conducted using SAS statistical software, version 8.01 (22).

Seven variables were tested in regression analyses: body mass index (BMI), number of nodes removed, number of positive nodes, size of tumor, simple tangents versus multifield irradiation, site of tumor, and race. Linear regression analysis results for all variables tested against arm and breast lymphedema are listed in Table 3. Chi-squared analyses and *t*-tests permitted alternative insight into the effect of category-type and continuous variables.

Table 3. Statistical Correlates of Lymphedema

	p-value			
	t-test[a]	χ^{2b}	Single regression	Multiple regression[c]
Lymphedema of the arm				
Body mass index	0.5836		NS	NS
Number of nodes removed	0.0040		0.0091	0.0458
Number of positive nodes	0.3106		NS	NS
Tumor size	0.0802		0.0025	0.0027
Multifield irradiation		0.0054	0.0053	NS
Site of tumor (upper outer quadrant)		0.8037	NS	NS
Race		0.1452	0.0740	NS
Lymphedema of the breast				
Body mass index	0.0432		0.0058	0.0038
No. of nodes removed	0.0598		0.0991	NS
No. of positive nodes	0.2123		NS	NS
Tumor size	0.9060		NS	NS
Multifield irradiation		0.4786	NS	NS
Site of tumor (upper outer quadrant)		0.0043	0.0042	0.0035
Race		0.3485	NS	NS

[a] *t*-test for continuous variables.
[b] Chi-squared for category variables.
[c] All seven variables used in regression.

The overall incidence of arm lymphedema was 7.6% (n = 18), for breast edema the incidence was 9.6% (n = 23), and for both arm and breast it was 1.3% (n = 3). Arm edema was present in four patients prior to radiotherapy (with an average tumor size of 2.1 cm and average total nodes sampled of 20). Three patients had breast lymphedema prior to radiation (two of three were upper outer quadrant cancers; mean BMI was markedly elevated at 44.5).

Using univariate regression analyses to assess arm lymphedema, significant variables were the number of nodes taken ($p = 0.0091$), the size of the tumor ($p = 0.0025$), and use of multifield irradiation ($p = 0.0053$). Of these three variables, tumor size and the number of nodes removed remained significant on a multivariate analysis, while multifield irradiation became nonsignificant. Chi-squared analyses found multifield irradiation to be significant ($p = 0.0054$); it being the only significant variable in the pool of noncontinuous variables. The t-tests (for continuous variables) showed significance for the number of nodes removed ($p = 0.0040$). Those with arm lymphedema had an average of 14.1 nodes removed; those without arm lymphedema had an average of 9.6 nodes removed. Increasing tumor size was suggestive for an effect but did not reach statistical significance ($p = 0.0802$). No patient with fewer than five nodes removed developed arm edema. There was no association between race, site of tumor, and increased BMI with risk of arm edema. Four cases of arm edema occurred prior to radiation; these patients had an average tumor size of 2.1 cm and a mean BMI of 29.2. However, the mean number of nodes taken in this group (n = 20) was markedly high.

Although BMI was not of significance for patients with arm lymphedema as a whole, the 3 (of 18) patients with the most severe arm edema (gross upper and forearm edema in spite of MLD and consistent sleeve use) were obese or extremely obese (mean BMI 49.9). Although axillary node dissection technically can be more difficult in the obese patient, no relation in the series between the number of nodes taken and BMI was found.

For breast edema, univariate regression analyses showed an increased BMI ($p = 0.0058$) and an upper outer quadrant tumor site ($p = 0.0042$) to be significant, and these two variables remained significant on a multivariate analysis. Likewise, t-tests showed significance for increased BMI ($p = 0.0432$) and chi-squared was significant for an upper outer quadrant tumor site ($p = 0.0043$). Of the 23 cases, 3 were severe enough that the breast was tense with fluid; in all cases there was at least initial erythema and/or a feeling of heaviness, frequent pain, and a marked visual disparity in breast size. These patients were often placed on trials of antibiotics for suspected mastitis, but without impact on the breast swelling. Several patients had punch biopsies of their skin to rule out an inflammatory breast recurrence. Five of these cases were present before radiotherapy; the majority showed up during or within 2 months of radiation (one case occurring 14 months after radiation).

We investigated the correlation between tumor size and risk of arm lymphedema, as there seemed no simple intuitive relationship. In the complete series of 240 patients, three patients failed locally with invasion of the axilla; all three developed arm edema. The initial tumor sizes of these three patients were 5.0 cm, 6.9 cm, and 8.0 cm, while the mean size for the series was 2.03 cm. If the multiple regression analyses are rerun with these three cases deleted, breast edema remains statistically related to an upper outer quadrant location ($p = 0.0039$) and BMI ($p = 0.0041$). However, for arm lymphedema, tumor size becomes nonsignificant on multiple regression ($p = 0.1355$), with the total number of nodes removed remaining as the only significant factor ($p = 0.0268$).

No cases of arm lymphedema occurred in the 44 patients treated without any axillary surgery whatsoever. In this cohort the average BMI was 30 and tumors in the upper outer quadrant comprised 38.6% (n = 17) of cases. One patient in this group (2.27%) with a tumor in the upper outer quadrant developed breast edema after lumpectomy and radiation.

Manual lymphatic drainage produced dramatic responses to breast edema, without any requirement for postmassage binding or other devices. Five patients had to return for treatment for breast reswelling over time—with a minimum time to reswelling of 6 months. Ultimately, after MLD, 21 of 23 breast edema patients showed only minor persistent swelling that was neither uncomfortable nor considered by the patient or physician to be cosmetically unsightly.

Manual lymphatic drainage produced significant responses in all arm lymphedema cases, as recorded by the therapists at each session. However, all patients required a compression sleeve. The longer-term results became hard to quantify because of variability in compliance with sleeve utilization. Those who wore the sleeve consistently were those who had more severe lymphedema and more dysfunction with that arm. Those with lesser edema often wore the sleeve only at times they thought to be high risk, such as during air travel, more vigorous activity, or at the first sign of increasing edema. Patients noncompliant with recommended sleeve usage often refused further MLD therapy. This "noncompliance" may be a function of out-of-pocket cost, time involved, discomfort, and variations in how individuals balanced the problems with sleeve use with those of lymphedema.

DISCUSSION

During this brief study period we experienced a dramatic variation in the extent of axillary surgery. As data accrues on the accuracy of SLND, limited postoperative sequelae, and long-term follow-up of patients having only SLND, many surgeons here and elsewhere are converting to SLND alone. However, during the transition, many surgeons took three to five extra non-SLNs as an axillary sampling if the intraoperative touch preparation of the SLN was negative. A few of the most conservative surgeons continued to routinely do simultaneous completion axillary dissection after a negative SLND, but those dissections included fewer nodes than their previous standard level 1–2 dissections in years past. The spectrum of dissections all within the same time period, without changes in radiation dose or technique, allowed for assessment of differences in impact of these varied dissections.

In this series the incidence of arm lymphedema was only 7.6%; although it could be higher had circumferential arm measurements been used to define cases. The rate is also likely to increase with longer follow-up. In a long-term study of breast cancer patients who received mastectomy and complete axillary dissection, 49% of patients had the sensation of lymphedema when followed out 20 years (4).

In our clinic, breast edema emerged as a more common problem, with 9.6% of patients showing signs and symptoms of significant lymphatic obstruction. For breast edema, regression analyses, *t*-tests, and chi-squared testing all point to two significant variables: upper outer quadrant location of the tumor and BMI. We may have seen this problem frequently because of the high BMI rate in our patients. In the 30 patients with noninvasive disease, whose axillae were not violated, no breast (or arm) edema was noted, suggesting lymphatic compromise did not occur with high BMI or upper outer quadrant tumor location without axillary violation as well.

Surgery in the upper outer quadrant of the breast may disturb the draining breast lymphatics. In addition, radiation to that region may compound the problem, especially since in these cases the boost dose is given to that region.

Breast edema signs and symptoms, including pain, redness, a feeling of heaviness, and poor cosmesis, were all worrisome for patients. Unless the patient showed leukocytosis, fever, signs of thrombosis, or a rapidly enlarging erythematous breast after recent surgery or obvious cause of infection (e.g., spider bite), we moved directly to MLD. Lymphatic obstruction mimics what many have reported on occasion as infectious cellulitis. MLD was very effective in reducing the edema, pain, and feeling of heaviness and improved cosmesis. The edema never disappeared entirely, however. Along with a discussion of the potential for arm lymphedema, our patients are now apprised of the significant risk of breast lymphedema.

The treatment of arm edema was far less simple and successful, and remains a major medical problem. The correlation found in our series and others with the extent of axillary surgery provide a strong argument for sentinel node biopsy alone when at all possible. The correlation with the size of the tumor may be related to more aggressive axillary surgery in such cases, which is not always simply defined by the number of nodes removed (17). Others have noted a similar correlation between tumor size and arm lymphedema (23,24). T3 and T4 cancers were more likely to have mastectomy; we had too few cases to demonstrate whether that operation itself increased lymphedema risk. The correlation of edema with tumor size is another rationale for stressing the benefits of early diagnosis.

Arm lymphedema remains a disease without a clear cure. Along with surgical and radiotherapeutic factors, others have noted predisposing factors for arm lymphedema, including cellulitis or thrombosis in the affected arm, extensive axillary involvement with the tumor, and cancer recurrence in the axilla. In contrast to our results, direct correlation with obesity has been noted by others in conservatively treated patients (25); as in our group, the lymphedema severity in obese patients was also noteworthy. The small number of lymphedema cases also may have limited our ability to pick up multifield irradiation as a risk factor in multivariate analysis. In 13 of the 49 cases in which multifield irradiation was utilized, the third field use was for inadequate axillary sampling, and these patients, thought to be at low risk for lymphedema, can dilute the effect of multifield irradiation after standard level 1–2 dissection. The issue of arm lymphedema with treatment of the draining nodes is of special concern, as more postmastectomy cases may receive multifield irradiation because of the Danish and Canadian trials (26,27).

The most common current therapies for arm edema include MLD, bandaging, and compressive sleeves. The randomized data for MLD are scant and mixed (28,29), although one can often see a dramatic reduction in arm size after several weeks of MLD. The technique is gaining in professional use in conjunction with compressive garments. After MLD, combined bandaging and subsequent compression sleeves can dramatically reduce lymphedema; although continued sleeve use appears to be the major factor in success (30). Compression garments help when worn regularly, but are a considerable hardship to wear consistently. They create their own distinct stigma, pains, and restriction of mobility. They are nonetheless clearly preferred by patients with severe lymphedema.

Institutions appear to define lymphedema in differing ways, making comparisons difficult. Whether very early intervention is critical remains uncertain (31), as is the duration of sleeve use each day (9). Patients do, however, appear to derive significant psychological benefit from organized attempts, even when not dramatically successful, to ameliorate lymphedema (32). Therapists cite concerns that stage I, reversible nonpitting edema will inevitably evolve into irreversible fibrotic nonpitting edema (33). There is perhaps better evidence for increases in edema over time than the evolution over time of distinct stages. There can be transient, spontaneous reversing edema, for example (22). Generally patients who have nonpitting edema or extensive pitting edema are less likely to respond to MLD and compressive therapy (31,34). A major concern remains whether very early asymptomatic lymphedema should be consistently referred for MLD.

Out-of-pocket cost can be appreciable and patients may be directed to wear a pressure garment for life, under the assumption that lymphedema consistently worsens over time. Two of the 23 patients with up to a 2 cm difference in forearm circumference deferred therapy and had spontaneous reduction in swelling from 6 to 12 months later.

In sum, conservative breast therapy in the modern era in our clinic resulted in a low incidence of arm lymphedema. However, for those with arm lymphedema, treatment remains fairly primitive and patients with significant arm edema are left with a major medical problem, a disability in some cases, a source of loss of quality of life, and certainly a poor cosmetic outcome. Our study confirms and updates a series from an earlier era of more aggressive surgery and radiotherapy for intact breast treatment in which lymphedema was directly correlated with the number of lymph nodes removed (17). None of our SLN-only patients thus far have developed arm lymphedema, nor have any noninvasive patients without axillary violation developed arm edema. Finally, we report a high incidence (9.6%) overall of significant symptomatic breast edema statistically related to BMI and treatment of tumors in the upper outer quadrant of the breast. The risk for breast edema in these latter patients rose to 16%. Fortunately MLD appears very effective for this particular problem.

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