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Arm Edema in Conservatively Managed Breast Cancer: Obesity Is a Major Predictive Factor[1]

To identify risk factors in the development of arm edema (AE) after conservative management of breast cancer, the authors prospectively measured differences in upper and lower arm circumference in 282 patients with stage I or II breast cancer who received radiation. AE was defined as a difference of 2.5 cm or more in either measurement between treated and untreated arms. Median follow-up was 37 months (range, 7–109 months). The crude frequency of AE overall was 19.5% (55 patients). In 21 patients (7.4%) AE was transient; 34 patients (12.1%) had persistent AE, which is the focus of this article. The 5-year actuarial incidence of persistent AE was 16%. The crude risk of persistent severe AE was 3.9%. Various factors were examined for their ability to enable prediction of AE. Treatment-related factors did not significantly enable prediction of AE, whereas factors related to patient size, such as body mass index, were strongly associated with both the frequency and severity of AE.

Index terms: Breast neoplasms, therapeutic radiology, 00.1299 • Extremities, abnormalities, 41.47, 42.47 • Extremities, measurement, 41.1299, 42.1299 • Lymphedema, 41.833, 42.833 • Obesity • Radiations, injurious effects, complications of therapeutic radiology, 41.47, 41.833, 42.47, 42.833

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CONSERVATIVE breast cancer management (CBCM) with local excision, axillary dissection, and primary radiation therapy is now accepted as equivalent to mastectomy in both survival and local control (1). Thus, cosmetic and functional outcomes have become central issues in the management of early-stage breast cancer. Complications can diminish the cosmetic advantages of CBCM over nonconservative management, with or without reconstruction. It is important to determine what, if any, treatment-related factors contribute to an increased risk of complications as well as to establish which subgroups of patients are at increased risk. Such findings may allow preventive measures to be taken. At minimum, appropriate counseling can be provided to those at high risk. In some circumstances, the physician, the patient, or both might chose an alternative treatment if the risk of an unacceptable complication is high.

Adverse cosmetic outcomes from conservative management of breast cancer can be divided into those in the breast itself and those in adjacent tissues. The former include breast edema, asymmetry, skin thickening, breast tissue fibrosis, telangiectasia, dimpling, and retraction. Poor functional and cosmetic results in tissues adjacent to the breast include arm edema (AE), shoulder dysfunction, rib fractures, and, rarely, pulmonary and cardiac complications. AE has been cited as the most common complication of CBCM (2–4). It can be a significant clinical problem and is often poorly managed with current therapeutic techniques.

The purpose of this article is to present data from our institution on the development of AE in patients undergoing primary radiation therapy as part of conservative management of breast cancer. The goals of this study are threefold: (*a*) to assess the actuarial risk of AE in a prospective and quantified fashion, (*b*) to determine which factors predispose patients to AE, and (*c*) to determine whether any of these factors are related to the severity of AE.

PATIENTS AND METHODS

We reviewed the records of 282 patients who received radiation at our institution as part of CBCM between 1980 and 1989. Diagnosis was made by means of initial excisional or needle biopsy. Treatment consisted of limited resection to clear margins, axillary lymph node dissection, and irradiation of the breast with or without the draining lymph nodes. In addition, 101 patients (35.8%) received adjuvant systemic treatment (Table 1).

Surgery of the axilla was performed at our institution by one of four breast surgeons in 239 patients (84.8%). The remaining patients underwent similar dissections elsewhere. Axillary dissections at our institution were all performed in a similar fashion, varying only with respect to the level of dissection. The length of axillary vein visualized during surgery varied, depending on the level of dissection. However, the venous adventitia was not removed, and the axillary tissue above the vein was left intact. The pectoralis minor muscle was only rarely excised—whenever lymph nodes were grossly cancerous during surgery. This muscle was never split without excision. During the procedure, the three levels of the axilla were tagged and coded as each was encountered. The pathologist counted the total number of nodes obtained as well as the number at each level that had positive findings. It is also a policy at our institution to clip the most superior extent of dissection to facilitate matching of a supraclavicular field, if needed.

In 185 patients (65.6%) axillary levels I–II were dissected. In 86 patients (30.5%)

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See also the editorial by Steinfeld (p 18) in this issue.

Abbreviations: AE = arm edema; BMI = body mass index; CAF = cyclophosphamide, doxorubicin hydrochloride, and 5-fluorouracil; CBCM = conservative breast cancer management; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; SCRT = supraclavicular radiation therapy.

Table 1
Characteristics of 282 Patients Who Underwent CBCM

A: Continuous Variable

Variable	Median	Range
Patient		
Age (y)	66	26–83
Weight (kg)	63	36–91
Height (cm)	163	145–181
BMI (kg/m²)	23.8	156–537
Chest wall separation (cm)	20	13–30
Treatment		
No. of lymph nodes dissected	18	1–63
MSKCC level 1–2 (n = 164)	17	6–63
Non-MSKCC level 1–2 (n = 27)	17	6–28
MSKCC level 1–3 (n = 74)	22	11–53
Non-MSKCC level 1–3 (n = 12)	25	15–41
Disease		
No. of lymph nodes (if any) positive for cancer	2.0	1–14

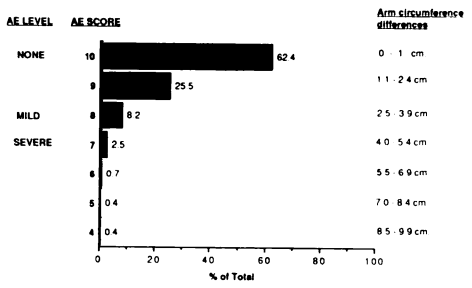
B: Categorical Variable

Variable	No. of Patients	Percentage of Total
Patient		
Cup size		
A	23	8.2
B	119	42.2
C	78	27.6
D	46	16.3
E	3	1.1
Unknown	13	4.6
Brassiere size (inches)		
32	15	5.3
34	90	31.9
36	93	33.0
38	41	14.5
40	17	6.0
42	7	2.5
44	4	1.4
46	2	0.7
Unknown	13	4.6
Treatment		
Level of dissection		
Sampling	2	0.7
I	6	2.1
I–II	185	65.6
I–III	86	30.5
Unknown	3	1.1
Hospital where axillary dissection was done and level of dissection was determined		
MSKCC	239	84.8
Sampling	0	0*
Level		
I	3	1.2*
I–II	161	67.4*
I–III	74	31.1*
Unknown	1	0.4*
Other institutions	43	15.2
Sampling	2	4.7*
Level		
I	3	7.0*
I–II	24	55.8*
I–III	12	27.9*
Unknown	2	4.7*
Portal areas treated with radiation		
SCRT	65	23.0
Internal mammary node	42	14.9
Tangents (inclusive)	280	99.3
Tangents only	205	72.7
Axilla	0	0.0
Systemic treatment		
None	180	63.8
Chemotherapy		
CMF(VP)	57	20.2
CAF or CMF before radiation therapy	15	5.3
Other	2	0.7
Hormonal therapy		
Tamoxifen citrate	27	9.6
Disease		
Clinical T stage		
TX (no primary found)	3	1.1
T1	214	75.9
T2	58	20.6
T3	1	0.4
Unknown	6	2.1
Pathologic N stage		
N0	200	70.9
N1	80	28.4
N2	1	0.4
Unknown	1	0.4
Location of primary tumor		
Outer	151	53.5
Other	128	45.4
Unknown	3	1.1

Note.—BMI = body mass index; CAF = cyclophosphamide, doxorubicin hydrochloride (Adriamycin; Adria Laboratories, Columbus, Ohio), and 5-fluorouracil; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; CMF(VP) = CMF, vincristine sulfate, and prednisone; MSKCC = Memorial Sloan-Kettering Cancer Center; N = node (TNM classification); SCRT = supraclavicular radiation therapy; T = tumor (TNM classification).
* Percentage of corresponding subtotal in column 2.

all three levels were removed. The other patients underwent either a level I or sampling procedure. All patients underwent axillary surgery. As shown in Table 1, the relative proportions of these procedures were similar for those with dissections performed at our institution or elsewhere. The median number of nodes obtained for each level of dissection is also given. These numbers are also comparable between our institution and the other institutions as a group.

All patients received their radiation therapy at our institution. Tangential breast fields were used to treat the entire breast with doses of 4,140–5,400 cGy (median, 4,680 cGy) by means of conventional fractionation. A boost dose was given to the primary site in 269 patients (95.4%). Electrons were used in 170 patients (60.3%) and iridium-192 in 74 patients (26.2%). The other patients received coned-down photon boosts. Boost doses ranged from 900 to 1,800 cGy. In 42 patients (14.9%) the internal mammary nodes were treated. Techniques used for this purpose included larger tangential breast fields, an anterior photon field, or a mixed-beam technique with use of photons and electrons. Sixty-five patients (23%) received radiation to a supraclavicular portal that also treated the apical undissected portion of the axilla. Supraclavicular radiation was delivered with a separate anterior field matched to the tangential fields by means of a protractor



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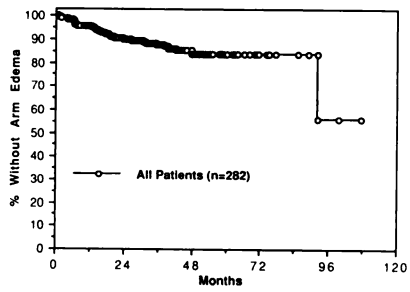

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Figures 1, 2. **(1)** Distribution of AE scores. **(2)** AE onset curve.

technique. The medial border of this field extended to the pedicles of the ipsilateral vertebral bodies. The lateral margin typically extended to the coracoid process of the scapula. The dose of supraclavicular radiation was calculated at 3 cm and was the same as the dose prescribed to the tangent fields. This field was rotated 10° to avoid the spinal cord. The decision to treat the supraclavicular region was most often based on a positive finding in axillary lymph nodes. Eighty-two percent of the 65 patients who received supraclavicular radiation therapy had positive axillary lymph nodes. In no case was the full axilla irradiated after dissection. Radiation was delivered with a 6-MV linear accelerator in 164 patients (58.2%), a cobalt-60 machine in 113 patients (40.1%), and a 10-MV linear accelerator in five patients (1.8%).

One hundred one patients (35.8%) received systemic treatment. This included chemotherapy in 74 patients (26.2%) and antiestrogens in 27 patients (9.6%). Overall, 81 patients (28.7%) had axillary lymph nodes with positive findings, but 76 patients (75.2%) who received systemic treatment had positive axillary findings. Sixty-three of the patients who received chemotherapy (85%) had lymph nodes with positive findings. If chemotherapy was given, the usual sequence of treatment was surgery first, chemotherapy second, and radiation therapy third. Chemotherapeutic regimens included CMF in 58 patients (78%) and CAF in 15 patients (20%).

Differences in arm circumference were assessed at regular patient follow-ups in our clinic every 3–12 months, depending on how much time had passed since treatment. At each follow-up appointment, arm measurements were obtained in a standardized fashion by a single observer. Measurements were made with a tape measure 13 cm above and 10 cm below the olecranon on both arms. The maximum difference between the treated and untreated sides for either set of measurements was scored and recorded in our data base. An AE score of 1– 10 was assigned to each range of differences in arm circumference (Fig 1). If the difference was 2.5 cm or greater, the patient was considered to have AE. A difference of 2.5–3.9 cm (AE score, 8) was considered to be mild AE, whereas a difference of 4 cm or less (AE score, 7 or lower) was defined as severe AE. Because the focus of this paper is on persistent AE, if any given patient's AE score returned to normal with follow-up, it was not scored as AE in the following analyses.

Median follow-up of the entire patient group was 37 months (range, 7–109 months). Two patients have an unknown survival status and four patients have died; none of these six patients had AE at their last follow-up examination. The median and range of follow-up for those with persistent AE were not significantly different from those of patients without AE or from the whole group of patients. Of the 34 patients who were scored as having persistent AE, all were examined within the past 12 months and 10 were examined within the past 6 months. Of those without AE, seven patients had been last examined at follow-up 2–3 years before November 1990, 29 had been last examined 1–2 years before November 1990, and 212 had been seen between November 1989 and November 1990. Thus, 87% of all patients had been last evaluated for AE within the 12 months before the writing of this article.

Curves indicating time to development of AE were drawn with the Kaplan-Meier product limit method. The interval was measured from the date of surgery until the date of documentation of AE or last follow-up. Comparisons between two or more distributions were evaluated with the Cox–Mantel test (5). The Cox proportional hazard method was also used to model the relationship between the time to development of edema and a set of explanatory or prognostic variables (6). The explanatory variables selected were those which were univariately significant ($P < .05$) or nearly significant ($P = .05$–.09). Relationships between categorical variables were examined with the χ^2 test.

RESULTS

Fifty-five of 282 patients had an AE score of 8 or lower at any time (crude frequency of any AE, 19.5%). These patients can be divided into two groups: those whose scores returned to 9 or 10 during the course of follow-up (transient AE) and those whose scores remained abnormal (persistent AE). Twenty-one patients had transient AE (crude frequency, 7.4%). Eighteen of these patients had an AE score of 8, and three had an AE score of 7. A second group (34 patients) had persistent AE (crude frequency, 12.1%). Twenty-three of these patients had an AE score of 8; seven, a score of 7; and four, scores of 4–6 (crude frequency of persistent severe AE, 3.9%). Three patients (14%) whose AE disappeared versus 11 of those with persistent AE (32.4%) had severe AE. Furthermore, four of the 11 patients with persistent severe AE had AE scores less than 7, whereas none of those with transient AE had scores this low. However, these differences were not statistically different ($P = .19$, χ^2 test).

The time to development of persistent AE is shown in Figure 2. For those who developed it, the median time to development of AE was 14 months (range, 2–92 months). Thirty-three of 34 patients (97%) who developed AE did so by 4 years. Only one patient developed AE later, after 7.7 years, with an AE score of 8. No known inciting factors existed in this patient. At 5 years the incidence of persistent AE for the whole group of patients was 16%, with 26 patients still at risk.

We evaluated several variables for their ability to help predict persistent AE. They can be grouped into three categories. The first category consists of treatment-related factors: level of axillary dissection, number of lymph nodes obtained at axillary dissection, hospital of axillary dissection, use and type of systemic treatment, and use of supraclavicular irradiation. The second category consists of disease-related factors: clinical tumor stage, pathologic node status, the number of lymph nodes with positive pathologic findings, and the location of the tumor in the breast. The third category consists of patient-related factors: age, weight, height, BMI, brassiere size, brassiere cup size, and chest wall separation. The chest wall separation is the distance between the posterior entrance points of the medial and lateral tangents measured at the time of simulation. The BMI, expressed as weight in kilograms divided by height in square meters, was recommended by the National Institutes of Health Consensus Development Conference in 1985 as an accurate index for the prediction of medically significant obesity. The minimum cut-off value recommended for defining obese adult women was 27.3 (7).

When univariate analysis was used, factors not statistically related to the development of AE were the follow-

ing: level of axillary dissection, number of nodes removed, hospital at which the dissection was done, SCRT, systemic treatment, total number of cancerous lymph nodes, location of the tumor in the breast, age, height, and cup size of brassiere (Table 2). The use of adjuvant systemic treatment ($P = .09$) and brassiere cup size ($P = .08$) were nearly significant. Factors that were significant in the development of AE as determined with univariate analysis were the following: positive pathologic findings in axillary nodes, clinical tumor stage, BMI, weight, chest wall separation, and brassiere size in inches (Table 3). Even within the subset of patients with a BMI less than 27.3 kg/m^2, the level of axillary dissection was not a significant factor. Examples of Kaplan-Meier curves used for the univariate analysis of BMI are shown in Figures 3 and 4.

The set of variables that was significant or nearly significant in univariate analysis was entered in a step-forward Cox procedure. The results indicated that the only variable significantly associated with the development of AE was BMI ($P < .0005$). This model was highly statistically significant ($P > .00005$). Subsequently, this entire set of variables was included in a single model, and another Cox proportional hazards analysis was performed. Again, the overall model was highly statistically significant ($P = .0005$), but none of the variables was significant individually. This finding can be ascribed to the large amount of intercorrelation among the continuous variables (BMI, height, weight, brassiere size, cup size, and chest wall separation) as well as among the categorical variables (eg, clinical T stage, pathologic nodal involvement, and the use of adjuvant systemic treatment). The presence of highly intercorrelated variables in a model detracts from the predictive power of any given variable by itself (Tables 4, 5).

BMI was the variable most closely associated with the development of AE. Moreover, the higher the BMI, the greater the frequency of AE. For example, among obese patients (who had the top 23% of BMI scores in our group of patients), the 5-year incidence of AE was 27.4% versus 12.5% for those with lower BMIs ($P = .002$) (Fig 3). In the top 15% of our group of patients, who had a BMI of $\geq$29.2 kg/m^2, the 5-year incidence of AE rose to 36%, compared with 12% for those with lower BMIs ($P < .0005$) (Fig 4).

Furthermore, not only was BMI related to the frequency of AE, but it was also related to increased frequency of severe AE. The proportion of patients with severe AE increased from 2.3% in nonobese patients to 9.2% in obese patients. When the nonobese patients were divided into two groups with the same number of patients in each group, increasing BMI continued to enable prediction of increasing severity of AE. The frequency of severe AE rose from no occurrence in the low-range BMI group to 4.6% in the middle-range group to 9.2% in obese patients. There was also a trend of increasing frequency of mild AE with increasing BMI. All these differences were statistically significant ($P = .007$, χ^2 test) (Tables 6, 7).

A plot of BMI versus AE score appears in Figure 5. The resulting Pearson correlation coefficient of -0.272 ($P = .0001$) indicates the association of increasing BMI with more severe AE.

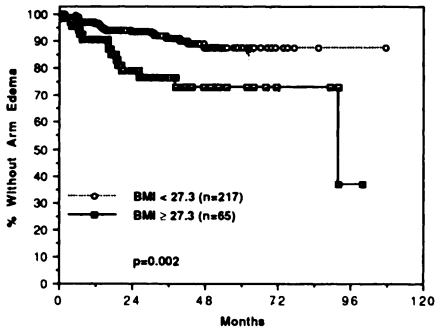
Table 2
Results of Univariate Kaplan–Meier Analysis: Factors That Are Not Significantly Related to AE

Factor	5-y Actuarial Incidence of AE after Radiation Therapy* (%)	*P* Value
Treatment		
Axillary dissection		
Level I ($n = 6$), I–II ($n = 185$)	15.5	.49
Level I–III ($n = 86$)	18.0	.49
No. of lymph nodes removed at axillary dissection		
1–15 ($n = 96$)	8.3	.19
>15 ($n = 182$)	18	.19
1–24 ($n = 227$)	14.8	1.0
>24 ($n = 51$)	13.4	1.0
Hospital where axillary dissection was done		
MSKCC ($n = 239$)	16.7	.14
Other ($n = 43$)	11.6	.14
SCRT		
None ($n = 216$)	15	.17
Any ($n = 65$)	18	.17
Systemic treatment		
None ($n = 216$)	14.0	.09
Any ($n = 101$)	19.0	.09
Chemotherapy ($n = 74$)	18.8	.16
None ($n = 180$)	14.0	.16
Hormonal ($n = 27$)	15.2	.14
None ($n = 180$)	14.0	.14
Chemotherapy	18.8	.73
Hormonal	15.2	.73
Disease		
No. of lymph nodes with positive findings		
1–3 ($n = 61$)	22.6	.84
>3 ($n = 19$)	19.4	.84
Patient		
Age (y)		
>69 ($n = 42$)	12.2	.77
≤69 ($n = 240$)	17.1	.77
>49 ($n = 87$)	14.1	.2
≤49 ($n = 195$)	17	.2
Height (cm)		
>168 ($n = 232$)	15.7	.95
≤168 (n = 50)	15.1	.95
Cup size of brassiere		
A–C ($n = 220$)	14	.08
D–E ($n = 49$)	24	.08

*Percentage of patients who developed persistent AE by 5 years after radiation therapy (patients who developed AE, died, or in whom follow-up was not available) versus those still at risk.

DISCUSSION

We prospectively quantified differences in arm circumference in a group of 282 patients with conservatively managed breast cancer who underwent treatment at our institution. The crude overall frequency of AE was 19.5%. This analysis focuses on those patients who developed persistent AE. The crude and 5-year actuarial frequencies of persistent AE were 12.1% and 16%, respectively. Fourteen patients (5%) developed severe



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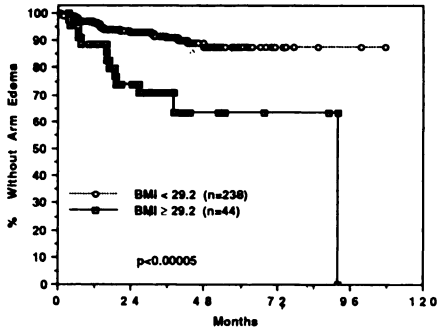

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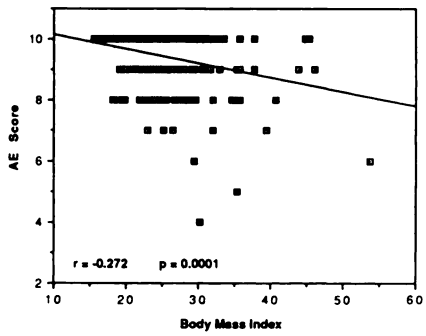

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Figures 3–5. (3, 4) Kaplan–Meier curves show the effect of BMI on AE. (5) Relationship of BMI to AE score.

Table 3
Results of Univariate Kaplan–Meier Analysis: Factors That Are Significantly Related to AE

Factor	5-y Incidence of AE (%)	*P* Value
Disease		
Pathologic findings in axillary node		
Negative (n = 202)	14.0	.05
Positive (n = 80)	20.3	.05
Clinical tumor stage		
T1 (n = 214)	14.0	.04
T2 (n = 58) & T3 (n = 1)	24.6	.04
Patient		
BMI (kg/m²)		
≤27.2 (n = 217)	12.5	.002
>27.2 (n = 65)	27.4	.002
≤29.2 (n = 238)	12.0	<.00005
>29.2 (n = 44)	36.0	<.00005
Weight (kg)		
≤71 (n = 217)	11	<.00005
>71 (n = 65)	32	<.00005
Chest wall separation (cm)		
≤22 (n = 221)	13	.0003
>22 (n = 58)	28	.0003
Brassiere size (inches)		
≤36 (n = 198)	13	.004
>36 (n = 71)	24	.004

Table 4
Cox Analysis of Prognostic Factors: Stepwise Analysis of All Significant or Nearly Significant Variables

A: Results of the χ^2 Test

Variable	Improvement (χ^2 Test)	*P* Value
BMI	13.93	<.0005
Clinical tumor stage	3.83	.07

B: Coefficient Divided by SEM

Variable	Coefficient	Coefficient/SEM	Exponent (Coefficient)
BMI	0.009	3.96	1.009
Clinical tumor stage	0.720	1.90	2.06

Note.—Global χ^2 = 24.79, two degrees of freedom (P < .0005), SEM = standard error of the mean.

AE at any time. In three of these 14 patients (21%) AE disappeared, leaving 11 patients (3.9% of the total population) with persistent severe AE.

In our univariate analyses, we found that treatment-related factors such as level of axillary dissection, SCRT, and the use of systemic therapy did not enable prediction of an increased risk of AE. Rather, factors related to patient size were statistically very significant. Obese women (defined as women with a BMI ≥ 27.3 kg/m²) had a risk of AE that was more than double that of the rest of the population (27.4% vs 12.5%). The ratio of AE risks rose to 3:1 when a higher BMI cut-off value (29.2 kg/m²) was used (36% vs 12%). Interestingly, although brassiere size in inches was significant, brassiere cup size was not predictive. Because the former is a measurement of chest circumference and the latter a measurement of breast size, this finding supports the idea that obesity and patient size are the important predictors rather than breast size per se.

When multivariate analysis was performed, BMI proved to be the only variable that significantly enabled prediction of AE. Furthermore, BMI enabled prediction of an increased risk of severe AE as well. For patients in the bottom 38th percentile of the BMI the risk of severe AE was 0%, whereas for obese women (in the top 23rd percentile) it was significantly higher at 9%.

Although the values for the crude frequencies of any AE or persistent AE fall within the wide range of values in conservative management of breast cancer reported in the literature (2%–22%, 70%) (2,4,8–18), one cannot easily compare the results from different studies. Authors have varied widely in the methods and rigor with which they have evaluated AE. Significant uncertainty results from studies in which actual performance of arm measurements in all patients is not reported. It is difficult to interpret retrospective studies in which clinical impressions of the presence or absence and severity of AE have been retrospectively culled from observers, and, in general, these studies tend to report lower frequencies of AE (18). Variations in length of follow-up also contribute to the variability in the reported data. Up to a cer-

tain point, those with longer periods of follow-up are also more likely to report higher frequencies of AE. Some authors have only reported crude frequencies, whereas others have included actuarial data. The number and frequency of measurements also affect reporting on the frequency of AE. Some have used one follow-up value, whereas others have taken multiple measurements. A single measurement, depending on when it is obtained, is likely to result in underestimation of the frequency of AE. Furthermore, it is only through multiple measurements that one can assess the number of patients in whom AE will disappear (21 of 55 patients [38%] in our study group).

Evidence supporting the use of a difference of 2.5 cm or greater in arm circumference as a definition of AE has been published previously. Pezner et al (19) measured differences in arm circumference in 35 healthy control subjects and found that such differences did not exceed 2.0 cm in any control subject, whereas in 20% the difference in arm circumference was 1.5–2.0 cm. They defined AE as either a difference of 2.5 cm or greater between the circumferences of treated and untreated arms or as pitting edema of the ipsilateral dorsum of the hand. The crude frequency of AE in their study was 14% (10 of 74 patients), and one of 14 patients had AE on the basis of pitting edema of the hand only. Their data are based on a single measurement obtained 5–41 months after the completion of radiation therapy.

Arm circumference measurements themselves are not without limitations. Pezner et al (19) point out that 20% of control subjects have a 1.5–2.0-cm asymmetry in arm circumference attributable to the greater muscle mass of the dominant hand. This asymmetry can affect the detection of AE. As an example, a right arm circumference normally 1.5 cm greater than the left would require a 1.0-cm increase in arm circumference for the right arm to be considered edematous, whereas for the left arm to be considered edematous, a 4.0-cm difference would be necessary. To overcome this limitation, longitudinal studies in each patient before and after treatment were proposed. Such data are not currently available. In addition, a variety of criteria for difference in arm circumference have been used to define AE in the literature (4,8,10,17,19). In some studies, any difference in arm circumference was classified as AE (4,17). Furthermore, other techniques such as optoelectric volumetry or other volumetric measurement made by means of water displacement (20,21), scintigraphy of lymph nodes, and computed tomography have been used to assess AE (21). Swedborg and Wallgren have claimed that measurements of arm volume are superior to differences in arm circumference (20), but little data on the use of these techniques in conservatively treated patients are currently available.

Although one measures arm circumferences, the criteria to define AE are not firmly established. Some authors have included pitting edema of the hand as sufficient criteria for AE; others have not. Some authors have required that a patient have symptoms of AE before making a diagnosis of AE. Gallagher et al (18) assessed arm swelling with measurements of circumference and volume in 100 patients undergoing CBCM. They reported that persistent symptomatic arm lymphedema occurred in 5% of their patients, whereas 30% developed transient swelling and 70% had measurable arm swelling. Further information on exact criteria was not provided in their abstract.

In general, significant caution is necessary in interpreting the reported

Table 5
Cox Analysis of Prognostic Factors: Proportional Hazard Regression Analysis Made with a Model Including All Significant or Nearly Significant Variables

Variable	Coefficient	Coefficient/SEM	Exponent (Coefficient)
BMI	0.011	1.42	1.01
Weight	−0.017	−0.52	0.98
Bra size	0.039	−0.35	0.98
Cup size	0.160	0.74	1.04
Separation	−0.017	−0.19	1.17
Pathologic findings in nodes (positive vs negative)	0.034	0.04	1.04
Clinical tumor (T1 vs T2)	0.7260	1.86	2.07
Systemic treatment (administration vs no administration)	−0.377	−0.48	0.69

Note.—Global χ^2 = 27.68, eight degrees of freedom (P = .0005).
SEM = standard error of the mean.

Table 6
Analysis of Relationship of Severity of AE with Increasing BMI in 282 Patients

	BMI (range)		
Degree of AE/Score	15.6–27.2	>27.2	Total
None/9–10	198 (91.2)	50 (76.9)	248
Mild/8	14 (6.5)	9 (13.8)	23
Severe/4–7	5 (2.3)	6 (9.2)	11
Total	217	65	282

Note.—Data in obese patients are compared with data in nonobese patients. In columns two and three, numbers outside parentheses are number of patients; numbers in parentheses are percentages. χ^2 = 10.67, two degrees of freedom, P = .005.

Table 7
Further Subdivision of Nonobese Patients into Two Equal Groups

	BMI (range)			
AE Level/Score	15.6–22.7	22.8–27.2	>27.2	Total No. of Patients
None/9–10	102 (94.4)	96 (88.1)	50 (76.9)	248
Mild/8	6 (5.6)	8 (7.3)	9 (13.8)	23
Severe/4–7	0 (0.0)	5 (4.6)	6 (9.2)	11
Total	108	109	65	282

Note.—In columns two through four, numbers outside parentheses are number of patients; numbers in parentheses are percentages. χ^2 = 14.06, four degrees of freedom, P = .007.

frequency of AE and in comparing reported results.

The same previously cited caveats in the interpretation of the frequency of AE can also be applied to the interpretation of factors purported to be associated with an increased risk of AE. Furthermore, in many studies no multivariate analysis has been performed, and thus it is difficult to determine which risk factors are most important. Nevertheless, a variety of factors have been associated with an increased risk of AE in breast cancer. This issue was first addressed with regard to mastectomy. In 1962, Britton and Nelson (22) reviewed 14 separate studies conducted between 1908 and 1960 and reported on the frequency of AE after radical mastectomy. The reported frequencies varied from 7% to 63% and did not seem to have changed much with time. The frequency appeared to be related to postoperative radiation therapy. The authors presented their own study of 114 patients with arm lymphedema after radical mastectomy and concluded that infection was of primary importance as an etiologic agent. They also noted that radiodermatitis, late fibrosis in the axilla secondary to radiation or surgery, and obstruction of the axillary vein were contributing factors. In a review published in 1977, Stillwell (23) wrote that postmastectomy AE appeared to be "... primarily and usually due to lymphatic obstruction and insufficiency." In very severe cases, he noted, there might also be obstruction of the axillary vein. This obstruction was usually due to scar formation around the vein, which was possibly related to the surgical procedure, wound infection, or fibrosis secondary to radiation therapy. He also commented that infection, trauma, obesity, excessive limb use, and local or generalized heating had been cited in the literature as precipitating or exacerbating factors. In general, studies of the frequency of AE after radical or modified radical mastectomy have cited the use of postmastectomy radiation therapy, postoperative wound complications or seromas, and obesity as factors related to the development of AE (19,22–33). Some studies have found decreased AE in patients undergoing modified radical versus radical mastectomy (24,31,32).

In patients treated with conservative surgery and primary radiation, factors that have been associated with an increased risk of AE include the addition of axillary radiation therapy to axillary lymph node dissection or the dose of axillary radiation (2,4,10,14,16), the extent of axillary dissection or the number of lymph nodes dissected (4,11,13,18,19), the use of chemotherapy (8,12), the use of SCRT (9), postoperative surgical complications (18), age (19), and the number of positive lymph nodes (2). Thus, much of the literature on CBCM has emphasized treatment-related factors. In general, however, patient-related factors, particularly those related to the patient's size, do not appear to have been examined in most of the published studies. In the study by Pezner et al (19), the only one in which it appears that patient weight was examined, weight greater than 150 lb (68.0 kg) enabled prediction for AE only in patients who were younger than 60 years old and had undergone axillary lymph node dissection. Their results showed that the age at diagnosis was the most important factor associated with AE. Axillary lymph node dissection was the second most important factor.

In contrast to the previous reports in the literature on CBCM, we found in our study that treatment-related factors were not significantly related to the risk of AE. Rather, patient-related factors, specifically those related to patient size and obesity, were powerful predictors for AE.

It is noteworthy that seroma formation was not prospectively analyzed in our series. A retrospective evaluation of this factor would be, as pointed out, severely limited. However, in a recently published prospective study involving a similar population at our institution, only 8% of patients had seroma formation that persisted longer than 30 days after surgery (38). No patients had axillary hematomas or wound infections. It is our impression that no increased frequency of AE exists in this subgroup of patients with seroma formation, although further follow-up is necessary.

As previously discussed, it is difficult to compare studies, and few studies of CBCM have examined the risks associated with obesity and increased patient size. On the other hand, there is support in the literature for obesity as a risk factor in postmastectomy AE. Obesity has been cited as a causative factor in mastectomy patients by a number of authors (23,24,26,34–37). Say and Donegan (24) reviewed the records of 1,531 patients who underwent mastectomy at the Ellis Fischel State Cancer Hospital, Columbus, Mo. Their data indicated that, in patients treated without adjuvant therapy, postoperative swelling of the arm was associated with both obesity and seroma formation. Prolonged operations and multiple transfusions were also associated with AE. They ascribed these findings to the possibility that obese patients might have poorer vascularity and require more technically demanding operations. They did not specifically analyze the frequency of infection, and no multivariate analysis was provided. Haagensen (26), who emphasized the role of infection, also considered obesity a causative factor and commented on the difficulty of avoiding infection in the obese patient. Stillwell (23) argued that the skin of an arm that was already large because of obesity may be less able to resist further enlargement than that of a small arm because of the physical relationship expressed in the Laplace law. Thus, the finding that obesity enables prediction of AE is supported in the postmastectomy literature but has not been fully evaluated in the CBCM literature.

In summary, our analysis of 282 patients identified BMI as the single most powerful predictor of the development of AE after conservative breast cancer management. Treatment-related factors were not statistically significant. ■

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