TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

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ABSTRACT

Background   In 1976, we initiated a randomized trial to determine whether lumpectomy with or without radiation therapy was as effective as total mastectomy for the treatment of invasive breast cancer.

Methods   A total of 1851 women for whom follow-up data were available and nodal status was known underwent randomly assigned treatment consisting of total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation. Kaplan–Meier and cumulative-incidence estimates of the outcome were obtained.

Results   The cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3 percent in the women who underwent lumpectomy and breast irradiation, as compared with 39.2 percent in the women who underwent lumpectomy without irradiation (P<0.001). No significant differences were observed among the three groups of women with respect to disease-free survival, distant-disease–free survival, or overall survival. The hazard ratio for death among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P=0.51). The hazard ratio for death among the women who underwent lumpectomy followed by breast irradiation, as compared with those who underwent total mastectomy, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P=0.74). Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the hazard ratio for death among the women who underwent postoperative breast irradiation, as compared with those who did not, was 0.91 (95 percent confidence interval, 0.77 to 1.06; P=0.23). Radiation therapy was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes.

Conclusions   Lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained. (N Engl J Med 2002;347:1233-41.)

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I N 1971, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the B-04 study, a randomized clinical trial conducted to resolve controversy over the surgical management of breast cancer. The 25-year findings from that study[1] showed that there was no significant difference in survival between women treated with the Halsted radical mastectomy and those treated with less extensive surgery. In 1973, we began to design a second randomized trial, B-06, to evaluate the efficacy of breast-conserving surgery in women with stage I or II breast tumors that were 4 cm or less in diameter. Patients were treated with lumpectomy, an operation that involved removal of enough normal breast tissue to ensure that the margins of the resected specimen were free of tumor. The outcome for women who were treated with lumpectomy alone or with lumpectomy and postoperative breast irradiation was compared with that for similar women who were treated with total mastectomy. Previous analyses[2-4] showed no significant differences in survival among the women in the three treatment groups and demonstrated a significant decrease in the rate of recurrent cancer in the ipsilateral breast after lumpectomy plus irradiation. We now report the 20-year findings.

METHODS

Study Design

Between August 8, 1976, and January 27, 1984, a total of 2163 women with invasive breast tumors that were 4 cm or less in their largest diameter and with either negative or positive axillary lymph nodes (stage I or II breast cancer) were randomly assigned to one of three treatments: total mastectomy, lumpectomy (which we initially called segmental mastectomy), or lumpectomy followed by breast irradiation. Axillary nodes were removed regardless of the treatment assignment. Written informed consent was provided by all women whose data were analyzed. The design of the trial, eligibility requirements, randomization procedures, surgical and irradiation techniques, and selected characteristics of the patients and the tumors have been described previously.[2-5]

The women treated with lumpectomy underwent tumor resection, with removal of sufficient normal breast tissue to ensure both tumor-free specimen margins and a satisfactory cosmetic result. Only the lower two levels of the axillary nodes were removed, whereas in the women who underwent total mastectomy, the ax-

illary nodes were removed en bloc with the tumor. The protocol stipulated that 50 Gy of radiation be administered to the breast, but not the axilla, in women who underwent lumpectomy and breast irradiation. Neither external-beam nor interstitial radiation was used as a supplemental boost. All women with one or more positive axillary nodes received adjuvant systemic therapy with melphalan and fluorouracil.[6] Lumpectomy-treated women whose resected-specimen margins were found on histologic examination to contain tumor underwent total mastectomy but continued to be followed for subsequent events.

Statistical Analysis

Two cohorts were considered for the analysis of end points. One cohort included all the women with follow-up information who had originally consented to participate in the study (2105 women); the other included eligible women with follow-up information who accepted the assigned treatment, and whose nodal status was known (1851 women). Analysis of the two cohorts yielded similar results. To facilitate comparison of the current findings with those presented in prior reports, only the results of the analysis of the latter cohort are reported here.

The end points for overall treatment comparisons were disease-free survival, distant-disease–free survival, and overall survival. The times to these end points were calculated from the date of surgery. The events included in our analysis of disease-free survival were the first recurrence of disease at a local, regional, or distant site; the diagnosis of a second cancer; and death without evidence of cancer. A first recurrence of a tumor in the chest wall or in the operative scar, but not in the ipsilateral breast, was classified as a local recurrence. The protocol specified that the occurrence of a tumor in the ipsilateral breast after lumpectomy would not be considered an event in the analysis of disease-free survival because women who underwent total mastectomy as the assigned treatment were not at risk for such an event. Instead, the occurrence of a tumor in the ipsilateral breast after lumpectomy was considered to be a cosmetic failure. Recurrences in the internal mammary, supraclavicular, or ipsilateral axillary nodes were classified as regional occurrences. Recurrences at other locations were classified as distant recurrences. For the analysis of distant-disease–free survival, events included distant metastases as first recurrences, distant metastases after a local or regional recurrence, and all second cancers, including tumors in the contralateral breast. The analysis of overall survival included all deaths.

The Kaplan–Meier method was used to estimate disease-free survival, distant-disease–free survival, and overall survival for each treatment group.[7] Estimates are reported with their standard errors. Treatments were compared with the use of log-rank tests for all available observation times.[8] Tests of heterogeneity were used for two-way and three-way comparisons of end points. Comparisons of the two lumpectomy groups included only the 1137 women whose surgical specimens had tumor-free margins. Cox proportional-hazards models were used to estimate hazard ratios.[9] A hazard ratio greater than 1 indicates a better outcome, on average, for women in the reference group, whereas a value of less than 1 indicates a worse outcome for women in that group. If the total-mastectomy group was included in a comparison, it was designated as the reference group. In comparisons involving only the lumpectomy groups, the group of women who underwent lumpectomy without irradiation was designated as the reference group.

In the lumpectomy groups, hazard rates for a recurrence in the ipsilateral breast as a first event were compared with the use of the log-rank test. A nonparametric method[10] was used to estimate the cumulative-incidence curves for recurrence in the ipsilateral breast as a first event, and Gray's K-sample test statistic[11] was used to determine whether the difference in cumulative incidence between the lumpectomy-treated groups was significant.

Differences among the treatment groups with respect to death from causes other than breast cancer were determined with the

use of the log-rank statistic, with all follow-up data censored after a recurrence or a diagnosis of cancer in the contralateral breast. The method of log-rank subtraction[12] was then used to determine differences with respect to deaths related to breast cancer. This approach obviates the difficulty of having to precisely determine causes of death after recurrence but does require an assumption of independence between causes of death related to breast cancer and other causes of death, conditional on treatment. We also estimated cumulative-incidence curves for deaths that occurred without evidence of a recurrence or a diagnosis of cancer in the contralateral breast and for deaths that followed a recurrence or the development of disease in the contralateral breast. We compared these cumulative-incidence curves among the three treatment groups, using Gray's K-sample test.

All reported P values are based on two-sided tests. P values less than or equal to 0.05 were considered to be statistically significant. The current analysis was based on follow-up information through December 31, 2001, that was received at the NSABP Biostatistical Center as of March 31, 2002. Sixty-nine percent of all the women included in the analysis either were followed for at least 20 years or were known to have died during the follow-up period. The percentage of women who were followed for less than 20 years was similar among the treatment groups.

RESULTS

The distribution of women among the three treatment groups is shown in Table 1. For 58 of the 2163 women who were enrolled, follow-up information was not available.[4] Of the remaining 2105 patients, 81 were ineligible; 36 of these women had noninvasive tumors. Of the 2024 eligible patients with follow-up data, 165 refused the assigned treatment, and 8 had unknown nodal status. Thus, 1851 patients were included in the primary analysis.

The distribution of the women among the treatment groups according to age, tumor size, and nodal status was similar.[2] About 60 percent of the women were 50 years of age or older. Women with small tumors (≤2.0 cm in diameter) and women with large tumors (2.1 to 4.0 cm in diameter) were uniformly distributed among the treatment groups. Slightly more than 50 percent of the women had small tumors, and slightly less than 50 percent had large tumors. Sixty-two percent of the women had negative nodes, 26 percent had one to three positive nodes, and 12 percent had four or more positive nodes. Although determination of the estrogen-receptor status of the tumor was not a study requirement, the status was determined for about 75 percent of the tumors in each of the treatment groups; 36 percent were negative for estrogen receptor and 64 percent were positive. Tumor was found in the margins of specimens removed from 64 of the 634 women assigned to lumpectomy and from 61 of the 628 assigned to lumpectomy and irradiation.

Recurrence in the Ipsilateral Breast after Lumpectomy

Breast irradiation decreased the likelihood of a recurrence in the ipsilateral breast in the group of 1137 lumpectomy-treated women whose surgical specimens

TABLE 1. DISTRIBUTION OF PATIENTS AND DURATION OF FOLLOW-UP
AMONG THE TREATMENT GROUPS.*

VARIABLE	TOTAL MASTECTOMY	LUMPECTOMY ALONE	LUMPECTOMY PLUS IRRADIATION
Enrolled (no.)	713	719	731
No follow-up data	21	20	17
Excluded (no.)	103	65	86
Refused assigned treatment	76	34	55
Ineligible	26	28	27
Unknown nodal status	1	3	4
Included in analysis of total mastectomy vs. lumpectomy with or without irradiation (no.)	589	634	628
Included in analysis of lumpectomy alone vs. lumpectomy plus irradiation (no.)	—	570	567
Time in study (yr)			
Mean	20.8	20.6	20.7
Range	17.9–25.6	17.9–25.6	17.9–25.7

*Of the 1262 women who underwent lumpectomy with or without irradiation, 125 were not included because of the presence of tumor at the margins of the resected specimen.

had tumor-free margins. The cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery was 14.3 percent among the women who underwent irradiation after lumpectomy and 39.2 percent among those who underwent lumpectomy without irradiation (P<0.001) (Fig. 1). The benefit of radiation therapy was independent of the nodal status. Among the women with negative nodes, 36.2 percent of those who did not receive radiation therapy and 17.0 percent of those who did had a recurrence in the ipsilateral breast within 20 years (P<0.001). Among the women with positive nodes, 44.2 percent of those who did not undergo irradiation and 8.8 percent of those who did had a recurrence in the ipsilateral breast (P<0.001). In the group of women treated with lumpectomy alone, 73.2 percent of these events occurred within the first 5 years after surgery, 18.2 percent occurred 5 to 10 years after surgery, and 8.6 percent occurred more than 10 years after surgery. In the group of women treated with lumpectomy followed by breast irradiation, 39.7 percent of recurrences in the ipsilateral breast were detected within the first 5 years, 29.5 percent at 5 to 10 years, and 30.8 percent after 10 years.

Disease-free Survival and Distant-Disease–free Survival

Of the 1851 women in the current analysis, 36.8 percent were alive and free of cancer (Table 2). The most frequent first events were distant recurrences (in 24.5 percent of the women). With the exception of the rate of local recurrence, which was lower in the group treated with lumpectomy followed by breast irradiation than in the other two groups, the distribution of all first events was fairly similar among the three groups of women.
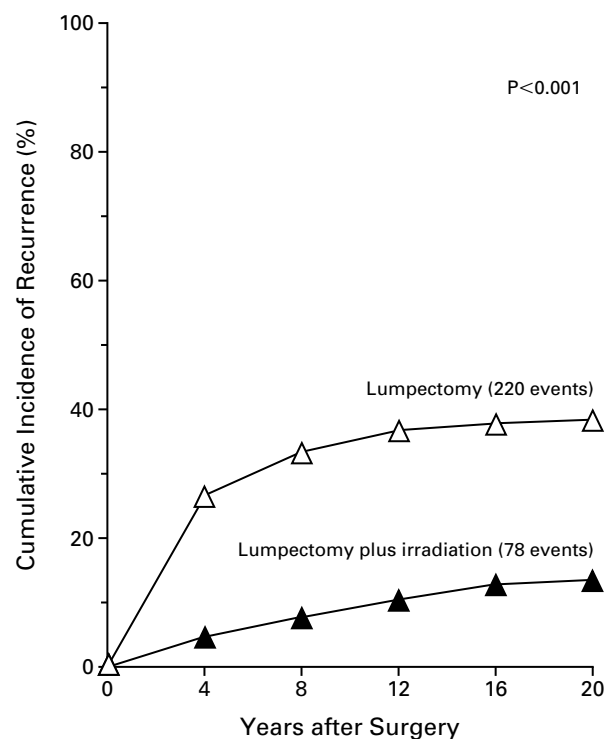

Figure 1. Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.

The data are for women whose specimens had tumor-free margins.

TABLE 2. FIRST REPORTED RECURRENCE AND OTHER FIRST EVENTS.*

EVENT	TOTAL MASTECTOMY (N=589)	LUMPECTOMY ALONE (N=634)	LUMPECTOMY PLUS IRRADIATION (N=628)
	no. of women (%)		
Recurrence	219 (37.2)	269 (42.4)	214 (34.1)
Local†	60 (10.2)	56 (8.8)	17 (2.7)
Regional	27 (4.6)	55 (8.7)	34 (5.4)
Distant	132 (22.4)	158 (24.9)	163 (26.0)
Diagnosis of cancer in contralateral breast	50 (8.5)	56 (8.8)	59 (9.4)
Diagnosis of second cancer‡	43 (7.3)	32 (5.0)	49 (7.8)
Death without evidence of breast cancer	59 (10.0)	51 (8.0)	69 (11.0)
Total	371 (63.0)	408 (64.4)	391 (62.3)
Alive, event-free	218 (37.0)	226 (35.6)	237 (37.7)

*The women in all groups underwent axillary dissection.

†Tumors in the ipsilateral breast after lumpectomy were not considered recurrences, and women in the lumpectomy groups who had such tumors were classified as event-free.

‡A second cancer was defined as any second primary cancer other than cancer in the contralateral breast.

There were no significant differences in disease-free survival among the three treatment groups (P=0.26) (Fig. 2A). The hazard ratio for a first event (diagnosis of recurrent disease or a second cancer or death without evidence of cancer) among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95 percent confidence interval, 0.92 to 1.21; P=0.47), and the hazard ratio for the women who underwent lumpectomy and breast irradiation, as compared with those who underwent total mastectomy, was 0.94 (95 percent confidence interval, 0.82 to 1.09; P=0.41). At 20 years, disease-free survival was 36±2 percent for the women who underwent total mastectomy, 35±2 percent for those who underwent lumpectomy alone, and 35±2 percent for those who underwent lumpectomy and breast irradiation. There was a nearly significant increase in disease-free survival for women who underwent lumpectomy and irradiation, as compared with those who underwent lumpectomy alone (hazard ratio, 0.87; 95 percent confidence interval, 0.75 to 1.01; P=0.07). At 20 years, disease-free survival was 35±2 percent for the women treated with lumpectomy alone and 36±2 percent for those treated with lumpectomy and postoperative irradiation.

There was no significant difference in distant-disease–free survival among the three treatment groups (P=0.34) (Fig. 2B). The hazard ratio for an event (diagnosis of distant disease or a second cancer) among women in the lumpectomy-alone group, as compared with the total-mastectomy group, was 1.11 (95 percent confidence interval, 0.94 to 1.30; P=0.21); the hazard ratio for the group treated with lumpectomy and irradiation, as compared with the total-mastecto-my group, was 1.01 (95 percent confidence interval, 0.86 to 1.18; P=0.95). At 20 years, distant-disease–free survival was 49±2 percent for the women treated with total mastectomy, 45±2 percent for those treated with lumpectomy alone, and 46±2 percent for those treated with lumpectomy plus irradiation. There was no significant difference in distant-disease–free survival between the women in the two lumpectomy groups who had specimens with tumor-free margins (hazard ratio, 0.89; 95 percent confidence interval, 0.75 to 1.04; P=0.15). At 20 years, distant-disease–free survival was 46±2 percent for the women treated with lumpectomy alone and 47±2 percent for those who received radiation therapy after lumpectomy.

Of the 702 first recurrences, 69 percent were detected within the first 5 years after surgery, and 11 percent after 10 years; 9 percent of local recurrences, 7 percent of regional recurrences, and 13 percent of distant recurrences were detected after 10 years (Table 3). Of the 165 tumors in the contralateral breast, 38 percent were detected within 5 years after surgery and 32 percent after 10 years.

Overall Survival

There was no significant difference in overall survival among the treatment groups (P=0.57) (Fig. 2C). The hazard ratio for death among the women treated with lumpectomy alone, as compared with those treated with total mastectomy, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P=0.51); the hazard ratio for the women treated with lumpectomy plus breast irradiation, as compared with those treated with total mastectomy, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P=0.74). At 20 years,
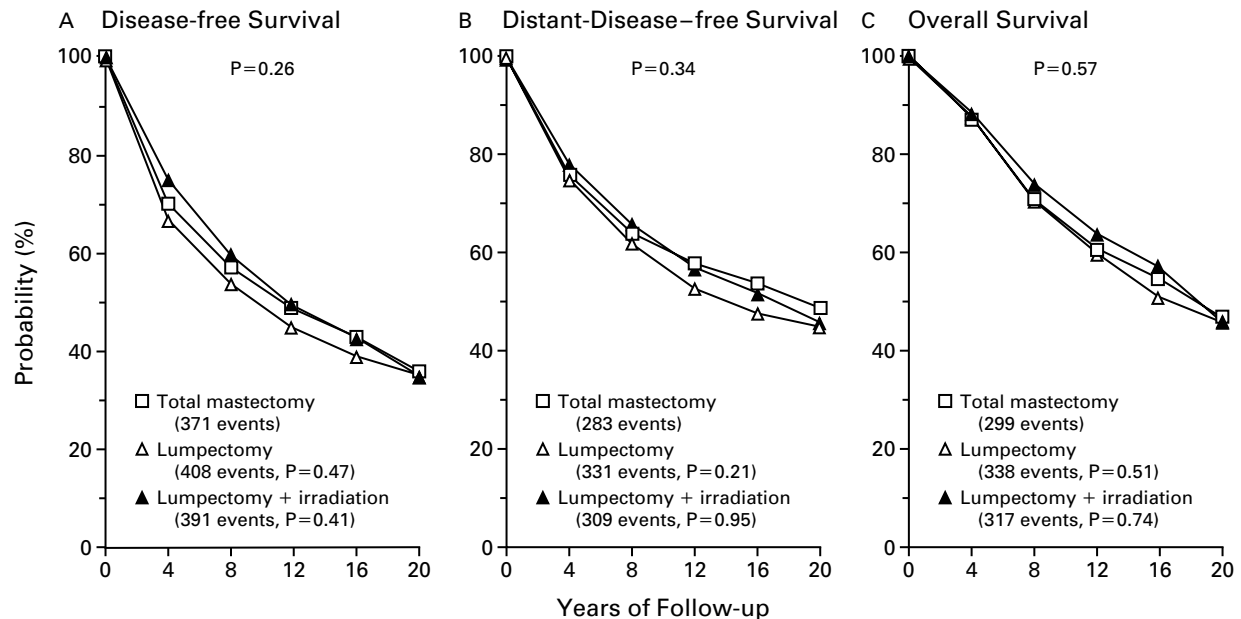
Figure 2. Disease-free Survival (Panel A), Distant-Disease–free Survival (Panel B), and Overall Survival (Panel C) among 589 Women Treated with Total Mastectomy, 634 Treated with Lumpectomy Alone, and 628 Treated with Lumpectomy plus Irradiation.

In each panel, the P value above the curves is for the three-way comparison among the treatment groups; the P values below the curves are for the two-way comparisons between lumpectomy alone or with irradiation and total mastectomy.

TABLE 3. FIRST BREAST-CANCER–RELATED EVENTS ACCORDING TO TREATMENT GROUP AND TIME OF OCCURRENCE.

EVENT AND YEARS OF FOLLOW-UP	TOTAL MASTECTOMY	LUMPECTOMY ALONE	LUMPECTOMY PLUS IRRADIATION	TOTAL
	number of women (percent)			
Any first recurrence				
≤5 yr	161 (74)	187 (70)	133 (62)	481 (69)
>5 and ≤10 yr	38 (17)	55 (20)	49 (23)	142 (20)
>10 yr	20 (9)	27 (10)	32 (15)	79 (11)
Local				
≤5 yr	47 (78)	43 (77)	5 (29)	95 (71)
>5 and ≤10 yr	9 (15)	10 (18)	7 (41)	26 (20)
>10 yr	4 (7)	3 (5)	5 (29)	12 (9)
Regional				
≤5 yr	24 (89)	44 (80)	26 (76)	94 (81)
>5 and ≤10 yr	2 (7)	8 (15)	4 (12)	14 (12)
>10 yr	1 (4)	3 (5)	4 (12)	8 (7)
Distant				
≤5 yr	90 (68)	100 (63)	102 (63)	292 (64)
>5 and ≤10 yr	27 (20)	37 (23)	38 (23)	102 (23)
>10 yr	15 (11)	21 (13)	23 (14)	59 (13)
Cancer in contralateral breast				
≤5 yr	19 (38)	25 (45)	19 (32)	63 (38)
>5 and ≤10 yr	11 (22)	17 (30)	21 (36)	49 (30)
>10 yr	20 (40)	14 (25)	19 (32)	53 (32)

survival was 47±2 percent among the women treated with total mastectomy, 46±2 percent among those treated with lumpectomy alone, and 46±2 percent among those treated with lumpectomy followed by breast irradiation. There was also no significant difference in survival between the two groups of lumpectomy-treated women who had specimens with tumor-free margins (hazard ratio for death among the women who underwent irradiation as compared with those who did not, 0.91; 95 percent confidence interval, 0.77 to 1.06; P=0.23). At 20 years, survival was 46±2 percent for the lumpectomy-alone group and 47±2 percent for the lumpectomy-plus-radiation group.

Figure 3 shows cumulative-incidence curves for all deaths regardless of the cause, for deaths that followed a recurrence or the development of cancer in the contralateral breast, and for deaths that occurred in the absence of any evidence of breast cancer among the women who underwent lumpectomy alone or lumpectomy followed by irradiation. As noted above, the cumulative incidence of deaths from all causes did not differ significantly between the two lumpectomy groups. However, on the basis of an analysis with the use of log-rank subtraction, lumpectomy followed by breast irradiation, as compared with lumpectomy alone, was associated with a marginally significant decrease in deaths due to breast cancer (hazard ratio, 0.82; 95 percent confidence interval, 0.68 to 0.99;

P=0.04). This survival advantage was partially offset by an increase in deaths from other causes (hazard ratio, 1.23; 95 percent confidence interval, 0.89 to 1.71; P=0.21). Other pairwise comparisons showed no significant differences in deaths due to breast cancer or other causes.

The cumulative incidence of death from any cause among the 1851 women was 53.5 percent at 20 years (Fig. 4A); 40.4 percent of the women died after a recurrence or a diagnosis of cancer in the contralateral breast, and 13.2 percent died without evidence of breast cancer. Among the women with negative nodes, the cumulative incidence of death from any cause was 47.7 percent (Fig. 4B); 32.0 percent of the women died after a treatment failure or a diagnosis of cancer in the contralateral breast, and 15.6 percent died in the absence of such an event. Among the women with positive nodes, the cumulative incidence of death was 63.3 percent (Fig. 4C); 54.2 percent of the women died after a breast-cancer–related event, and 9.1 percent died in the absence of such an event.

DISCUSSION

After 20 years of follow-up, we found no significant difference in overall survival among women who underwent mastectomy and those who underwent lumpectomy with or without postoperative breast irradiation. The results of other studies support our finding that there was no decrease in overall survival after
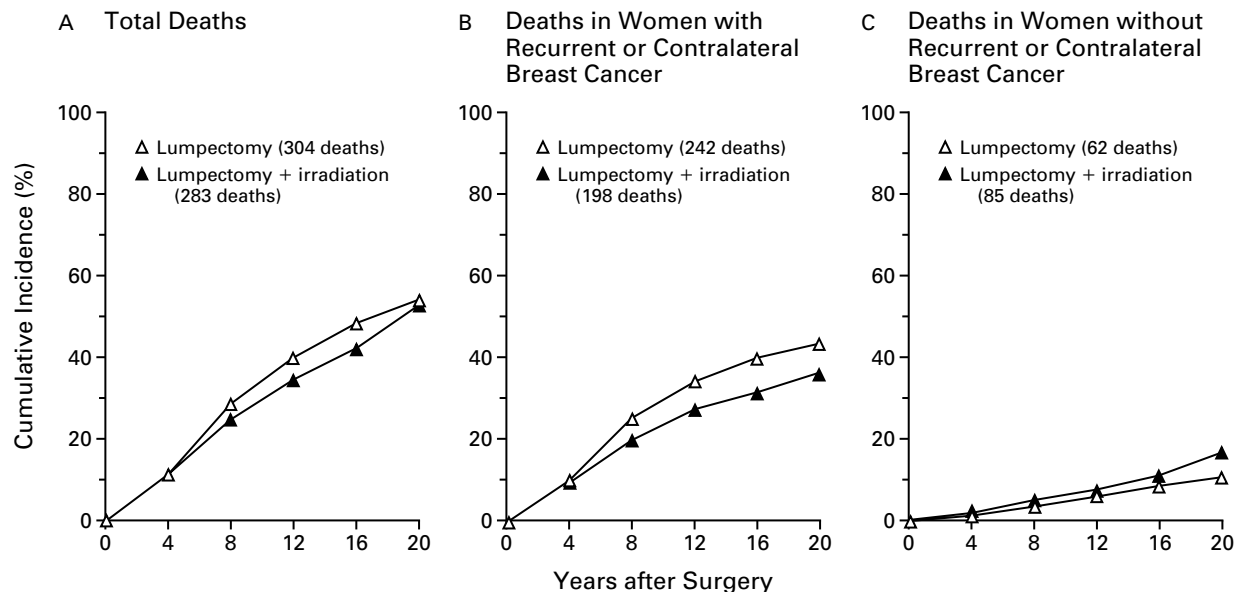

Figure 3. Cumulative Incidence of Death from Any Cause (Panel A), Death Following a Recurrence or a Diagnosis of Contralateral Breast Cancer (Panel B), and Death in the Absence of a Recurrence or Contralateral Breast Cancer (Panel C) among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.

Data are for women whose specimens had tumor-free margins.

breast-conserving surgery.[13-17] The 1995 meta-analysis reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG),[12] which included trials of breast conservation and axillary dissection with and without radiation therapy and trials that compared mastectomy with breast-conserving surgery plus radiotherapy, found no significant difference in overall mortality at 10 years. The results were similar regardless of whether data from the NSABP B-06 trial were included. A more recent meta-analysis by the EBCTCG,[18] which estimated the proportional effects of radiation therapy on cause-specific mortality among women treated with breast-conserving surgery and axillary dissection, showed a marginally significant reduction in the risk of death due to breast cancer after lumpectomy and irradiation (P=0.04). This reduction was offset by an increase in the risk of death from causes other than breast cancer (P=0.05). With regard to cause-specific mortality, our results are in accordance with those of the recent meta-analysis.[18] There has been concern that postoperative breast irradiation may increase the risk of cancer in the contralateral breast. Such an increase was not observed in our trial or in a recent retrospective study.[19]

Although breast-conserving surgery has generally been accepted as a treatment for invasive breast cancer, there is less agreement about whether lumpectomy as performed by our group or quadrantectomy as performed by the Milan group[13] is preferable. The two operations are different in both magnitude and biologic concept. We used a short, curvilinear or transverse incision to remove the tumor and sufficient normal tissue to ensure that the inked margins of the resected specimen were free of tumor.[20] An en bloc dissection was not carried out, not even for tumors in the upper outer quadrant of the breast, and no skin, pectoral fascia, or muscle was removed. Nodal dissection was limited to the lower two levels of the axilla. The procedure was performed in women with tumors that were 4 cm or less in diameter. In subsequent studies, women with tumors up to 5 cm in diameter were candidates for the procedure. Women of any age and with negative or positive axillary nodes were candidates, regardless of the location of the tumor in the breast and of the particular characteristics of the tumor.

A quadrantectomy, as initially described,[21] was used for tumors that were 2 cm or less in diameter. With this procedure, a long radial incision was made, and the tumor was removed with a 2-to-3-cm cuff of normal breast tissue. Skin, pectoral fascia, and the pectoralis minor muscle were also removed. An en bloc dissection was used to remove lesions in the upper outer quadrant, and a total axillary dissection was performed. Because of the extent of the surgery, it is often not possible to obtain a satisfactory cosmetic result. Thus, although the quadrantectomy is a breast-conserving procedure, like the modified radical or simple mastectomy, it retains features of the Halsted approach. Lumpectomy, however, represents a complete departure from the Halsted procedure and the biologic principles regarding its use.[22]

It would be inappropriate to choose a breast-conserving operation on the basis of a comparison of the
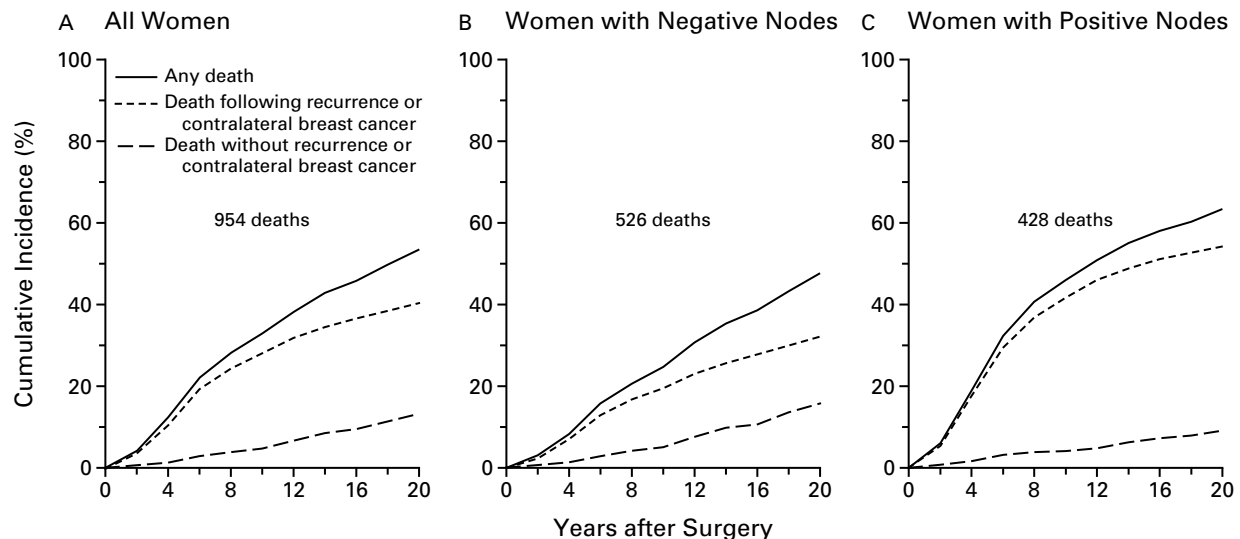

Figure 4. Cumulative Incidence of Death from Any Cause, Death Following a Recurrence or a Diagnosis of Contralateral Breast Cancer, and Death in the Absence of a Recurrence or Contralateral Breast Cancer among All 1851 Women (Panel A), 1156 Women with Negative Axillary Nodes (Panel B), and 695 Women with Positive Axillary Nodes (Panel C).

recurrence rates in the current NSABP and in the study by Veronesi et al., reported elsewhere in this issue of the *Journal*,[23] because differences in the patient populations in the two trials, rather than in the extent of the operative procedure, might account for any difference in recurrence rates. In the quadrantectomy trial, all the women had tumors that were 2 cm or less in diameter, and more than 70 percent of the women had negative nodes, whereas in our trial, 45 percent of the women had tumors that were more than 2 cm in diameter, and nearly 40 percent had positive nodes.[24]

Our findings at 20 years still show that lumpectomy and breast irradiation, as compared with lumpectomy alone, significantly decrease the incidence of a recurrence in the ipsilateral breast. Nevertheless, it has been argued that, if a wider margin of normal breast tissue surrounding the tumors had been removed, there would have been fewer ipsilateral recurrences.[25] However, systemic therapy is now administered after lumpectomy, regardless of nodal status, to reduce the risk of distant metastases, and such therapy also reduces the rate of recurrent cancer in the ipsilateral breast. In the B-06 trial, only women with positive nodes received chemotherapy, and the regimen was less effective than current regimens. Thus, the incidence of recurrence is lower with current approaches. In NSABP trials conducted after B-06, the incidence of recurrent cancer in the ipsilateral breast among women with negative nodes who received systemic therapy in addition to radiation therapy was about 6 percent after more than 10 years of follow-up.[26]

A substantial proportion of events in our study occurred after five years of follow-up. This finding supports the need for long-term follow-up. Our findings also indicate the need for information about the cause of death in clinical trials with long-term follow-up, particularly among women with negative nodes. Cumulative mortality at 20 years was nearly four times that at 5 years among the women with negative nodes in our study. That difference was related more to an increase in mortality from causes other than breast cancer than to an increase in mortality from breast cancer. Thus, with increasing follow-up, overall mortality becomes less indicative of mortality related to breast cancer.

APPENDIX

The following institutions and principal investigators participating in the National Surgical Adjuvant Breast and Bowel Project contributed to this study: Albany Regional Cancer Center, New York — T.J. Cunningham; Albert Einstein College of Medicine, New York — H. Volk; Baptist Medical Center, Oklahoma City — K.K. Boatman; Baylor University Medical Center, Waco, Tex. — L. Dragon; Billings Interhospital Oncology Project, Billings, Mont. — D.B. Myers; Boston University, Boston — P. Deckers; Bryn Mawr Hospital, Bryn Mawr, Pa. — T.G. Frazier; Community Clinical Oncology Program, Billings Interhospital Project, Billings, Mont. — N. Hammond; Community Clinical Oncology Program, Central New York, Syracuse — K. Gale; Community Clinical Oncology Program, Midwest, Kansas City, Mo. — K.H. Hanson; City of Faith Medical and Research Center, Tulsa, Okla. — A.F. Hoge; City of Hope Medical Center, Duarte, Calif. — J. Terz; Cross Cancer Institute, Edmonton, Alta., Canada — S. 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