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Long-Term Complications Associated With Breast-Conservation Surgery and Radiotherapy

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Background: Breast-conservation surgery plus radiotherapy has become the standard of care for early-stage breast cancer; we evaluated its long-term complications.

Methods: We selected patients treated with surgery and radiotherapy between January 1990 and December 1992 (an era in which standard radiation dosages were used) with follow-up for at least 1 year. Patients were prospectively monitored for treatment-related complications. Median follow-up time was 89 months.

Results: A total of 294 patients met the selection criteria. Grade 2 or higher late complications were identified in 29 patients and included arm edema in 13 patients, breast skin fibrosis in 12, decreased range of motion in 4, pneumonitis in 2, neuropathy in 2, fat necrosis in 1, and rib fracture in 1. Arm edema was more common after lumpectomy plus axillary node dissection than after lumpectomy alone. Arm edema occurred in 18% of patients who underwent surgery plus irradiation of the lymph nodes and 10% who underwent surgery without nodal irradiation.

Conclusions: Breast-conservation surgery plus radiotherapy was associated with grade 2 or higher complications in only 9.9% of patients. Half of these complications were attributable to axillary dissection, it is hoped that lower complication rates can be achieved with sentinel lymph node biopsy.

Key Words: Breast cancer—Radiotherapy—Complication—Morbidity—Arm edema.

Breast-conservation surgery plus radiotherapy (breast-conservation therapy) has become the standard of care for early-stage breast cancer. Breast-conservation therapy has been demonstrated to result in survival equivalent to that seen with mastectomy in both retrospective[1,2] and prospective[3–6] studies.

Several complications attributable to the combination of conservative surgery and radiotherapy for treatment of breast cancer have been documented in the literature. These complications include arm edema, clinical pneumonitis, persistent chest wall or breast pain, breast fibrosis, fat necrosis, prolonged skin breakdown, rib fracture, cardiac complications, neuropathy, and axillary vein thrombosis.[7–12] Fear of radiotherapy and its side effects can be a significant factor in patients' choice of therapy.[13] We investigated the long-term complications associated with breast-conservation surgery and radiotherapy in a cohort of patients treated at our institution with a consistent treatment technique and radiation dosage.

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METHODS

Patients

We selected all patients treated with breast-conservation therapy at The University of Texas M. D. Anderson Cancer Center between January 1990 and December

1992. The patient population for this study was drawn from our breast-conservation database, which includes patients treated between 1970 and 1995. The 1990 to 1992 time period was selected because a substantial proportion of the patients treated during this time period were treated with radiation techniques similar to those in use today and because selecting this time interval provided 8 years of potential follow-up for treatment-related complications. Patients for whom <1 year of outcome data was available were excluded from the study. Patients who did not undergo radiotherapy and patients who received radiotherapy at another institution were also excluded from the study.

Surgical Therapy

Patients were evaluated before surgery by a breast surgical oncologist and a radiation oncologist. Mastectomy was discussed as a treatment option with all patients. Patients with multicentric disease, large tumor size relative to breast size, or contraindications to radiotherapy were considered ineligible for breast-conservation therapy as primary surgical treatment.

Tumors were excised with the aim of complete tumor removal with grossly normal tissue margins of at least 1 cm. If surgical margins were pathologically positive, a re-excision was performed. Radiopaque hemoclips were placed at the margins of resection in most cases to assist the radiation oncologist in treatment planning.

Axillary lymph node dissection (ALND) was performed through a separate axillary incision and included level I and II lymph nodes. The axillary vein was identified but not stripped. The pectoralis minor muscle was not routinely divided.

Radiotherapy and Adjuvant Systemic Therapy

During the study period, the radiation treatment technique was changed from the use of cobalt-60 (^{60}Co) gamma rays to the use of photons from a linear accelerator. The percentage of patients undergoing breast-conservation therapy who were treated with a linear accelerator increased from approximately 25% in 1990 to approximately 75% in 1992. Radiotherapy was delivered according to the following standard treatment policy. The breast was treated through medial and lateral tangential fields with a median dose of 50 Gy in 25 fractions over 5 weeks. In selected patients, a third field used to treat the supraclavicular fossa and axillary apex was matched to the cranial edge of the tangent breast fields. In general, this third field was added when four or more axillary lymph nodes were involved or when extracapsular disease >2 mm was present. In addition, for patients with extensive extracapsular disease, a separate posterior field was also used to bring the total dose to 40 Gy to a point in the mid axilla. For patients with microscopic deposits in the axillary fat or if the axilla was not dissected, the dose was increased to 50 Gy. Internal mammary node radiation (with a separate matched medial electron field) was occasionally used. This treatment was given only to patients with inner or central tumors with positive axillary lymph nodes whose anatomy and tumor bed location allowed for a junction of the matched field that did not compromise coverage of the breast tissue at risk. Photons, electrons, or both were used for treatment of the supraclavicular region and axillary apex. The internal mammary portals were treated primarily with electrons to minimize irradiation of the heart and lung. All patients who received chemotherapy had completion of all chemotherapy before irradiation.

Evaluation of Complications

Patients were observed regularly and were seen at least once a year at the M. D. Anderson Cancer Center. As part of routine care, patients were monitored prospectively for treatment-associated complications. Arm circumferences were measured in patients who complained of arm swelling or appeared on physical examination to have arm swelling. Arm measurements were performed 10 cm above the lateral condyle and 10 cm below the lateral condyle with the arm in supinated position. Arm circumference was measured in the contralateral arm for comparison. Patients who reported intermittent arm edema but had no objective findings of arm edema were scored as having grade 1 arm edema.

For this study, patient charts were retrospectively reviewed for complications. Every effort was made to register all probable treatment-related complications, even if they were minor or produced no symptoms. Complications were scored by using a grading system developed by two of the authors (E.A.S. and M.D.M.) for institutional protocols (Table 1). Pigmentation changes of the skin and telangiectasias were not included in the analysis.

Statistical Analysis

The SPSS™ 10.0 software package (SPSS Inc., Chicago, IL) was used for statistical analysis. Descriptive statistics were performed to assess the frequency distribution. The differences between the medians of continuous variables were tested by the Mann-Whitney *U*-test. The incidence of each complication was compared between patients in treatment groups by using Pearson's χ^2 or Fisher's exact test. *P* values of $\leq .05$ were considered to be statistically significant.

TABLE 1. *Grading of breast-conservation therapy complications*

Type	Grade 1	Grade 2	Grade 3	Grade 4
Arm edema	<3 cm above elbow	>3 cm below elbow	Impaired function	Total loss of function
Soft tissue fibrosis	Mild	Moderate	Impaired ROM	
Soft tissue necrosis	Mild	Resection required	Flap/graft required	Chest wall resection required
Pneumonitis	Mild	Moderate	Hospitalization required	Life-threatening
Pulmonary fibrosis	Asymptomatic: abnormal PFTs or CXR	Exertional dyspnea	Dyspnea with normal activity	Dyspnea at rest
Rib fracture	One rib	Two or three ribs	More than five ribs	
Limitations in range of motion	Joint stiffness or pain on medication	Moderate intermittent or constant joint pain		Severe limitation of function
Plexopathy	Subjective symptoms	Mild objective symptoms	Impaired function	Paralysis
Other	Mild	Moderate	Severe	Life-threatening

PFTs, pulmonary function tests; CXR, Chest x-ray; ROM, range of motion.

RESULTS

Patient and Treatment Characteristics

A total of 294 patients met the selection criteria for the study. The median patient age was 52 years (range, 22–88 years). The median pathologic tumor size was 1.5 cm (range, .5–5.5 cm). Eighty-two patients (28%) underwent re-excision of the tumor site at M. D. Anderson. Final excision margins were positive in 9 patients (3%), negative in 265 (90%), and unknown in 20 (7%).

Two-hundred sixty patients (88%) underwent ALND. Seventy-two (28%) of the 260 patients who had ALND had histologically positive nodes. Eighteen (53%) of the 34 patients who did not undergo ALND had ductal carcinoma-in-situ. Of the 16 patients who had invasive tumors and did not undergo ALND, 6 were 65 years of age or older, and 9 had tumors smaller than 2 cm.

One hundred forty-one patients were treated with ^{60}Co gamma rays, and 153 were treated with photons (151 patients received 6×; 2 received 18×) in the study, allowing comparison of the two treatment groups. Boosts were given to the primary tumor site in 185 patients (63%); 15 (5%) of these patients were treated with interstitial implants. For the remaining 170 patients, a boost of 10 Gy in 5 days was delivered to the tumor bed with electrons of appropriate energy.

Additional radiation fields were used to treat the supraclavicular field and axillary apex in 120 patients (44%), to supplement the mid axillary region in 38 patients (12.9%), to treat the internal mammary nodes in 39 patients (13%), and to treat the chest wall in 6 patients (2%). Three patients (1%) received a boost to the supraclavicular region and axillary apex for node-positive disease in these basins.

One hundred ninety-seven patients (67%) received adjuvant systemic therapy. One hundred twenty-three patients (42%) received adjuvant chemotherapy, and 100 (34%) received tamoxifen. Patients were followed up for a median of 89 months (range, 13–126 months).

Complications

Grade 2 or higher complications were identified in 29 patients (9.9%) and are listed in Table 2. They included arm edema in 13 patients (4.5%), breast skin fibrosis in 12 (4%), decreased range of motion in 4 (1.4%), pneumonitis in 2 (.7%), neuropathy in 2 (.7%), fat necrosis in 1 (.3%), rib fracture in 1 (.3%), shoulder stiffness without decreased range of motion in 1 (.3%), and shrinkage of breast size requiring use of a breast prosthesis in 1 (.3%). One patient (.3%) had mild esophagitis that responded to sucralfate. No cardiac

TABLE 2. *Long-term complications of breast-conservation therapy*

	Grade, n (%)				
Complication	1	2	3	4	Total
Arm edema	27 (9.2)	9 (3.1)	4 (1.4)	0	40 (13.6)
Breast thickening/fibrosis	73 (24.8)	11 (3.7)	1 (.3)	0	85 (28.9)
Axillary fibrosis	5 (1.7)	0 (0)	0	0	5 (1.7)
Fat necrosis	1 (.3)	1 (.3)	0	0	2 (.7)
Pneumonitis	0 (0)	2 (.7)	0	0	2 (.7)
Pulmonary fibrosis	6 (2.0)	0 (0)	0	0	6 (2.0)
Rib fracture	0 (0)	1 (.3)	0	0	1 (.3)
Decreased range of motion	10 (3.4)	4 (1.4)	0	0	14 (4.8)
Neuropathy	0 (0)	2 (.7)	0	0	2 (.7)
Other	1 (.3)	2 (.7)	0	0	3 (1.0)

mortality or sarcomas had occurred in the series at the time of this writing.

Arm Edema

Arm edema of any grade occurred in 40 (13.6%) of the 294 patients in our series. An actuarial curve of the occurrence of arm edema is presented in Fig. 1. Although arm edema occurred at a median time of 17 months, it was detected as early as 1 month and as late as 109 months after surgical treatment. Arm edema was still present on last follow-up in 25 (63%) of the 40 patients with arm edema. Four patients had limited range of motion because of arm edema; one patient required assistance with activities of daily living. Eight (20%) of the 40 patients with arm edema were treated with a pressure garment, 4 (10%) were treated with a pneumatic compression device, and 3 (7.5%) were treated with manual lymphatic drainage. Four (10%) of the 40 patients with arm edema developed arm cellulitis, compared with 4 (1.6%) of the 254 patients without arm edema (P = .002). Two of the patients developed arm edema after an episode of cellulitis or lymphangitis.

Arm edema was more common after lumpectomy plus ALND than after lumpectomy alone (15% vs. 3%; P = .05; Table 3); all of the 13 patients who had grade 2 or greater edema had undergone an ALND. Arm edema was not associated with the number of lymph nodes removed or the number of histologically positive lymph nodes. Patients who developed arm edema had a higher median weight than patients without arm edema (74 vs. 67 kg; P = .01). Patient age, pathologic or clinical tumor size, and adjuvant chemotherapy did not affect the risk of arm edema.

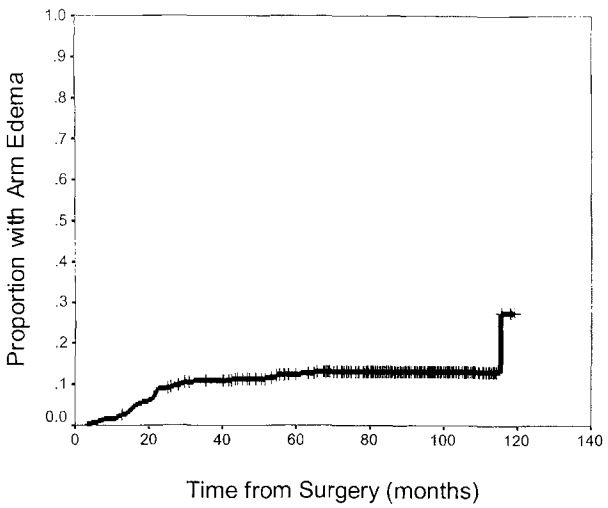

FIG. 1. Actuarial occurrence of arm edema in patients undergoing breast-conservation therapy.

TABLE 3. *Determinants of arm edema*

Variable	Patients with edema (n = 40)	Patients without edema (n = 254)	P value
Surgery			
Lumpectomy only	1	33	.05
Lumpectomy and ALND	39	221	
Nodal irradiation			
Yes	23	107	.07
No	17	147	
Patient weight, median (kg)	74	67	.01

ALND, axillary lymph node dissection.

Arm edema occurred in 18% of patients who underwent surgery accompanied by irradiation of the breast and axillary lymph nodes, compared with 10% of patients who underwent surgery but did not receive nodal irradiation (P = .07). Ten of the 13 patients with grade 2 or greater arm edema had received nodal irradiation. The incidence of arm edema by axillary treatment is listed in Table 4. There was no difference in the arm edema rate of patients who received electron treatment to the supraclavicular field compared with those who were treated with photons. The risk of arm edema was similar in patients who received irradiation to the breast with ^{60}Co gamma rays and patients who were treated with photons from a linear accelerator.

Breast Fibrosis

Thickening or fibrosis of the skin overlying the breast occurred in 85 (29%) of the 294 patients, but only 12 patients (4%) experienced grade 2 or 3 fibrosis. Breast fibrosis was more frequent in patients treated with additional radiation fields (38% vs. 21%; P = .001) and in patients who received a boost (33% vs. 22%; P = .041). The median clinical tumor size was 2.5 cm in patients with breast fibrosis and 2.0 cm in patients without breast fibrosis (P = .005). The median pathologic tumor size was 1.6 cm in patients with breast fibrosis and 1.4 cm in patients without breast fibrosis (P = .068). The median

TABLE 4. *Rate of arm edema by axillary treatment*

Treatment	Total No. patients	No. Patients with arm edema (%)
ALND plus		
Breast irradiation only	135	17 (12)
SCF irradiation	88	15 (17)
SCF and axillary irradiation	25	5 (20)
No ALND		
Breast irradiation only	23	0 (0)
SCF irradiation	2	0 (0)
SCF and axillary irradiation	7	0 (0)

ALND, axillary lymph node dissection; SCF, supraclavicular field.

age of patients with breast fibrosis was 53 years compared with 51 years for patients without fibrosis ($P = .064$). Patient weight, use of chemotherapy or hormonal therapy, and treatment with a ^{60}Co unit did not affect the overall incidence of fibrosis. Two patients in the series had previously placed breast implants; both patients developed capsular contractures that required intervention.

Neuropathy

Two patients in the series developed significant neurological symptoms. The first patient underwent lumpectomy and ALND. After surgery, the patient developed sensitivity of the skin overlying the breast and persistent axillary pain that necessitated narcotics and temporary nerve blocks. The second patient had supraclavicular lymph node involvement at presentation. She underwent a lumpectomy under local anesthesia without ALND because of her risk of perioperative cardiac complications. After the operation, she received 50 Gy of irradiation to the breast, 50 Gy to the supraclavicular fields, and 50 Gy to the midaxilla, with a 21-Gy posterior axillary supplement. The patient subsequently developed pain in the ipsilateral shoulder; this pain radiated down her arm. She had limited range of motion because of the pain.

Local and Systemic Recurrence

At a median follow-up of 89 months, 19 patients (6.4%) developed a locoregional recurrence, and 32 (10.9%) had developed a systemic recurrence. Seven of the 32 patients with systemic recurrence also had a local recurrence; local recurrences were detected before the systemic recurrence in 4 patients and were detected simultaneously with the systemic recurrence in 3 patients. None of the patients with local recurrence had positive surgical margins. Nine of the patients with local recurrence had a boost. Two hundred fifty-one patients (85.4%) were alive at last follow-up.

DISCUSSION

This study has shown that breast-conservation surgery and radiotherapy were associated with grade 2 or higher late complications in only 9.9% of patients. In 1989, Stotter et al.[14] reported the results of breast conservation in 536 patients treated at our institution. In that study, symptomatic pneumonitis occurred in 5% of patients, moderate to severe breast fibrosis occurred in 10%, and rib fractures occurred in 3%. In this study, we found a significant decrease in the incidence of these radiation-associated complications with modern radiotherapy techniques. The incidence of arm edema, however, did not significantly decrease. Although thickening or fibrosis of the skin overlying the breast was common in our series, occurring in 29% of patients, only 4% of patients experienced grade 2 or 3 fibrosis. Our study is limited because of its retrospective nature, making it more difficult to distinguish between surgical scarring and fibrosis. Surprisingly, treatment with a ^{60}Co unit did not increase the incidence of fibrosis. Similar to what has been reported by Borger et al.,[15] breast fibrosis was more frequent in patients with larger tumors, in patients treated with additional radiation fields, and in patients who received a boost. The use of a radiation boost has previously been reported to adversely affect cosmetic outcome.[10] These findings further justify our current emphasis on achieving surgically negative margins by reexcision when possible, rather than relying on a radiation boost for local control.

Arm edema was the dominant complication in our series. Grade 2 (>3-cm difference in arm circumference) or greater arm edema occurred in 4.5% of the patients. This incidence of arm edema is similar to what has previously been reported in the literature.[16–20] In our series, arm circumferences were measured in patients who subjectively complained of arm swelling or appeared on physical examination to have arm swelling. Because objective assessment reveals a higher incidence of arm edema than does subjective assessment, we might have found a higher arm edema rate if routine arm measurements had been performed. Kissin et al.[21] found that subjective lymphedema occurred in 14% of patients, but on volumetric assessment, 26% of patients were found to have lymphedema. Gallagher and Algird[22] assessed arm swelling in 100 patients by measuring circumference and volume and reported that persistent lymphedema occurred in 5%, transient swelling occurred in 30%, and measurable swelling occurred in 70% of the patients.

In agreement with what has been reported by others, we found that the risk of arm edema was largely determined by the addition of ALND to the surgical treatment.[10,23,24] In contrast to the findings from other studies,[10,11,24–26] the number of lymph nodes removed and the use of adjuvant chemotherapy did not significantly increase the risk of arm edema in our series. There was a trend toward increased risk of arm edema in patients who received nodal irradiation. This supports the findings of Zissiadis et al.,[7] who reported that the rate of moderate to severe arm edema was 5% in patients treated with surgery alone, 2% in those treated with radiation alone, and 23% in those treated with surgery and radiation.

The median weight of patients who developed arm edema was higher than that of patients who did not develop edema. This result confirms the findings of Werner et al.[27] and Roses et al.[16] Werner et al.[27] found that among 282 patients treated with breast-conservation surgery and radiation for stage I and II breast cancer, the treatment-related factors did not significantly predict the risk of arm edema. In contrast, body mass index was strongly associated with both the frequency and severity of arm edema. Roses et al.[16] similarly found that after level I and II axillary dissection, the only predictor of arm edema on multivariate analysis was heavy and obese body habitus. Further studies are needed to determine the possible links between patient weight and increased risk of lymphedema; these may include altered tissue sensitivity to radiation because of increased fat content, differences in radiotherapy technique, or higher lymphatic pressure after axillary dissection because of a larger tissue volume being drained. The increased risk of lymphedema with higher body weight should be kept in mind during preoperative patient counseling. Weight reduction may be explored as a preventive or treatment strategy for lymphedema.

In a recent study by Roses et al.,[16] 200 patients who had undergone axillary surgery at least 1 year earlier (112 patients treated with breast-conservation surgery, 88 treated with mastectomy) were evaluated for arm swelling. The authors reported an objective difference in arm circumference at a single site of >2 cm in 13.5% of patients. They concluded that characterization of level I or II axillary dissection as a procedure with significant complications is not justified. Our findings lead us to a different conclusion. Although the incidence of grade 2 or higher arm edema (>3-cm difference below the elbow) in our series was 4.5%, many of these patients required specialized treatments, including pressure garments, manual lymphatic drainage, or the use of a pneumatic pressure device. Four patients (1.7%) had edema severe enough to limit their range of motion; one of these required assistance with activities of daily living. Thus, when it did occur, arm edema seemed to have a great effect on patients' quality of life.

Patients with arm edema have been reported to have an increased lifetime risk for the development of cellulitis in the ipsilateral arm,[28] and this was the case in our study. It is interesting to note that two of our patients developed arm edema after an episode of cellulitis or lymphangitis. Similarly, Petrek et al.[29] reported that 56% of patients who developed arm edema stated that their first arm infection or injury occurred before or at the same time that the arm edema was noted. This indicates not only that lymphatic stasis can predispose to bacterial infections, but also that infections can lead to arm edema, presumably through inflammation and fibrosis. Patient education is crucial in prevention and early intervention.

Axillary surgery was the most important risk factor for sequelae of breast-conservation therapy in our series. This finding further emphasizes the importance of current efforts to determine whether adequate prognostic information can be obtained by alternative and less invasive procedures. Over the past decade, several molecular markers have been proposed to predict the biological behavior of the tumor[30–36]; however, no single biological marker has been able to replace the prognostic information gained from axillary nodal status. In the near future, however, it may be possible to screen for a panel of molecular markers to determine the biological aggressiveness of each patient's tumor, potentially obviating axillary lymph node staging. Until a panel of markers is verified prospectively and becomes widely available, we will continue to rely on axillary status for prognostic information. Sentinel lymph node biopsy performed by experienced surgeons has been shown to be an alternative to ALND for the assessment of nodal status in breast cancer patients.[37–40] It is hoped that lower rates of arm edema can be achieved with the use of sentinel lymph node biopsy with or without nodal irradiation. Whether axillary dissection has an actual survival benefit will be definitively answered in the upcoming years with the American College of Surgeons Oncology Group Protocol Z0011, in which patients who are undergoing breast-conserving surgery who have sentinel lymph node metastases receive adjuvant systemic therapy and breast irradiation and are randomly assigned to completion ALND or no immediate axillary surgery.

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