REANALYSIS AND RESULTS AFTER 12 YEARS OF FOLLOW-UP IN A RANDOMIZED CLINICAL TRIAL COMPARING TOTAL MASTECTOMY WITH LUMPECTOMY WITH OR WITHOUT IRRADIATION IN THE TREATMENT OF BREAST CANCER

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Abstract *Background.* Previous findings from a clinical trial (Protocol B-06) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) indicated the worth of lumpectomy and breast irradiation for treating breast cancer. After the discovery by NSABP staff members of falsified information on patients enrolled in the study by St. Luc Hospital in Montreal, separate audits were conducted at St. Luc Hospital and other participating institutions. We report the results of both audits and update the study findings through an average of 12 years of follow-up.

Methods. Patients with either negative or positive axillary nodes and tumors 4 cm or less in diameter were randomly assigned to one of three treatments: total mastectomy, lumpectomy followed by breast irradiation, or lumpectomy without irradiation. Three cohorts of patients were analyzed. The first cohort included all 2105 randomized patients, who were analyzed according to the intention-to-treat principle. The second cohort consisted of 1851 eligible patients in the first cohort with known nodal status who agreed to be followed and who accepted their assigned therapy (among those excluded were 6 patients from St. Luc Hospital who were declared ineligible because of falsified biopsy dates). The third cohort consisted of the patients in the second cohort minus the 322 eligible patients from St. Luc Hospital (total, 1529 patients).

Results. Regardless of the cohort, no significant differences were found in overall survival, disease-free survival, or survival free of disease at distant sites between the patients who underwent total mastectomy and those treated by lumpectomy alone or by lumpectomy plus breast irradiation. After 12 years of follow-up, the cumulative incidence of a recurrence of tumor in the ipsilateral breast was 35 percent in the group treated with lumpectomy alone and 10 percent in the group treated with lumpectomy and breast irradiation ($P<0.001$).

Conclusions. Our findings continue to indicate that lumpectomy followed by breast irradiation is appropriate therapy for women with either negative or positive axillary nodes and breast tumors 4 cm or less in diameter. (N Engl J Med 1995;333:1456-61.)

FINDINGS from a clinical trial (Protocol B-06) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) to evaluate lumpectomy in the treatment of breast cancer have been reported previously in the *Journal*.[1,2] Life-table estimates five and eight years after surgery indicated that 90 percent of women who underwent lumpectomy followed by breast irradiation remained free of cancer in the ipsilateral breast. The rates of disease-free survival, survival free of disease at distant sites, and overall survival were not significantly different from those among patients who underwent either total mastectomy or lumpectomy alone. As a consequence of these and other findings, lumpectomy and breast irradiation have become accepted in the surgical approach to the treatment of breast cancer.[3]

In February 1991, staff members at the NSABP headquarters verified that St. Luc Hospital in Montreal, one of the centers participating in the study, had submitted falsified information on patients. These findings were immediately reported to the appropriate governmental agencies. The Office of Research Integrity supervised personnel from the NSABP and the National Cancer Institute (NCI) in an audit of St. Luc's records.[4,5] In March 1994, the NCI began a special audit of 37 of the 89 institutions participating in Protocol B-06 to assess the quality of data submitted. The results of this audit are reported elsewhere in this issue of the *Journal*.[6]

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The authors of this paper are the authors who participated in the current reanalysis. The institutions and principal investigators that participated in this study are listed in the Appendixes of papers previously published in the *Journal* (1985; 312:672-3 and 1989;320:827-8).

Supported by a Public Health Service grant (NCI-U10-CA-12027) from the National Cancer Institute and by a grant (ACS-RC-13) from the American Cancer Society.

In the current report, we present information from both audits and update the Protocol B-06 findings through an average of 12 years of postrandomization follow-up. We have also analyzed the data after excluding all St. Luc patients with falsified data and all St. Luc patients.

METHODS

Study Design and Eligibility of Patients

Eligibility requirements, the design of the study, surgical and radiation techniques used, characteristics of the patients and tumors, and the distribution of patients among treatment groups have been described previously.[1,2,5] Patients with either negative or positive axillary nodes and tumors 4 cm or less in diameter (stage I and II breast cancer) were randomly assigned to one of three treatments: total mastectomy, lumpectomy followed by breast irradiation, or lumpectomy without irradiation. The protocol specified that the lower two levels of axillary nodes be removed regardless of the treatment assignment.

Patients were enrolled between April 8, 1976, and January 27, 1984. A prerandomization procedure was implemented in January 1978; according to this procedure, patients were randomly assigned to treatment before consent was obtained. After the treatment assignment had been made by the NSABP Biostatistical Center, the protocol was discussed with the patient, who gave written consent if she accepted the assigned treatment or agreed to be followed. Of the 2163 patients who entered the study, 1573 (73 percent) were assigned to treatment through the prerandomization procedure.

Patients who had undergone a lumpectomy and in whom the margins of the resected specimen were not tumor-free were to undergo a total mastectomy. However, they remained in the group to which they had originally been assigned. Tumor was evident in the specimen margins in approximately 10 percent of patients treated with lumpectomy, 78 percent of whom subsequently had a mastectomy.

Patients who had had a total mastectomy as treatment for a recurrence of tumor in the ipsilateral breast after lumpectomy remained in the group to which they had originally been assigned. Mastectomy was performed in 81 percent of these patients. The remainder underwent a second lumpectomy, either because they refused to undergo mastectomy or because a medical problem precluded mastectomy. Patients who underwent mastectomy because of a recurrence of the tu-

mor were considered to have had a "cosmetic" failure but not a treatment failure, unless the tumor was so extensive that it could not be completely removed by mastectomy.

The events used in the analyses of disease-free survival were first recurrences of disease, second cancers, and death without recurrence of cancer. Recurrence of tumor in the ipsilateral breast was not designated an event in determining disease-free survival, since the patients who initially underwent total mastectomy were not at risk for such a recurrence. Events used in the analysis of distant disease were distant metastasis as the first recurrence, distant metastasis after a local or regional recurrence, and a second cancer, including a tumor in the contralateral breast. Overall survival refers to survival with or without recurrence of disease.

Distribution of Patients

The distribution of the patients among the three treatment groups in the various cohorts used for the analyses is shown in Table 1. Of the 2163 patients randomized, 2105 agreed to be studied and had follow-up data available. These 2105 patients were included in the intention-to-treat analyses, and are hereafter referred to as cohort A.

Of the 2105 women included in the intention-to-treat analyses, 254 were removed from the analyses for various reasons (Table 1), leaving 1851 patients (the current-update cohort, or cohort B). Data on these 1851 patients formed the basis of our updated analysis. Among the 254 women excluded were 170 who consented to be followed in the study but who were not included in cohort B because they refused the assigned therapy; 152 of these women were randomly assigned to treatment before they had signed consent forms (prerandomization), and 18 after they had signed. Cohort B also excludes six patients from St. Luc Hospital who were declared ineligible because the dates of the first positive biopsy had been falsified. Two patients in cohort B were not used in a previous analysis of this protocol[2] because they withdrew consent after participating in the study. The patients are included in this analysis up to the time of their withdrawal. Cohort C comprised all the patients in cohort B minus 322 patients enrolled in the study by St. Luc Hospital. These 322 patients were eligible, had known nodal status, accepted the assigned treatment, and were followed.

Statistical Analysis

Life tables were computed by the actuarial method.[7] The length of time to treatment failure was calculated from the time of the initial operation. The summary chi-square test was used to compare the distributions of the time to treatment failure after adjustment for the number of positive nodes.[9-11] All P values relate to two-sided log-rank tests. Tests for heterogeneity of outcomes among the three treatments were performed for each cohort throughout the entire follow-up (referred to in this report as the global P value). Numbers and statistics (event-free rates, relative odds ratios and their 95 percent confidence intervals, and P values) for pairwise comparisons in summary tables are cumulative through the end of 12 years of observation. In comparisons of the group treated by total mastectomy with each of the groups treated by lumpectomy, relative odds with values greater than 1 indicate a better outcome for patients treated by lumpectomy, whereas relative odds less than 1 indicate a better outcome for those treated by total mastectomy. Tests were adjusted for the number of nodes involved (0, 1 to 3, 4 to 9, ≥10). In accordance with recently recommended statistical methods[12,13] for estimating the probability of a recurrence of tumor in the ipsilateral breast in the presence of competing risks — that is, recurrences at other sites or death — cumulative incidence curves are used. This differs from our previous reports[8,14] in which life-table estimates and cumulative hazard rates were used to present such information.

Information on survival, disease-free survival, and distant-disease–free survival is presented for cohorts A, B, and C. Information on the recurrence of tumor in the ipsilateral breast after lumpectomy with breast irradiation and without it has been obtained from all cohorts but is presented only for the 1851 women in cohort B.

Falsifications of Data on Patients from St. Luc Hospital

Of the 354 patients enrolled in the trial by St. Luc Hospital, 118 were assigned to total mastectomy, 119 to lumpectomy, and 117 to lumpectomy and breast irradiation. Descriptions of the falsifications have been reported previously.[4,5] False biopsy dates were submitted for six patients (1.7 percent), or 0.3 percent of all patients who underwent randomization: three treated by total mastectomy, two treated by lumpectomy, and one treated by lumpectomy and breast irradiation. As of the cutoff date for this report, September 30, 1993, all six patients had up-to-date follow-up information. Five of the six were node-negative, and all six were alive on the cutoff date. One had distant metastasis, which was reported after the publication of our 1989 report.[2] Two had a recurrence of tumor in the ipsilateral breast and were included in previously published analyses.[1,2]

The NCI Audit

Between March 28 and July 20, 1994, on-site audits of the records of 1554 randomized patients in Protocol B-06 (86 percent of the randomized patients excluding those enrolled at St. Luc Hospital) were carried out to ascertain whether additional falsifications could be identified and to verify patients' eligibility and outcome end points.[6] In addition, the National Death Index was searched to identify deaths not previously found. The data base for the current reanalysis was obtained by merging the NSABP summary file with the audited NCI data base. The file for the current analysis was closed on March 19, 1995, although at that time, there was a discrepancy between the audit findings and the NSABP records for six patients. In one of the six cases, follow-up information was available to the NSABP Biostatistical Center but not to the auditors. The NCI audit used clinical information on the site of the first treatment failure in the other five cases. However, histologic confirmation was not available. NCI audit findings were used in this reanalysis, except for the six cases with discrepant findings, when NSABP records were used. The results did not change, regardless of whether NSABP records or NCI audit findings were used for these six patients.

The audit did not change the number of patients included in the current update (cohort B). Although one additional patient was found to be ineligible, she had never been included in published analyses because she had refused her assigned treatment.

Results

Survival

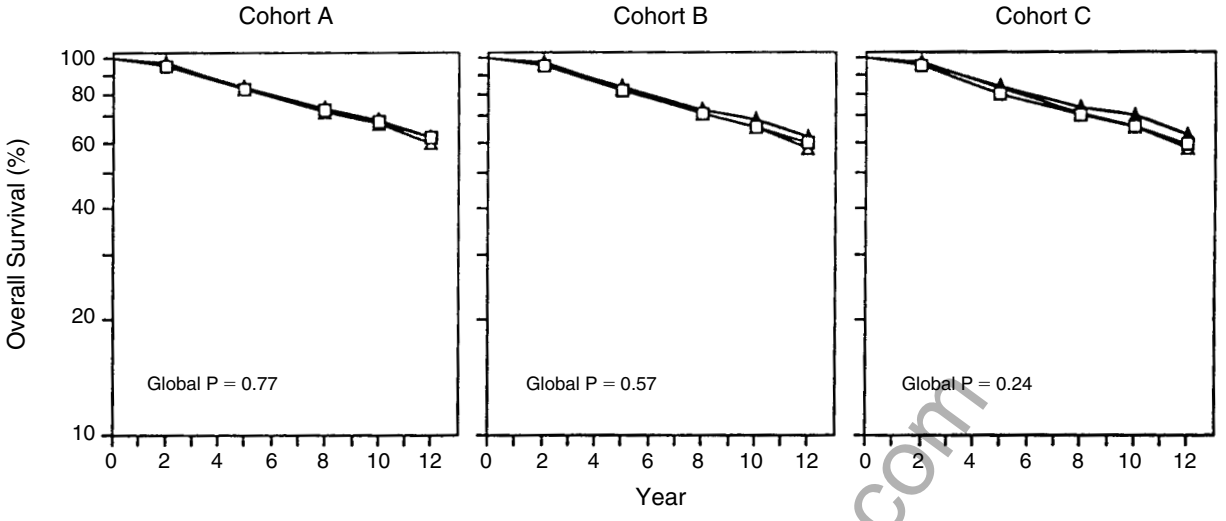
When overall survival in the three treatment groups was examined in each of the three cohorts, no significant differences were found (Fig. 1). The overall surviv-

Table 1. Distribution of Patients among Treatment Groups in the Various Cohorts Used in the Analyses of Data from Protocol B-06.

Cohort	Total Mastectomy	Lumpectomy	Lumpectomy + Irradiation	Total
Total no. of randomized patients	713	719	731	2163
A (no. of patients)	692	699	714	2105
Declined to participate*	21	19	17	57
Not included because of insufficient follow-up data	0	1	0	1
Mean time after randomization (mo)	150	149	149	149
B (no. of patients)	589	634	628	1851
Not included because of noninvasive cancer	9	12	15	36
Refused assigned treatment	77	36	57	170
Ineligible because of falsified data provided by St. Luc Hospital	3	2	1	6
Ineligible for other reasons†	13	12	9	34
Not included because nodal status unknown	1	3	4	8
Mean time after randomization (mo)	150	149	150	150
C (no. of patients)	494	520	515	1529
Not included because enrolled by St. Luc Hospital	95	114	113	322
Mean time in study (mo)	151	149	150	150

*Patients refused to sign the consent form or withdrew before treatment began.

†Patients did not meet at least one criterion necessary for eligibility.



No. of Patients/No. of Deaths

□ Total mastectomy	692/250	589/224	494/192
△ Lumpectomy	699/270	634/254	520/212
▲ Lumpectomy + irradiation	714/256	628/229	515/180
Total	2105/776	1851/707	1529/584

Figure 1. Life-Table Analysis Showing Overall Survival among Patients in the Three Cohorts Who Were Treated by Total Mastectomy, Lumpectomy, or Lumpectomy and Breast Irradiation.
The number of deaths includes those occurring after 12 years.

al estimates at 12 years were similar in the three cohorts for patients treated with lumpectomy and breast irradiation: 62 percent in both cohort A (patients analyzed according to the intention to treat) and cohort B (the current-update cohorts, consisting of the patients in cohort A minus the 254 excluded for the reasons listed in Table 1) and 63 percent in cohort C (consisting of the patients in cohort B minus all patients enrolled by St. Luc Hospital) (Table 2). In all three cohorts, overall survival among patients treated by lumpectomy and breast irradiation was the same as or slightly greater than that among patients treated by total mastectomy. Overall survival in all three cohorts was similar for patients who had undergone a total mastectomy and patients treated by lumpectomy.

When survival was analyzed according to nodal status, there was no significant heterogeneity among the three treatment groups for either patients with node-negative cancer or patients with node-positive cancer in any of the cohorts (data not shown).

Disease-free Survival and Distant-Disease–free Survival

As with overall survival, when disease-free survival was analyzed in each of the cohorts, the outcome was similar among the three treatment groups (Fig. 2). The estimates of disease-free survival at 12 years for patients treated by lumpectomy and breast irradiation were 50 percent in cohorts A and C and 49 percent in cohort B (Table 3).

When overall distant-disease–free survival was analyzed in each cohort, no significant differences were found among the three treatment groups (Fig. 3). When pairwise comparisons were made in each of the cohorts between the group treated by total mastectomy and each of the lumpectomy-treated groups, there were no significant differences in overall distant-disease–free survival during the 12 years of follow-up (data not shown).

When disease-free survival and distant-disease–free survival were analyzed for patients with node-negative cancer in the three cohorts, significant or nearly significant differences were observed among the treatment groups (data not shown). Significantly or nearly significantly higher percentages of patients with node-negative cancer treated by total mastectomy or lumpectomy and breast irradiation remained free of disease and free of distant disease than of patients with node-negative cancer treated by lumpectomy. However, in patients with node-positive cancer, there were no significant differences in disease-free and distant-disease–free survival in any of the three cohorts.

Tumor in the Ipsilateral Breast after Lumpectomy with or without Breast Irradiation

The likelihood of the recurrence of tumor in the ipsilateral breast was evaluated in a total of 1137 patients treated with lumpectomy whose specimen margins were histologically free of tumor (Fig. 4). Radiation therapy resulted in a marked decrease in the rate of recurrence of tumor in the ipsilateral breast. For the 12 years of follow-up, the cumulative incidence of tumor recurrence was 35 percent in the group treated by lumpectomy alone and 10 percent in those treated by lumpectomy and breast irradiation ($P<0.001$). In patients with node-negative cancer, the cumulative incidence was 32 percent and 12 percent, respectively. Among the patients with node-positive cancer, all of whom also received chemotherapy, the decrease in the likelihood of recurrence of tumor in the ipsilateral breast was more evi-

Table 2. Survival Estimates for All Treatment Groups after 12 Years of Follow-up.

Cohort and Treatment Group	Dead	Censored*	Alive	Survival†	Relative Odds of Survival (95% CI)‡	P Value
		no. of patients		%		
A (n = 2105)						
Total mastectomy	240	283	169	62	—	
Lumpectomy	257	282	160	60	0.95 (0.80–1.13)	0.57
Lumpectomy + irradiation	241	290	183	62	1.02 (0.86–1.22)	0.80
B (n = 1851)						
Total mastectomy	216	224	149	60	—	
Lumpectomy	242	247	145	58	0.96 (0.80–1.15)	0.66
Lumpectomy + irradiation	215	250	163	62	1.07 (0.89–1.29)	0.49
C (n = 1529)						
Total mastectomy	186	187	121	59	—	
Lumpectomy	201	204	115	58	1.01 (0.82–1.24)	0.95
Lumpectomy + irradiation	168	211	136	63	1.18 (0.95–1.46)	0.12

*Refers to patients who were alive at the most recent contact but who had been followed for less than 12 years.

†Life-table estimates were adjusted for the number of positive nodes (0, 1 to 3, 4 to 9, or ≥10).

‡In all cases, the reference group is the group that underwent total mastectomy. CI denotes confidence interval.

dent after lumpectomy and breast irradiation than after lumpectomy alone (5 percent vs. 41 percent).

Discussion

In planning a strategy for the reanalysis of data in this study, we encountered numerous issues that were difficult to resolve. The literature is sparse regarding how fraudulent or altered data should best be handled.[15] The options available to us for dealing with patients made ineligible because of fraudulent data ranged from including all data from all patients, regardless of whether falsified information was submitted, to excluding all data from all patients enrolled by St. Luc Hospital. An intermediate strategy was to exclude only the patients with falsified entry information. Findings from St. Luc Hospital are not presented separately, since examining a subgroup of a much larger cohort of patients may result in unreliable conclusions. Because of the variations in findings among institutions, the chance of obtaining false positive findings (i.e., type I errors) is increased.

In previous analyses of Protocol B-06,[1,2] two analytic components were used: the intention-to-treat principle,[16-18] according to which eligibility criteria are ignored and patients are analyzed according to their randomized treatment assignment (cohort A), and the "clinically analyzable," or "analysis-per-protocol," strategy, similar to the one designated in this report as the current update (cohort B). According to the latter strategy, patients who, for example, are ineligible for the protocol, have refused the assigned treatment, have noninvasive cancers, or have unknown nodal status are removed from the cohort used for analysis. In our initial report of the results of Protocol B-06,[1] we indicated that these two cohorts were used and that, since the conclusions of the resulting analyses did not differ, the findings presented were those obtained by the analysis-per-protocol strategy.

In the current report, we have continued to use this strategy. The only difference between the current-update cohort in this paper and the current-update cohort in our previous reports is that in this paper six St. Luc patients with data falsifications were regarded as

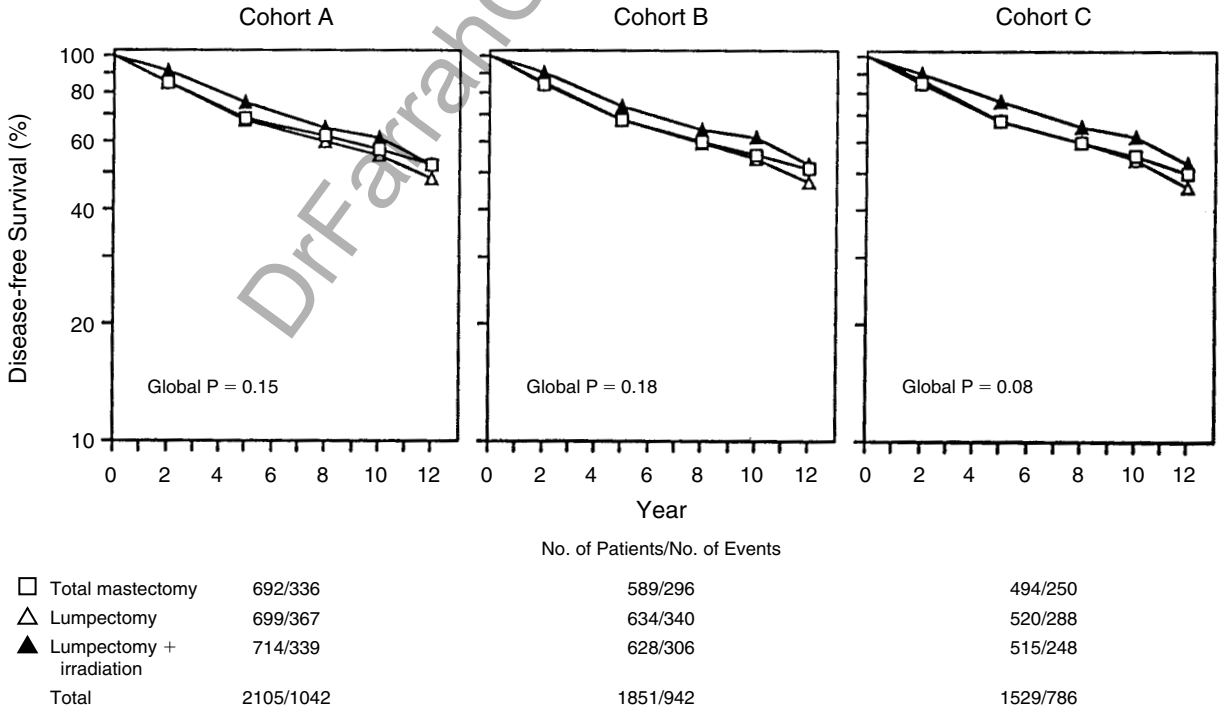


Figure 2. Life-Table Analysis Showing Disease-free Survival among Patients in the Three Cohorts Who Were Treated by Total Mastectomy, Lumpectomy, or Lumpectomy and Breast Irradiation.

The number of events includes those that occurred after the 12-year follow-up period.

Table 3. Estimates of Disease-free Survival for All Treatment Groups after 12 Years of Follow-up.*

Cohort and Treatment Group	No. of Events	Censored†	Disease Free	DFS‡	Relative Odds of DFS (95% CI)§	P Value
		no. of patients		%		
A (n = 2105)						
Total mastectomy	322	227	143	51	—	
Lumpectomy	356	219	124	48	0.92 (0.79–1.07)	0.27
Lumpectomy + irradiation	332	240	142	50	1.05 (0.90–1.22)	0.53
B (n = 1851)						
Total mastectomy	285	177	127	50	—	
Lumpectomy	331	192	111	47	0.94 (0.80–1.10)	0.43
Lumpectomy + irradiation	299	205	124	49	1.08 (0.91–1.27)	0.39
C (n = 1529)						
Total mastectomy	243	150	101	49	—	
Lumpectomy	279	157	84	45	0.94 (0.79–1.12)	0.50
Lumpectomy + irradiation	242	170	103	50	1.12 (0.94–1.34)	0.21

*DFS denotes disease-free survival, and CI confidence interval.

†Refers to patients who were free of events at the most recent contact but who had been followed for less than 12 years.

‡Life-table estimates were adjusted for the number of positive nodes (0, 1 to 3, 4 to 9, or ≥10).

§In all cases, the reference group is the group that underwent total mastectomy.

six additional ineligible patients and were thus deleted from the clinically analyzable cohort of patients.

To allay concern generated by the St. Luc falsifications, we also analyzed our data after eliminating all patients enrolled by St. Luc Hospital. The outcomes and conclusions did not change. Though the removal of all St. Luc patients from future analyses might seem appropriate, there are compelling reasons not to do so.[15,18] A large-scale removal of data is justifiable if the existence of patients is fabricated, randomization is compromised, end-point information is altered, or the number of falsifications is large. However, the audit of the St. Luc data for Protocol B-06, in which records from multiple sources were examined for all patients, revealed no evidence of such falsifications.[5] The false information concerned the eligibility status of a small number of patients and was altered before the patients underwent randomization. Under these circumstances, eliminating the 128 St. Luc patients who died, as well as those who are still alive — all of whom agreed to participate and to contribute to the study — is antithetical to the appropriate analysis of large, randomized, multicenter clinical trials.[18] Furthermore, in principle, the falsifications encountered would not have been expected to bias the outcome. Our findings support that contention. Thus, it is appropriate to include all St. Luc patients with follow-up data in future intention-to-treat analyses.[18]

The findings and conclusions reported for 12 years of follow-up are in accord with those reported after 5 and 8 years of follow-up.[1,2] They indicate that there is no significant heterogeneity in survival, disease-free survival, or distant-disease–free survival among the three treatment groups, regardless of which of the cohorts was used for the analyses.

The value of radiation therapy in reducing the incidence of tumor in the ipsilateral breast after lumpectomy continues to be an important factor. Current findings show a 10 percent cumulative incidence of tumor

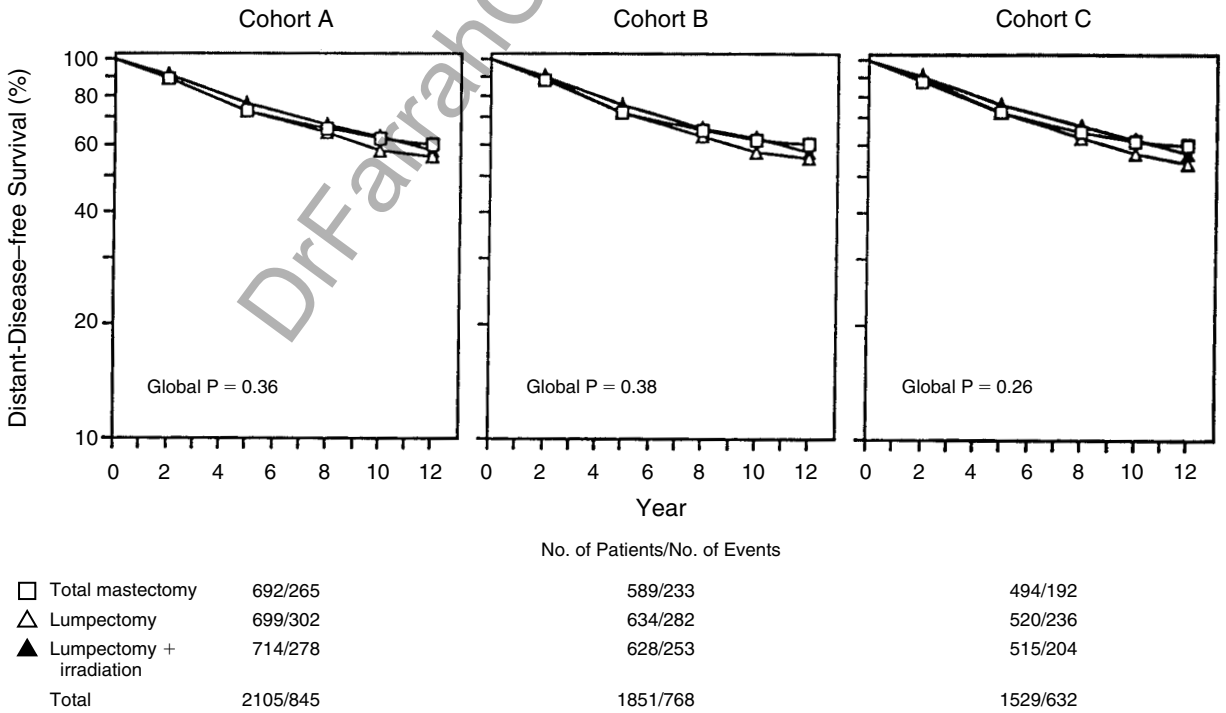


Figure 3. Life-Table Analysis Showing Distant-Disease–free Survival among Patients in the Three Cohorts Who Were Treated by Total Mastectomy, Lumpectomy, or Lumpectomy and Breast Irradiation.

The number of events includes those that occurred after the 12-year follow-up period.

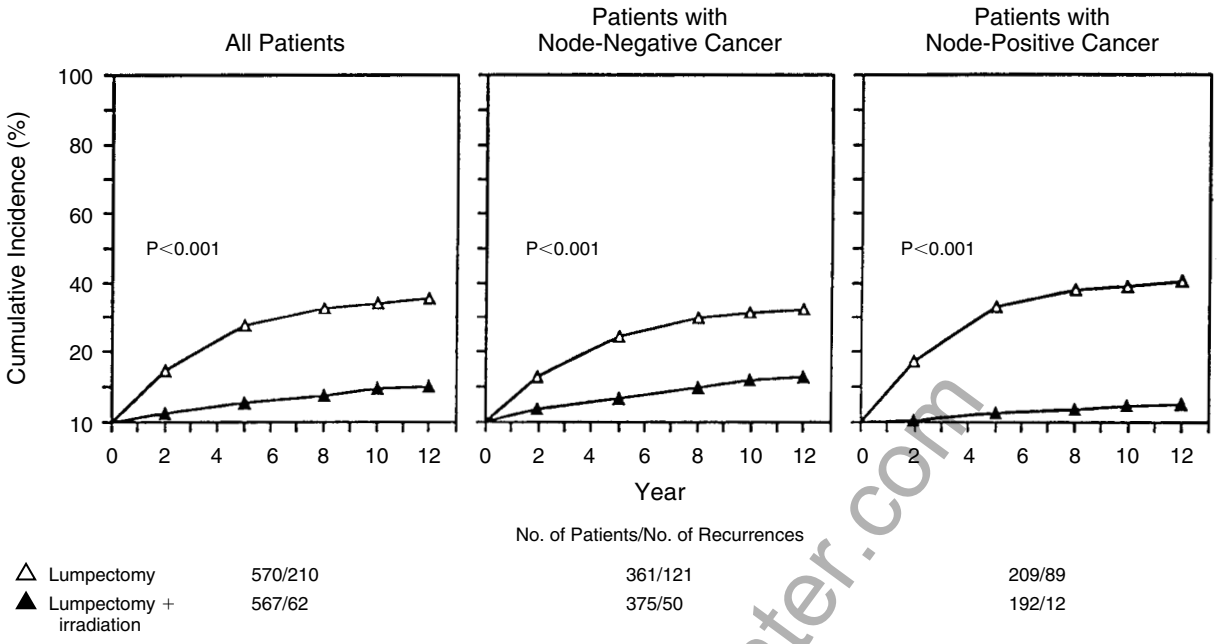


Figure 4. Life-Table Analysis Showing the Cumulative Incidence of Recurrence of Tumor in the Ipsilateral Breast after Lumpectomy or Lumpectomy and Breast Irradiation in 1137 Patients in the Current-Update Cohort (Cohort B) Who Had either Negative or Positive Nodes and Tumor-Negative Specimen Margins.

The P values were calculated from average annual rates of recurrence in the ipsilateral breast. The number of recurrences includes those that occurred after the 12-year follow-up period.

recurrence after 12 years of follow-up among patients who underwent irradiation, as compared with 35 percent for those who underwent no irradiation. These values are lower than those previously reported[8,14] since they estimate the probability of a recurrence of tumor in the ipsilateral breast in the presence of competing risks — that is, recurrences at other sites and deaths. Of particular importance are the findings in patients with node-positive cancer treated by lumpectomy, who also received radiation and systemic therapy. The cumulative incidence of recurrent tumors in the ipsilateral breast was only 5 percent in this group at 12 years of follow-up. This low incidence precludes one from considering positive axillary nodes as a contraindication to breast-conserving surgery.

This report should eliminate any remaining uncertainty surrounding Protocol B-06 as a result of the disclosure of data falsifications at St. Luc Hospital. After 12 years of follow-up, findings continue to indicate that lumpectomy followed by breast irradiation is appropriate therapy for women with stage I or II breast cancer. The safeguards incorporated into the design of the study prevented the actions of a single person from materially affecting the findings and conclusions — an assurance that cannot be made for studies that lack such safeguards. We believe that this report confirms the worth of meticulously conducted large multicenter, prospective, randomized clinical trials and should restore the confidence of physicians and patients in such trials.

References

1. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985;312:665-73.
2. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1989;320:822-8.
3. Consensus statement: treatment of early-stage breast cancer. NIH Consensus Development Conference, June 18–21, 1990. Vol. 8. No. 6. Bethesda, Md.: National Institutes of Health, 1990:1-19.
4. Fisher B, Redmond CK. Fraud in breast-cancer trials. N Engl J Med 1994; 330:1458-60.
5. Division of Research investigations report. Washington, D.C.: Office of Research Integrity, 1993. (DHHS publication no. (ORI) 91-08.)
6. Christian MC, McCabe MS, Korn EL, et al. The National Cancer Institute audit of the National Surgical Adjuvant Breast and Bowel Project Protocol B-06. N Engl J Med 1995;333:1469-74.
7. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chronic Dis 1958;8:699-712.
8. Fisher B, Anderson S. Conservative surgery for the management of invasive and noninvasive carcinoma of the breast: NSABP trials: National Surgical Adjuvant Breast and Bowel Project. World J Surg 1994;18:63-9.
9. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-70.
10. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. J R Stat Soc [A] 1972;135:185-206.
11. Hankey BF, Myers MH. Evaluating differences in survival between two groups of patients. J Chronic Dis 1971;24:523-31.
12. Korn EL, Dorey FJ. Applications of crude incidence curves. Stat Med 1992; 11:813-29.
13. Dignam JJ, Weissfeld LA, Anderson SJ. Methods for bounding marginal survival distribution. Stat Med 1995;14:1985-98.
14. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet 1991;338:327-31.
15. Neaton JD, Bartsch GE, Broste SK, Cohen JD, Simon NM. A case of data alteration in the Multiple Risk Factor Intervention Trial (MRFIT). Control Clin Trials 1991;12:731-40.
16. Gail MH. Eligibility exclusions, losses to follow-up, removal of randomized patients, and uncounted events in cancer clinical trials. Cancer Treat Rep 1985;69:1107-13.
17. Lewis JA, Machin D. Intention to treat — who should use ITT? Br J Cancer 1993;68:647-50.
18. Collins R, Peto R, Gray R, Parrish S. Large-scale randomized evidence: trials and overviews. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford textbook of medicine. 3rd ed. Oxford, England: Oxford University Press, 1996.