

TWENTY-FIVE-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING RADICAL MASTECTOMY, TOTAL MASTECTOMY, AND TOTAL MASTECTOMY FOLLOWED BY IRRADIATION

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ABSTRACT

Background In women with breast cancer, the role of radical mastectomy, as compared with less extensive surgery, has been a matter of debate. We report 25-year findings of a randomized trial initiated in 1971 to determine whether less extensive surgery with or without radiation therapy was as effective as the Halsted radical mastectomy.

Methods A total of 1079 women with clinically negative axillary nodes underwent radical mastectomy, total mastectomy without axillary dissection but with postoperative irradiation, or total mastectomy plus axillary dissection only if their nodes became positive. A total of 586 women with clinically positive axillary nodes either underwent radical mastectomy or underwent total mastectomy without axillary dissection but with postoperative irradiation. Kaplan–Meier and cumulative-incidence estimates of outcome were obtained.

Results No significant differences were observed among the three groups of women with negative nodes or between the two groups of women with positive nodes with respect to disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival. Among women with negative nodes, the hazard ratio for death among those who were treated with total mastectomy and radiation as compared with those who underwent radical mastectomy was 1.08 (95 percent confidence interval, 0.91 to 1.28; $P=0.38$), and the hazard ratio for death among those who had total mastectomy without radiation as compared with those who underwent radical mastectomy was 1.03 (95 percent confidence interval, 0.87 to 1.23; $P=0.72$). Among women with positive nodes, the hazard ratio for death among those who underwent total mastectomy and radiation as compared with those who underwent radical mastectomy was 1.06 (95 percent confidence interval, 0.89 to 1.27; $P=0.49$).

Conclusions The findings validate earlier results showing no advantage from radical mastectomy. Although differences of a few percentage points cannot be excluded, the findings fail to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy. (N Engl J Med 2002;347:567-75.)

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THE Halsted radical mastectomy, an en bloc removal of the breast, muscles of the chest wall, and contents of the axilla, was the “established and standardized operation for cancer of the breast in all stages, early or late”¹ for most of the 20th century. However, by the mid-1960s, dissatisfaction with results after radical mastectomy and anecdotal information regarding other procedures led some surgeons to advocate more extensive surgery and others to promote more limited operations.² New information about tumor metastases also suggested that less radical surgery might be just as effective as the more extensive operations that were being performed.³

To help resolve the clinical controversy, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the B-04 clinical trial in August 1971 (participants in the original NSABP study are listed in the Appendix). The aims of the study were to determine whether patients with either clinically negative or clinically positive axillary nodes who received local or regional treatments other than radical mastectomy would have outcomes similar to those achieved with radical mastectomy. Previous findings from this trial demonstrated differences in control of local disease but failed to show a significant difference in either survival free of distant disease or overall survival among the groups of women with negative nodes or between the groups of women with positive nodes.⁴⁻⁷ The 25-year findings reported here support the earlier results.

METHODS

Clinical Trial

Between July 1971 and September 1974, after providing written informed consent, 1765 women with primary operable breast cancer were randomly assigned to treatment. One third of those with clinically negative axillary nodes underwent Halsted radical mastectomy and axillary dissection, one third underwent total mastectomy without axillary dissection but with regional irradiation, and one third underwent total mastectomy alone. One half of the women with clinically positive nodes underwent radical mastectomy; the other half underwent total mastectomy and regional irradiation. Women with clinically negative nodes who had had total mastectomy with

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neither axillary dissection nor irradiation and who subsequently had pathologically positive axillary nodes in the absence of other manifestations of disease then underwent axillary dissection. None of the women received adjuvant systemic therapy. About 70 percent of the women in each group were 50 years of age or older at the time of entry. On pathological examination, the mean (\pm SD) diameter of the largest tumor was 3.3 ± 2.0 cm in women with negative nodes and 3.7 ± 2.0 cm in women with positive nodes.

Radiation therapy was administered with supervoltage equipment. Women with negative nodes received 5000 rad (50 Gy; rad was the unit of absorbed dose formerly used) in 25 fractions; node-positive women received an additional boost of 10 to 20 Gy. A dose of 45 Gy in 25 fractions was delivered to both the internal mammary nodes and the supraclavicular nodes. Tangential fields were used to treat the chest wall with 50 Gy in 25 treatments. An independent radiotherapy monitoring committee and radiologic-physics center conducted oversight of radiation quality. Compliance with radiation therapy and its relation to treatment outcome have been reported previously.⁸

Statistical Analysis

End points for the comparisons among treatment groups were disease-free survival, relapse-free survival, distant-disease-free survival, and overall survival. Times to those end points were calculated from the date of mastectomy. Tumor recurrences in the chest wall, the surgical scar, or both were classified as local recurrences. Recurrences in supraclavicular, subclavicular, or internal mammary nodes or in the ipsilateral axilla of patients treated with either radical mastectomy or total mastectomy and regional irradiation were considered regional recurrences. Women with negative nodes who had total mastectomy alone and who subsequently had ipsilateral positive nodes that required axillary dissection were not considered to have had a recurrence unless the nodes could not be removed, a problem that occurred in one patient. Events considered in the determination of disease-free survival were the first local, regional, or distant recurrence of tumor; contralateral breast cancer or a second primary tumor other than a tumor in the breast; and death of a woman who had no evidence of cancer. Events considered in the estimation of relapse-free survival were the first local, regional, or distant recurrence or an event in the contralateral breast that was judged to be a recurrence. Distant recurrences that occurred either as the first recurrence or after a local or regional recurrence, contralateral breast cancers, and other second primary cancers were considered in the estimation of distant-disease-free survival. All deaths were included in the calculation of overall survival.

The Kaplan-Meier method was used to estimate curves for disease-free survival, distant-disease-free survival, relapse-free survival, and overall survival for each treatment group.⁹ Estimates are provided with their standard errors. Comparisons of the treatments were made with the use of log-rank tests of the available data for all observation times.¹⁰ Cox proportional-hazards models were fit in order to estimate hazard ratios.¹¹ The nonparametric method¹² was used to estimate the cumulative incidence curves for local, regional, and distant recurrences as first events, and Gray's K-sample test statistic¹³ was used to test the statistical significance of differences in cumulative incidence among the treatments. We estimated the cumulative incidence of death after a recurrence or a diagnosis of contralateral disease and the cumulative incidence of death without a recurrence or a diagnosis of contralateral disease.

All reported P values are two-sided. P values of 0.05 or lower are considered to indicate statistical significance. Analyses are based on all follow-up information received at the NSABP Biostatistical Center as of March 31, 2001. Eighty-seven percent of all analyzed patients were either followed for at least 25 years or were known to have died before that time. The treatment groups are well balanced in terms of the percentage of patients with follow-up of less than 25 years.

RESULTS

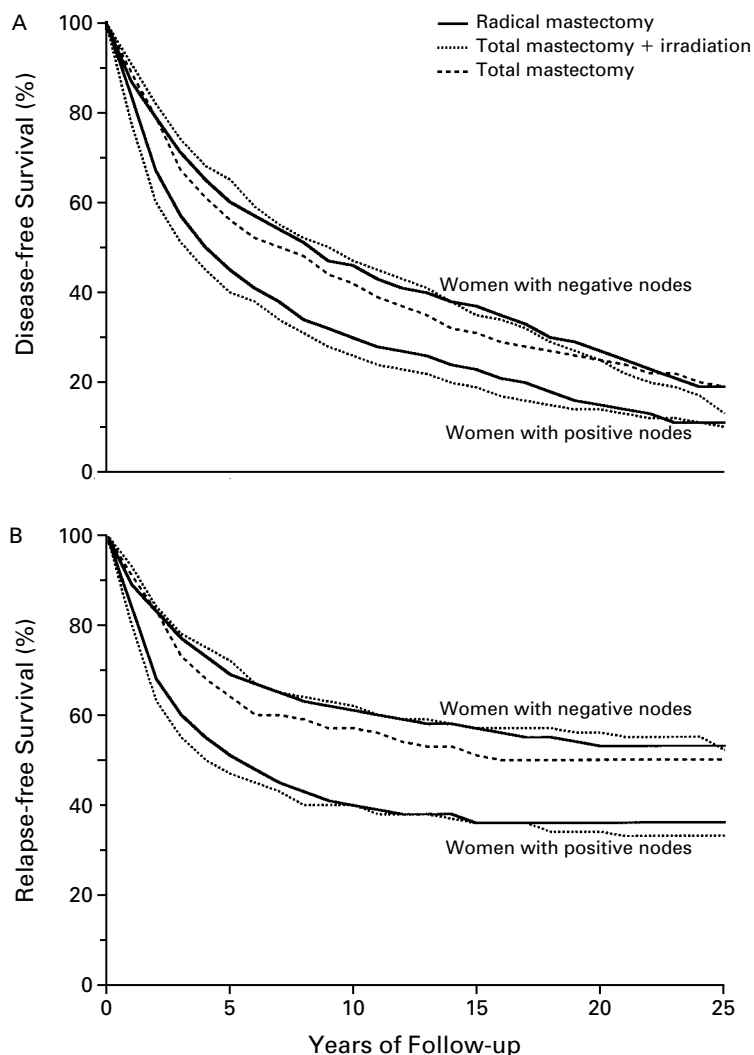
Disease-free Survival and Relapse-free Survival

No significant difference in disease-free survival was observed among the groups of women with negative nodes ($P=0.65$) (Fig. 1A). At 25 years, the estimated disease-free survival (\pm SE) was 19 ± 2 percent in the radical-mastectomy group, 13 ± 2 percent among women treated with total mastectomy and radiation therapy (hazard ratio, 1.06; 95 percent confidence interval, 0.90 to 1.25; $P=0.49$), and 19 ± 2 percent among those treated with total mastectomy alone (hazard ratio for the comparison with the radical-mastectomy group, 1.07; 95 percent confidence interval, 0.91 to 1.27; $P=0.39$). Similarly, in the groups that underwent total mastectomy, there was no significant difference between women who received radiation therapy and those who did not (hazard ratio, 1.02; 95 percent confidence interval, 0.87 to 1.21; $P=0.78$). Among women with positive nodes, there was no significant difference in disease-free survival between the groups; disease-free survival was 11 ± 2 percent in the radical-mastectomy group and 10 ± 2 percent in the group treated with total mastectomy plus radiation therapy (hazard ratio, 1.12; 95 percent confidence interval, 0.94 to 1.33; $P=0.20$).

No significant difference in relapse-free survival was observed among the three groups of women with negative nodes ($P=0.46$) (Fig. 1B). The estimated relapse-free survival among such women was 53 ± 3 percent in the radical-mastectomy group, 52 ± 4 percent among women treated with total mastectomy and radiation therapy (hazard ratio, 0.96; 95 percent confidence interval, 0.76 to 1.21; $P=0.74$), and 50 ± 3 percent among women who had a total mastectomy (hazard ratio for the comparison with the radical-mastectomy group, 1.14; 95 percent confidence interval, 0.91 to 1.42; $P=0.27$). There was also no significant difference between the groups treated with total mastectomy (hazard ratio, 1.18; 95 percent confidence interval, 0.94 to 1.48; $P=0.15$). Among women with positive nodes, the estimated relapse-free survival was 36 ± 3 percent among those treated with radical mastectomy and 33 ± 3 percent among those treated with total mastectomy and radiation therapy (hazard ratio, 1.09; 95 percent confidence interval, 0.89 to 1.35; $P=0.40$).

Distribution and Time to Occurrence of First Events

Only 20 percent of women with negative nodes and 13 percent of women with positive nodes were alive and event-free after 25 years of follow-up (Table 1). Regardless of nodal status, most first events were related to distant recurrences of tumor and to deaths that were unrelated to breast cancer. The detection of cancer at other sites was relatively infrequent. The frequency of events varied little either among the groups



No. AT RISK			
Negative nodes			
Radical mastectomy	362	170	45
Total mastectomy + irradiation	352	177	39
Total mastectomy	365	159	45
Positive nodes			
Radical mastectomy	292	92	21
Total mastectomy + irradiation	294	83	23

Figure 1. Disease-free Survival (Panel A) and Relapse-free Survival (Panel B) during 25 Years of Follow-up after Surgery among Women with Clinically Negative Axillary Nodes and Women with Clinically Positive Axillary Nodes.

There were no significant differences among the groups of women with negative nodes or between the groups of women with positive nodes in either analysis.

with negative nodes or between those with positive nodes.

The cumulative incidence of local or regional recurrence varied among the groups of women with negative nodes ($P=0.002$ for the three-way comparison) (Fig. 2A) and was lowest in the group treated

with total mastectomy and radiation therapy. The benefit from radiation therapy was related to a significant reduction in local recurrence. There were no significant differences among the three groups in the cumulative incidence of distant recurrence as a first event ($P=0.61$) (Fig. 2A). Among women with pos-

TABLE 1. DISTRIBUTION OF ALL FIRST EVENTS ACCORDING TO TREATMENT GROUP.

EVENT	WOMEN WITH NEGATIVE NODES		WOMEN WITH POSITIVE NODES		ALL WOMEN (N=1665)	
	RADICAL MASTECTOMY (N=362)	TOTAL MASTECTOMY (N=365)	TOTAL MASTECTOMY PLUS	TOTAL MASTECTOMY PLUS		
			RADIATION THERAPY (N=352)	RADIATION THERAPY (N=294)		
			number (percent)			
Any event	281 (78)	287 (79)	292 (83)	254 (87)	258 (88)	1372 (82)
Any recurrence*	135 (37)	156 (43)	131 (37)	165 (57)	168 (57)	755 (45)
Local	19 (5)	26 (7)	5 (1)	23 (8)	8 (3)	81 (5)
Regional	15 (4)	23 (6)	15 (4)	22 (8)	33 (11)	108 (6)
Distant	101 (28)	107 (29)	111 (32)	120 (41)	127 (43)	566 (34)
Contralateral breast cancer	19 (5)	26 (7)	32 (9)	13 (4)	15 (5)	105 (6)
Second primary cancer†	23 (6)	19 (5)	28 (8)	12 (4)	17 (6)	99 (6)
Dead, no evidence of cancer	104 (29)	86 (24)	101 (29)	64 (22)	58 (20)	413 (25)
Alive, event-free	81 (22)	78 (21)	60 (17)	38 (13)	36 (12)	293 (18)

*Data are for any recurrence other than a recurrence in the contralateral breast.

†Data are for any second primary cancer other than breast cancer.

itive nodes, there was no significant difference between the groups in the cumulative incidence of local or regional recurrence ($P=0.67$) (Fig. 2B). There was a significant reduction in the incidence of local recurrence after radiation therapy, but not in the incidence of regional recurrence or the incidence of distant recurrence ($P=0.44$) (Fig. 2B).

In the 1079 women with clinically negative nodes, 68.3 percent of all breast-cancer-related events occurred within the first 5 years of follow-up, and 14.6 percent occurred after 10 years of follow-up (Table 2). Of the events that occurred within the first five years, 65.1 percent were distant recurrences and 10.3 percent were contralateral breast cancer. After 10 years, there were relatively few breast-cancer-related events. Among the 586 women with clinically positive nodes, 81.7 percent of breast-cancer-related events occurred within the first 5 years of follow-up and 5.0 percent occurred after 10 years of follow-up (Table 2). Two thirds (68.1 percent) of all breast-cancer-related events that occurred in women with positive nodes within the first five years were distant recurrences.

Distant-Disease-free Survival and Overall Survival

There was no significant difference in distant-disease-free survival among the groups of women with negative nodes ($P=0.63$ for the three-way comparison) (Fig. 3A). At 25 years, the probability (\pm SE) was 46 ± 3 percent among women who underwent radical mastectomy, 38 ± 3 percent among women treated with total mastectomy plus radiation therapy

(hazard ratio, 1.08; 95 percent confidence interval, 0.88 to 1.34; $P=0.44$), and 43 ± 3 percent among those who underwent total mastectomy alone (hazard ratio for the comparison with the radical-mastectomy group, 1.10; 95 percent confidence interval, 0.89 to 1.35; $P=0.39$). There was also no significant difference between the groups treated with total mastectomy (hazard ratio, 1.02; 95 percent confidence interval, 0.83 to 1.25; $P=0.85$). Among the women with positive nodes, there was no significant difference in distant-disease-free survival between women who underwent radical mastectomy and those treated with total mastectomy plus radiation therapy (32 ± 3 percent and 29 ± 3 percent, respectively [hazard ratio, 1.07; 95 percent confidence interval, 0.87 to 1.32; $P=0.51$]).

There was no significant difference in overall survival among the groups of women with negative nodes ($P=0.68$ for the three-way comparison) (Fig. 3B). At 25 years, overall survival was 25 ± 3 percent among women treated with radical mastectomy (259 deaths), 19 ± 2 percent among those treated with total mastectomy plus radiation therapy (274 deaths) (hazard ratio, 1.08; 95 percent confidence interval, 0.91 to 1.28; $P=0.38$), and 26 ± 3 percent among those treated with total mastectomy alone (259 deaths) (hazard ratio for the comparison with the radical-mastectomy group, 1.03; 95 percent confidence interval, 0.87 to 1.23; $P=0.72$). Survival in the group that underwent total mastectomy was not significantly different from that among women treated with total mastectomy

RADICAL VERSUS TOTAL MASTECTOMY

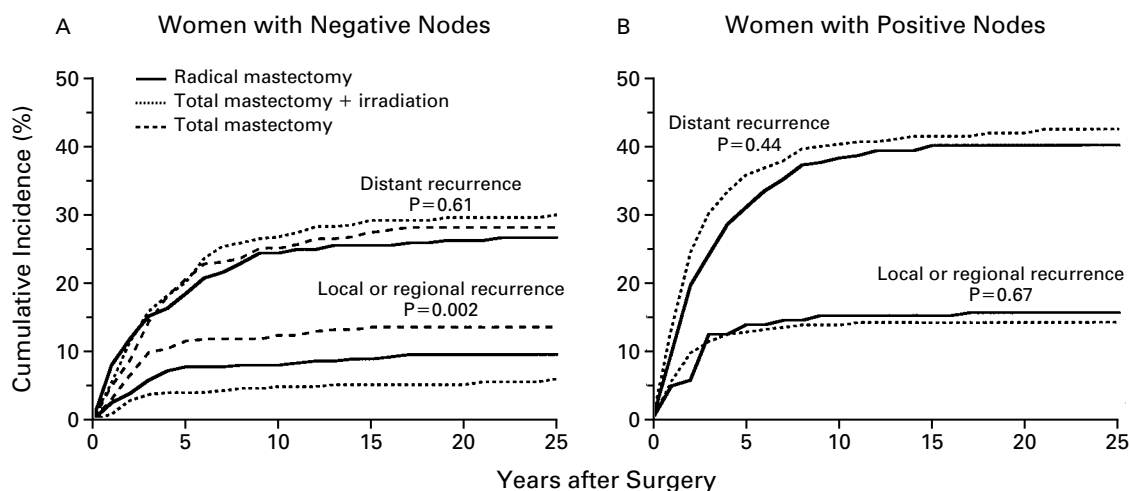


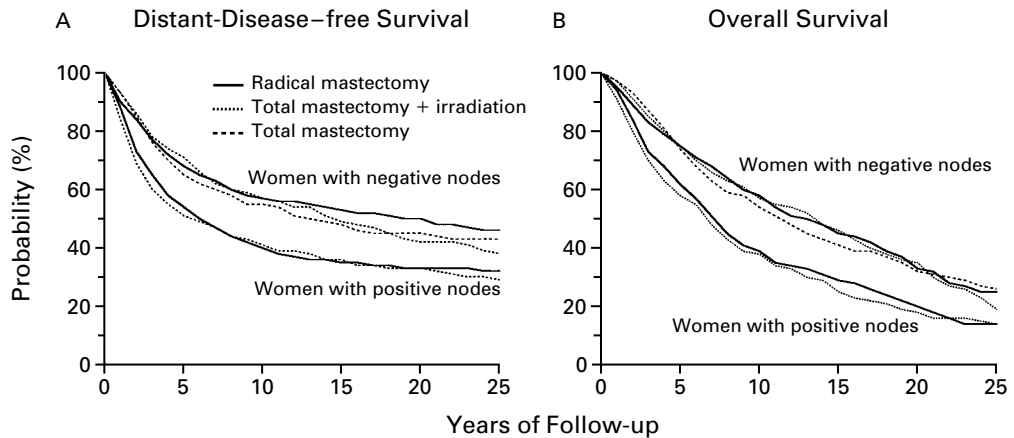
Figure 2. Cumulative Incidence of Local or Regional Recurrence and Distant Recurrence during 25 Years of Follow-up after Surgery among Women with Clinically Negative Axillary Nodes (Panel A) and Women with Clinically Positive Axillary Nodes (Panel B), According to Treatment Group.

In Panel A, the P values are for the three-way comparisons among treatment groups.

TABLE 2. DISTRIBUTION OF FIRST BREAST-CANCER-RELATED EVENTS ACCORDING TO TREATMENT AND TIME OF OCCURRENCE.

EVENT DURING FOLLOW-UP*	WOMEN WITH NEGATIVE NODES			WOMEN WITH POSITIVE NODES	
	RADICAL MASTECTOMY (N=362)	TOTAL MASTECTOMY (N=365)	TOTAL MASTECTOMY PLUS RADIATION THERAPY (N=352)	RADICAL MASTECTOMY (N=292)	TOTAL MASTECTOMY PLUS RADIATION THERAPY (N=294)
	no./total no. (%)				
Any first recurrence					
≤5 yr	98/135 (73)	120/156 (77)	88/131 (67)	133/165 (81)	145/168 (86)
>5 and ≤10 yr	22/135 (16)	21/156 (13)	28/131 (21)	25/165 (15)	16/168 (10)
>10 yr	15/135 (11)	15/156 (10)	15/131 (11)	7/165 (4)	7/168 (4)
Local					
≤5 yr	15/19 (79)	24/26 (92)	3/5 (60)	20/23 (87)	6/8 (75)
>5 and ≤10 yr	1/19 (5)	2/26 (8)	2/5 (40)	3/23 (13)	1/8 (12)
>10 yr	3/19 (16)	0/26	0/5	0/23	1/8 (12)
Regional					
≤5 yr	13/15 (87)	18/23 (78)	11/15 (73)	20/22 (91)	31/33 (94)
>5 and ≤10 yr	0/15	1/23 (4)	1/15 (7)	1/22 (5)	2/33 (6)
>10 yr	2/15 (13)	4/23 (17)	3/15 (20)	1/22 (5)	0/33
Distant					
≤5 yr	70/101 (69)	78/107 (73)	74/111 (67)	93/120 (78)	108/127 (85)
>5 and ≤10 yr	21/101 (21)	18/107 (17)	25/111 (23)	21/120 (18)	13/127 (10)
>10 yr	10/101 (10)	11/107 (10)	12/111 (11)	6/120 (5)	6/127 (5)
Contralateral breast cancer					
≤5 yr	10/19 (53)	15/26 (58)	10/32 (31)	9/13 (69)	8/15 (53)
>5 and ≤10 yr	2/19 (11)	4/26 (15)	8/32 (25)	3/13 (23)	4/15 (27)
>10 yr	7/19 (37)	7/26 (27)	14/32 (44)	1/13 (8)	3/15 (20)

*Years given are years of follow-up.



No. AT Risk						
Negative nodes						
Radical mastectomy	362	174	47	362	218	59
Total mastectomy + irradiation	352	181	41	352	216	56
Total mastectomy	365	170	50	365	209	59
Positive nodes						
Radical mastectomy	292	99	23	292	120	27
Total mastectomy + irradiation	294	93	28	294	115	32

Figure 3. Survival Free of Distant Disease (Panel A) and Overall Survival (Panel B) during 25 Years of Follow-up after Surgery among Women with Clinically Negative Axillary Nodes and Women with Clinically Positive Axillary Nodes.

There were no significant differences among the groups of women with negative nodes or between the groups of women with positive nodes in either analysis.

plus radiation therapy (hazard ratio, 0.96; 95 percent confidence interval, 0.81 to 1.13; $P=0.60$). In women with positive nodes, overall survival in the radical mastectomy group was 14 ± 2 percent (244 deaths); overall survival was also 14 ± 2 percent among women who received total mastectomy plus radiation therapy (247 deaths) (hazard ratio, 1.06; 95 percent confidence interval, 0.89 to 1.27; $P=0.49$).

The cumulative incidence of death among the 1665 eligible patients was 80 percent during the 25 years of follow-up; 49 percent died after a recurrence or contralateral breast cancer, 31 percent died without a diagnosis of any breast-cancer-related event, and 20 percent were alive at last follow-up (Fig. 4A). When analyzed according to the nodal status of patients, the cumulative incidence of death after a recurrence or a diagnosis of contralateral breast cancer was 40 percent in women with negative nodes and 67 percent in women with positive nodes. A total of 36 percent of women with negative nodes and 22 percent of those with positive nodes died without such an event, and 24 percent and 11 percent of the two groups, respectively, were alive at last follow-up (Fig. 4B and 4C).

There was no significant difference in the cumulative incidence of death unrelated to breast cancer

between all women who were treated with radical mastectomy and all those who had a total mastectomy followed by radiation therapy, regardless of nodal status ($P=0.79$). Similarly, when these treatments were analyzed within groups defined according to nodal status, there were no significant differences in the cumulative incidence of death unrelated to breast cancer ($P=0.96$ for the comparison between women with negative nodes and $P=0.72$ for the comparison between women with positive nodes).

Positive Axillary Nodes after Total Mastectomy without Radiation Therapy

A total of 68 of the 365 women with negative nodes who underwent total mastectomy without radiation therapy (18.6 percent) subsequently had pathological confirmation of positive ipsilateral nodes. Involved nodes were identified within 2 years after surgery in 51 of the 68 women, more than 2 years but within 5 years after surgery in 10 women, more than 5 years but within 10 years after surgery in 6 women, and more than 10 years but within 25 years after surgery in 1 woman. The median time from mastectomy to the identification of positive axillary nodes was 14.8 months (range, 3.0 to 134.5).

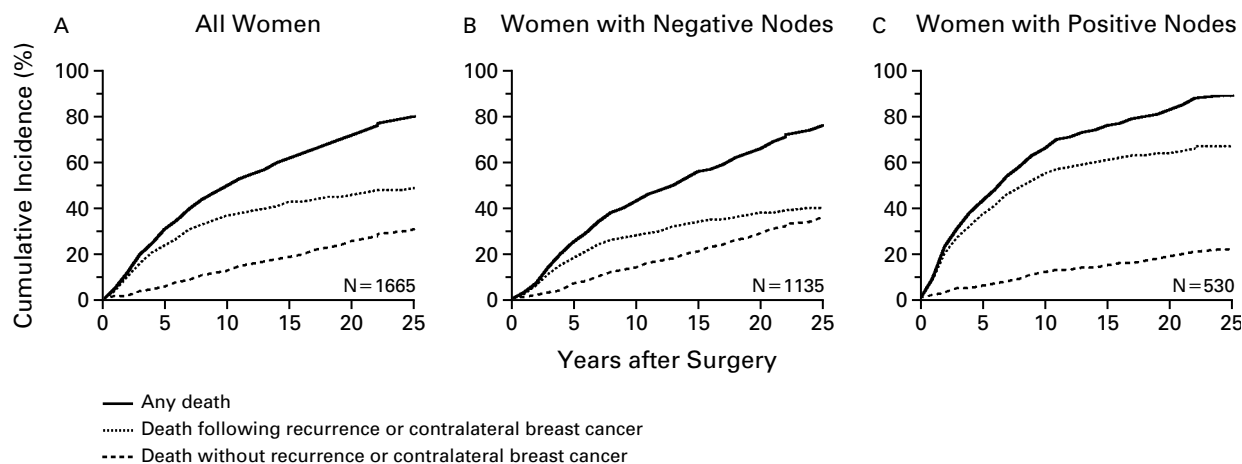


Figure 4. Cumulative Incidence of Death, of Death Following Recurrence or Contralateral of Breast Cancer among All Women (Panel A), Women with Clinically Negative Axillary Nodes (Panel B), and Women with Clinically Positive Axillary Nodes (Panel C).

DISCUSSION

An important finding of our study is that about 40 percent of the women with clinically negative nodes who were treated with radical mastectomy had pathological confirmation of tumor-positive axillary lymph nodes.¹⁴ Because the women in our study were randomly assigned to the treatment groups, we estimate that about 40 percent of those who underwent total mastectomy alone had positive nodes that were not removed at the time of initial surgery. Only about half of these women subsequently received a diagnosis of positive axillary nodes as a first event. Some investigators have suggested that we have underestimated the frequency of the delayed occurrence of positive axillary nodes because, they contend, patients with nodes that became positive after a distant recurrence should also have been included.¹⁵ They believe that axillary dissection in all women with clinically negative axillary nodes is justified. Their thesis may have merit in terms of achieving local control of disease; however, our data indicate that leaving positive nodes unresected did not significantly increase the rate of distant recurrence or breast-cancer-related mortality.

Our findings have also been questioned¹⁵⁻¹⁸ because lymph nodes were sometimes found in specimens removed during operations designated as total mastectomy alone. This criticism ignores the fact that there was a profound difference in surgical management of the axilla between women treated with radical mastectomy and those who underwent total mastectomy alone.¹⁴ However, no nodes were found in 65 percent of specimens obtained during total mastectomy, and 23 percent contained only one to five nodes. In the radical-mastectomy group, by contrast, only about 2 percent

of resected specimens contained 1 to 5 nodes; the median number of nodes was 16.

After 25 years of follow-up, we found no survival advantage from radiation therapy after total mastectomy in women with clinically negative nodes. These results are in accord with those of other investigators: after 10 years of follow-up, they found no significant difference in the survival of patients who, after simple mastectomy without dissection of the axillary nodes, received either regional irradiation or no irradiation.^{19,20} Our findings differ, however, from those of three studies that reported a decrease in overall mortality of about 10 percent.²¹⁻²³ The use of various systemic therapies in conjunction with postoperative radiation therapy may have relevance to these variable survival outcomes. Another reason for the differences may relate to the fact that the incidence of local recurrence in nonirradiated women in control groups differed among the studies, suggesting that base-line characteristics of the patients and the tumors might have varied among studies, rendering it difficult to make comparisons between studies. For example, about 40 percent of the women in the group with clinically negative nodes in our study had pathologically positive nodes, whereas in the three studies showing a decrease in mortality, about 90 percent of women had pathologically positive nodes.

In some respects, the findings of a meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)²⁴ are similar to ours. That group noted an overall survival benefit of 1.2 percent among women who received postoperative radiation therapy. With regard to cause-specific mortality, the meta-analysis further noted a significant

reduction in the rate of death from breast cancer at 20 years that was partially offset by a significant increase in deaths unrelated to breast cancer. If it were possible to eliminate the long-term hazard associated with radiation therapy, the results reported by the EBCTCG would suggest an absolute increase in 20-year survival of about 2 to 4 percent. In the B-04 trial, differences between the rate of death without recurrence and the rate of death after recurrence did not differ statistically among study groups. Because our study population was smaller than that considered in the meta-analysis, it is unlikely that we would have detected a small advantage from radiation therapy in the rate of deaths from breast cancer or a small disadvantage from radiation therapy in the rate of deaths unrelated to breast cancer on the order of those estimated in the meta-analysis.

When the B-04 trial began, it was popularly believed that five years could be viewed as a milestone and that women who lived for five years free of disease were likely to have been "cured." However, our findings demonstrate that a substantial proportion of events occurred after five years among both women with negative nodes and those with positive nodes. Twenty-five percent of all first distant recurrences and 50 percent of all contralateral breast cancers were detected after five years, which indicates the need for long-term follow-up, particularly in the evaluation of patients with a good prognosis.

Finally, our findings indicate the need to differentiate between deaths that were related to breast cancer and those that resulted from other causes. In women with negative nodes who were followed for more than five years, the estimate of overall mortality became less indicative of mortality related to breast cancer, because the incidence of death unrelated to breast cancer increased at a faster rate than did the incidence of death related to breast cancer. After 25 years of follow-up, the observation that 31 percent of patients died without a recurrence of breast cancer indicates the need for accurate information about the cause of death in women with long-term follow-up.

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APPENDIX

The following institutions and principal investigators participated in the NSABP B-04 study at the time of enrollment of patients: Albert Einstein College of Medicine, New York — H. Volk; Boston City Hospital (Tufts University), Boston — C.W. Kaiser; Creighton University, Omaha, Nebr. — C.H. Organ; State University of New York Downstate Medical Center, New York — B. Gardner; Ellis Fischel State Cancer Hospital, St. Louis — W. Donegan; Fitzsimons General Hospital, Aurora, Colo. — R.M. Hirata; French and Polyclinic Medical School, New York — J. McManus; Geisinger Medical Center, Danville, Pa. — C.W. Konvolinka; Harbor General Hospital (UCLA), Los Angeles — J.R. Benfield; Harrison S. Martland Hospital, Newark, N.J. — B.F. Rush, Jr.; Hennepin County General Hospital, Minneapolis — C.R. Hitchcock; Jewish General Hospital, Montreal — R.G. Margolese; Louisiana State University, New Orleans — I. Cohn, Jr.; Medical College of Pennsylvania, Philadelphia — D. Cooper; Medical College of Virginia, Richmond — W. Lawrence, Jr.; Metropolitan Hospital, Detroit — J.F. Weiksnar; Michael Reese Hospital, Chicago — R.H. Evans; Montefiore Hospital, New York — R.G. Rosen; Mount Sinai Hospital, New York — G.J. Lesnick; St. Vincent's Hospital, New York — T. Nealon, Jr.; Temple University, Philadelphia — W. Maier; University of Arkansas, Little Rock — K. Westbrook; University of California, San Diego — M.J. Orloff; University of Illinois, Chicago — T.K. Das Gupta; University of Iowa, Iowa City — R.L. Lawton; U.S. Naval Hospital, San Diego, Calif. — T.J. Guzik; University of Pennsylvania, Philadelphia — E.E. Rosato; University of Pittsburgh, Pittsburgh — B. Fisher; University of Rochester, Rochester, N.Y. — W.B. Patterson; University of Texas, San Antonio — A.B. Cruz, Jr.; University of Texas, Galveston — E.B. Rowe; University of Vermont, Burlington — R.S. Foster; Washington University, St. Louis — H. Butcher; Wayne State University, Detroit — A.J. Walt.

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