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## TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED STUDY COMPARING BREAST-CONSERVING SURGERY WITH RADICAL MASTECTOMY FOR EARLY BREAST CANCER

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### ABSTRACT

**Background** We conducted 20 years of follow-up of women enrolled in a randomized trial to compare the efficacy of radical (Halsted) mastectomy with that of breast-conserving surgery.

**Methods** From 1973 to 1980, 701 women with breast cancers measuring no more than 2 cm in diameter were randomly assigned to undergo radical mastectomy (349 patients) or breast-conserving surgery (quadrantectomy) followed by radiotherapy to the ipsilateral mammary tissue (352 patients). After 1976, patients in both groups who had positive axillary nodes also received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil.

**Results** Thirty women in the group that underwent breast-conserving therapy had a recurrence of tumor in the same breast, whereas eight women in the radical-mastectomy group had local recurrences ( $P < 0.001$ ). The crude cumulative incidence of these events was 8.8 percent and 2.3 percent, respectively, after 20 years. In contrast, there was no significant difference between the two groups in the rates of contralateral breast carcinomas, distant metastases, or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7 percent in the group that underwent breast-conserving surgery and 41.2 percent in the radical-mastectomy group ( $P = 1.0$ ). The respective rates of death from breast cancer were 26.1 percent and 24.3 percent ( $P = 0.8$ ).

**Conclusions** The long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy. Breast-conserving surgery is therefore the treatment of choice for women with relatively small breast cancers. (N Engl J Med 2002;347:1227-32.)

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THE radical mastectomy introduced by Halsted<sup>1</sup> was the treatment of choice for breast cancer of any size or type, regardless of the patient's age, for 80 years. Apart from a few modifications, such as enlarging the extent of the dissection to include the internal mammary nodes or reducing it to spare the pectoralis muscles, the Halsted mastectomy was performed as originally described throughout this period. The possibility of attempting a surgical procedure that would conserve the breast was not widely considered during those years.<sup>2,3</sup>

In 1969, a randomized study to compare radical mastectomy with breast-conserving surgery, which was termed "quadrantectomy," was approved by the World Health Organization Committee of Investigators for Evaluation of Methods of Diagnosis and Treatment of Breast Cancer.<sup>4</sup> The recruitment of patients began at the Milan Cancer Institute in 1973, after the new procedure was standardized, and preliminary data showing that survival rates were equal after radical and breast-conserving surgery were published in 1977<sup>5</sup> and 1981.<sup>6</sup>

The main criticism of the data was that they were too preliminary; patients with small breast cancers must be followed for a very long time, even decades, to ensure that the evaluation of the efficacy of any new treatment is accurate. We carefully monitored the 701 women in the trial for up to 29 years, and we now report the results.

### METHODS

#### Study Design

Enrollment in the trial began in 1973 and ended in May 1980 after the recruitment of 701 patients who had breast cancers with

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a maximal diameter of 2 cm or less on physical examination (stage T1) and no palpable axillary nodes (N0). Patients who were older than 70 years of age or who had a history of cancer were excluded. The patients underwent excisional biopsy under general anesthesia, and those who had an infiltrating carcinoma that was no more than 2 cm in diameter on gross examination and microscopic examination of a frozen section were stratified according to menopausal status and randomly assigned to undergo either radical (Halsted) mastectomy alone or a breast-conserving quadrantectomy in combination with complete axillary dissection and postoperative radiotherapy to the ipsilateral mammary tissue. The details of the surgical techniques and the radiation procedures have been described previously.<sup>5,6</sup> A complete axillary dissection was performed, and radiotherapy was delivered to the breast at a dose of 50 Gy plus a boost of 10 Gy. From 1973 to 1975, 33 patients with axillary metastases were further randomly assigned to receive additional radiotherapy to the supraclavicular and internal mammary nodes (40 to 45 Gy over a period of four to five weeks) and 23 to receive no further radiotherapy ( $P=0.22$  for the difference in the numbers of patients in the two subgroups).

Beginning in 1976, all patients with positive axillary nodes were given 12 monthly cycles of chemotherapy according to the following schedule: 100 mg of cyclophosphamide per square meter of body-surface area per day orally for 14 days and 40 mg of methotrexate per square meter plus 600 mg of fluorouracil per square meter intravenously on days 1 and 8. Chemotherapy was begun 15 to 30 days after radical mastectomy and simultaneously with radiotherapy in the group assigned to breast-conserving therapy. No patient received tamoxifen during the trial or follow-up. For the first 10 years, patients were seen at the clinic every 3 months and underwent a complete examination, including chest and skeletal radiography, liver ultrasonography, and mammography, every year. Thereafter, the patients were seen once a year and underwent annually routine mammography. Other examinations were performed whenever they were clinically indicated. Three patients were lost to follow-up. The median follow-up was 20 years. The main data for all patients were recorded, updated, and stored in an automated data system after the accuracy of the data was verified.

### Statistical Analysis

The estimated crude cumulative incidence of recurrent tumor in the same breast in the quadrantectomy group and local recurrence in the radical-mastectomy group, as well as of contralateral-breast carcinomas, regional or distant metastases, and other primary tumors, whichever occurred first, was calculated according to a competing-risk framework, as described by Marubini and Valsecchi,<sup>7</sup> and compared with use of the Gray test.<sup>8</sup> The time to the occurrence of these events was computed from the date of surgery. Because of the limited number of end-point events, multivariate analyses were deemed an inappropriate method of comparing the effects of treatment on recurrent tumor in the same breast and local recurrences among stratified patients. For exploratory purposes, we computed the event rate (the cumulative number of events during follow-up) according to the main characteristics of the patients and the disease.

The overall survival curves for each treatment group were obtained with use of the Kaplan–Meier method and compared with use of the log-rank test.<sup>9</sup> Because of the long follow-up period, many deaths were not caused by breast cancer. Therefore, we also estimated the cause-specific mortality rate on the basis of available information on the cause of death, using a competing-risk framework and the Gray test. We validated this approach by estimating the crude cumulative cause-specific mortality rate on the basis of life-tables,<sup>10</sup> rather than information on the cause of death, since such information is often unreliable and unsuitable for statistical analyses. All tests were two-sided, and a  $P$  value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

Of the 701 patients who entered the trial, 349 underwent a radical (Halsted) mastectomy and 352 underwent breast-conserving surgery. The primary carcinoma was palpable in 698 patients, whereas it was discovered only on mammography in 3 patients. The mean ( $\pm$ SD) age of the patients was  $51\pm 10.1$  years in the radical-mastectomy group and  $50\pm 10.4$  years in the quadrantectomy group. At base line, similar proportions of patients in the two groups were premenopausal, had tumors that were less than 1 cm in diameter, had a tumor in the upper or central quadrant or the lower quadrant, had a history of biopsy, and had axillary-node metastases (Table 1).

### Recurrent Tumors

The probability of recurrent tumor was significantly higher in the group that received breast-conserving therapy than in the radical-mastectomy group (30 of 352 vs. 8 of 349 patients,  $P<0.001$ ) (Fig. 1). The mean ( $\pm$ SE) crude cumulative incidence of recurrent tumor in the same breast was  $8.8\pm 3.2$  percent after 20 years among patients treated with breast-conserving surgery and  $2.3\pm 0.8$  percent in the radical-mastectomy group. Of the 30 patients with a recurrent tumor in the same breast, 29 underwent total mastectomy and 1 patient underwent a second local resection. Of these 30 cases of recurrent tumor, 10 appeared in the scar and were thus defined as true recurrences, whereas 20 occurred in other quadrants of the breast and were therefore classified as second ipsilateral carcinomas.

Table 2 shows the event rates according to age, tumor size, and the extent of axillary-node involvement

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE WOMEN WHO UNDERWENT RADICAL MASTECTOMY AND THOSE WHO UNDERWENT BREAST-CONSERVING THERAPY.**

CHARACTERISTIC	RADICAL MASTECTOMY (N=349)	BREAST-CONSERVING THERAPY (N=352)	P VALUE
	percent		
Premenopausal	53.9	56.8	0.4
Tumor <1 cm in diameter*	44.4	46.0	0.7
Tumor in upper or central quadrant	72.4	75.8	0.3
Tumor in lower quadrant	27.6	24.2	0.3
Previous biopsy	13.7	14.8	0.7
No. of axillary-node metastases	24.6	27.0	0.5
1–3	18.9	21.9	0.3
>3	5.7	5.1	0.7

\*Information on tumor size was missing for 53 women (22 in the radical-mastectomy group and 31 in the group that received breast-conserving therapy).



**Figure 1.** Crude Cumulative Incidence of Local Recurrences after Radical Mastectomy and Recurrences in the Same Breast after Breast-Conserving Therapy.

at base line. In the radical-mastectomy group, the overall rate of local recurrences was low (average, 0.17 per 100 woman-years of observation) and was not significantly affected by the patient's age and the size of the tumor at base line. The rate of recurrences was relatively high among women with more than three axillary nodes containing metastases, but the importance of this finding is uncertain because of the small number of such patients. In the group that received breast-conserving therapy, the average event rate was almost four times as high (0.63 per 100 woman-years of observation) as the rate in the radical-mastectomy group. The rate in this group varied with age and was high-

est among the women who were 45 years of age or younger at base line (1.05 per 100 woman-years of observation).

When true recurrences and second ipsilateral carcinomas were considered separately, the rates were 0.21 and 0.42 per 100 woman-years of observation, respectively. The timing of the two kinds of events also differed: true recurrences appeared a median of 92 months after quadrantectomy, and second ipsilateral carcinomas appeared a median of 117 months afterward. In comparison, the median time to local recurrence was 54 months in the radical-mastectomy group.

#### Other Events

Table 3 shows the cumulative incidence of neoplastic events other than local recurrences and recurrences in the same breast. There were no statistically significant differences between the two groups in the 20-year crude cumulative incidence of contralateral-breast carcinomas, distant metastases, or other primary cancers. The overall rate of contralateral-breast cancer was 0.66 per 100 woman-years of observation, a figure that was nearly identical to the rate of recurrent tumors in the same breast in the group that received breast-conserving therapy (0.63 per 100 woman-years of observation).

#### Mortality

Of the 701 women who entered the trial, 308 died — 152 in the radical-mastectomy group and 156 in the group that received breast-conserving therapy.

**TABLE 2.** RATES OF LOCAL RECURRENCES AMONG WOMEN WHO UNDERWENT RADICAL MASTECTOMY AND OF RECURRENT TUMOR IN THE SAME BREAST AMONG WOMEN WHO UNDERWENT BREAST-CONSERVING SURGERY, ACCORDING TO BASE-LINE CHARACTERISTICS.

CHARACTERISTIC	RADICAL MASTECTOMY (N=349)		BREAST-CONSERVING THERAPY (N=352)	
	NO. OF PATIENTS WITH RECURRENCE	RATE/100 WOMAN-YR*	NO. OF PATIENTS WITH RECURRENCE	RATE/100 WOMAN-YR*
Overall	8	0.17	30	0.63
Age at local recurrence or recurrence in same breast				
≤45 yr	3	0.18	18	1.05
46–60 yr	3	0.14	8	0.34
>60 yr	2	0.24	4	0.54
Diameter of primary tumor†				
≤1 cm	4	0.18	12	0.51
>1 cm	4	0.19	14	0.69
No. of axillary nodes involved				
0	5	0.13	26	0.74
1–3	1	0.12	3	0.26
>3	2	1.09	1	0.64

\*The rate is per 100 woman-years of observation.

†Information on tumor size was missing for 53 women (22 in the radical-mastectomy group and 31 in the group that received breast-conserving therapy).

**TABLE 3.** NUMBERS AND CRUDE CUMULATIVE INCIDENCE OF EVENTS OVER THE 20-YEAR PERIOD IN THE TWO GROUPS OF PATIENTS.

EVENT	RADICAL MASTECTOMY		BREAST-CONSERVING THERAPY		P VALUE*
	NO. OF EVENTS	RATE/100 WOMAN-YR	NO. OF EVENTS	RATE/100 WOMAN-YR	
Contralateral-breast carcinoma	34	10.2	29	8.7	0.5
Distant metastases	83	24.3	82	23.3	0.8
Other primary cancers	30	8.8	31	9.1	0.9

\*P values were calculated with use of the Gray test.

Among these women, 177 (57 percent) died of breast cancer (86 in the radical-mastectomy group and 91 in the group that received breast-conserving therapy), 42 (14 percent) died of other primary cancers, and 73 (24 percent) died of nonneoplastic diseases. The cause of death could not be ascertained in 16 patients (5 percent). The overall survival curves overlapped in the two groups (Fig. 2). Twenty years after surgery, the rate of death from all causes was 41.2 percent in the radical-mastectomy group and 41.7 percent in the group that received breast-conserving therapy ( $P=1.0$ ). The observed rate of death from breast cancer was 24.3 percent and 26.1 percent, respectively ( $P=0.8$ ), similar to the rates expected on the basis of calculations in age-matched Italian women (23.6 percent and 24.8 percent, respectively). The survival curves were also similar when the two groups were stratified according to the size of the primary carcinoma at base line (Fig. 3).

Among the 33 patients with positive axillary nodes who were assigned to receive additional radiotherapy to the supraclavicular lymph nodes in the early years of the study, the mortality rate was 64 percent (21 of 33), as compared with a rate of 48 percent (11 of 23) among the 23 similar patients who were assigned to receive no additional radiotherapy ( $P=0.08$ ).

### DISCUSSION

Our results show that the long-term survival of women with early breast cancer who were treated with breast-conserving surgery and postoperative radiotherapy to the ipsilateral breast was virtually identical to the rate among women who underwent radical mastectomy. After a median follow-up of 20 years, the overall and breast-cancer-specific survival rates were also similar in the two groups. Our observation is in line with the 20-year results of trial B-06 of the National Surgical Adjuvant Breast and Bowel Project, presented by Fisher et al. elsewhere in this issue of the *Journal*.<sup>11</sup> These results should dispel any lingering doubts about the safety and efficacy of breast-conserving surgery as a treatment for breast cancer.

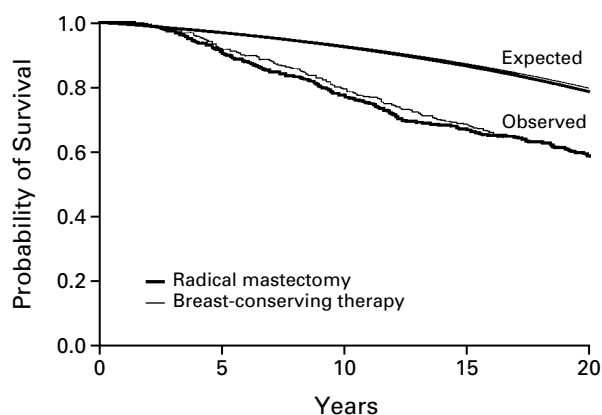
Our finding that the survival rate was the same in both groups, even though the rate of local recurrences was higher in the group that received breast-conserving therapy, supports the original basis of our trial — namely, that the prognosis of breast cancer is linked to the presence or absence of occult distant foci of metastatic cells and not to the extent of local surgery.

The goal of the surgical technique we used was complete removal of the primary carcinoma, together with the removal of a generous amount of the surrounding normal breast tissue (extending 1.5 to 2.0 cm from the edge of the tumor). The objective was to dissect the entire area from which the tumor originated. Portions of the overlying skin and deep muscular fascia were also removed. The operation was termed “quadrantectomy” to indicate the extent of the resection.

With the use of this technique and postoperative radiotherapy, the cumulative incidence of recurrent tumor in the conserved breast was only 8.8 percent after 20 years of follow-up. The rate of such recurrences was nearly identical to the rate of contralateral-breast cancer (0.63 per 100 woman-years and 0.66 per 100 woman-years of observation, respectively), suggesting that many of the former tumors were actually new primary carcinomas.

The patients assigned to radical mastectomy underwent the classic Halsted procedure, because at the time the study began, the modified radical mastectomy had not been accepted by most surgeons. If we had compared breast-conserving surgery with modified radical mastectomy, the difference in the rate of local recurrences between the two groups might have been smaller than the difference with the Halsted procedure.

We found that the rate of recurrence of tumors in the same breast in the group that received breast-conserving therapy was highest among women who were 45 years of age or younger at the time of surgery. This finding is in keeping with the common pathological findings of multifocality and multicentricity in breast cancers in young women.



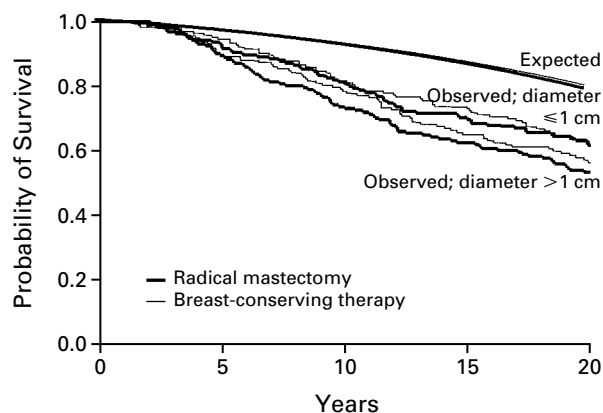
**Figure 2.** Kaplan–Meier Estimates of Survival after Radical Mastectomy or Breast-Conserving Therapy.

The two lower curves correspond to observed survival, taking into account deaths from any cause. The upper curves (which are almost identical in the two groups) show the expected survival rate on the basis of mortality rates in age-matched cohorts of Italian women.

Although scattered radiation beams certainly reached the opposite breast, the incidence of contralateral-breast carcinomas was lower in the group that underwent breast-conserving surgery plus radiotherapy than in the radical-mastectomy group. This finding suggests that the doses of radiotherapy delivered in the study were not carcinogenic.<sup>12</sup> Among 56 patients with positive axillary nodes who were assigned to receive either prophylactic supraclavicular radiotherapy or no such treatment, the respective mortality rates were 64 percent and 48 percent.

Patients with intraductal noninvasive carcinomas were not eligible for our trial. Other studies have shown that a breast-conserving approach should also be the treatment of choice for women with in situ breast carcinomas that are relatively small.<sup>13,14</sup> Our data apply only to patients with a primary tumor of limited size (maximal diameter, 2 cm). Other studies have successfully used breast-conserving procedures in women with larger primary tumors.<sup>15-17</sup> In clinical practice it is important to consider the size of the primary tumor in relation to the size of the breast, because quadrantectomy is technically difficult in patients with small breasts and large cancers. In these women, mastectomy with immediate reconstruction may be the best choice.

The 20-year rate of death from breast cancer in node-negative patients who received no systemic adjuvant therapy was 20.8 percent. This result is notable, because 20 to 30 years ago the results of pathological examination of the lymph nodes were not as accurate as they are now. In our recent trial involving



**Figure 3.** Kaplan–Meier Estimates of Survival after Radical Mastectomy or Breast-Conserving Therapy, According to the Size of the Primary Carcinoma.

The two upper curves (which are almost identical in the two groups) show the expected survival rate on the basis of mortality rates in age-matched cohorts of Italian women. The four lower curves show the survival rates in the two groups stratified according to the maximal diameter of the breast cancer at base line.

patients with the same stage of disease as patients in our earlier study (T1 and N0), 36 percent had positive axillary nodes on pathological examination, as compared with 26 percent in the earlier trial (unpublished data). For this reason, we believe that about 10 percent of the patients who were originally considered to be node-negative were actually node-positive.

We believe that the use of a breast-conserving procedure that is associated with a high quality of life is one reason for the increasing awareness of and participation in early-detection programs on the part of women. The early results of our study were confirmed by other European and American trials in 1983<sup>16</sup> and 1985.<sup>17</sup> We believe that as a result of these trials, about 300,000 women with early breast cancer worldwide each year undergo breast-conserving surgery rather than radical mastectomy.

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