

TEN-YEAR RESULTS OF A COMPARISON OF CONSERVATION WITH MASTECTOMY IN THE TREATMENT OF STAGE I AND II BREAST CANCER

JOAN A. JACOBSON, M.D., DAVID N. DANFORTH, M.D., KENNETH H. COWAN, M.D., TERESA D'ANGELO, B.S., SETH M. STEINBERG, PH.D., LORI PIERCE, M.D., MARC E. LIPPMAN, M.D., ALLEN S. LICHTER, M.D., ELI GLATSTEIN, M.D., AND PAUL OKUNIEFF, M.D.

Abstract Background. Breast-conservation therapy for early-stage breast cancer is now an accepted treatment, but there is still controversy about its comparability with mastectomy. Between 1979 and 1987, the National Cancer Institute conducted a randomized, single-institution trial comparing lumpectomy, axillary dissection, and radiation with mastectomy and axillary dissection for stage I and II breast cancer. We update the results of that trial after a median potential follow-up of 10.1 years.

Methods. Two hundred forty-seven patients with clinical stage I and II breast cancer were randomly assigned to undergo either modified radical mastectomy or lumpectomy, axillary dissection, and radiation therapy. The 237 patients who actually underwent randomization have been followed for a median of 10.1 years. The pri-

mary end points were overall survival and disease-free survival.

Results. At 10 years overall survival was 75 percent for the patients assigned to mastectomy and 77 percent for those assigned to lumpectomy plus radiation ($P=0.89$). Disease-free survival at 10 years was 69 percent for the patients assigned to mastectomy and 72 percent for those assigned to lumpectomy plus radiation ($P=0.93$). The rate of local regional recurrence at 10 years was 10 percent after mastectomy and 5 percent after lumpectomy plus radiation ($P=0.17$) after recurrences successfully treated by mastectomy were censored from the analysis.

Conclusions. In the management of stage I and II breast cancer, breast conservation with lumpectomy and radiation offers results at 10 years that are equivalent to those with mastectomy. (N Engl J Med 1995;332:907-11.)

CONSERVATIVE therapy in the management of early-stage carcinoma of the breast, once controversial, is now an established alternative to mastectomy. Several randomized studies in Europe and North America that address various aspects of conservative treatment of breast cancer have accumulated a median of 10 or more years of follow-up.¹⁻⁵ All of them confirm that breast-conserving local therapies and more radical surgical therapies yield similar rates of survival. (However, the largest of these randomized clinical trials, the National Surgical Adjuvant Breast Project [NSABP] B-06 trial, was affected by an episode of misconduct,⁶ and reanalysis of this trial after expunging of fraudulent data and extensive auditing has not yet been published.)

The National Cancer Institute's early breast-cancer trial comparing lumpectomy, axillary dissection, and radiation with modified radical mastectomy has now accumulated a median potential follow-up of 10.1 years (median potential follow-up is defined here as the median follow-up if all patients had survived). This paper updates our previous report, which was based on a median of 5.7 years of follow-up,^{7,8} and compares findings with those of other randomized trials for conservative management of early-stage breast cancer. Our trial was conducted separately from the other randomized North American trial — the NSABP B-06 trial — and differed from it somewhat in terms of eligibility and design. The updated results of our single-institution ran-

domized trial continue to show no significant difference in overall survival or disease-free survival between the two treatment groups.

METHODS

Patients

Previous reports^{7,8} of this trial included a detailed description of the study design, eligibility requirements, radiation and surgical techniques, and statistical methods and a comparison of the characteristics of the patients in each treatment group. Briefly, between July 1979 and December 1987, 247 patients given a diagnosis of clinical stage I or II (T1 or T2, which included tumors with diameters of up to 5 cm; N0 or N1; M0) invasive carcinoma of the breast were enrolled in the trial. Eligible patients had no prior cancer, no evidence of metastatic disease, a single invasive lesion without multiple palpable or mammographically suspicious areas, no concurrent or previous occurrence of cancer in the contralateral breast, and no evidence of Paget's disease, and were not pregnant or breast-feeding. A comparison of the patients' characteristics showed no significant differences between the two groups.⁷ Patients were stratified according to age (<50 years vs. ≥ 50 years) and clinical nodal status (positive vs. negative). Patients were randomly assigned to undergo total mastectomy with complete axillary dissection or to follow a program of breast conservation consisting of excisional biopsy, complete axillary dissection, and radiation therapy. Fully informed consent was obtained from each patient before randomization. Ten patients (six assigned to mastectomy and four to breast conservation) declined to undergo their assigned treatment; they were treated elsewhere and not evaluated further. Thus, 237 patients remained in the study: 116 in the mastectomy group and 121 in the breast-conservation group. These patients were previously analyzed in June 1989 after a median follow-up of 68 months. The present analysis, with data updated through November 1993, extends the median potential follow-up to 121 months, with a range of 71 to 172 months (5.9 to 14.3 years). Three patients were lost to follow-up, and data on them were censored after 4.8, 6.2, and 8.8 years of follow-up. They all were disease-free at last known follow-up.

Techniques

Patients randomly assigned to undergo mastectomy underwent a Patey modified radical mastectomy with a complete axillary dissection (level I to III).⁹ The chest wall was not irradiated postoperatively. Optional breast reconstruction was elected by 68 of the 116 patients (59 percent). Patients randomly assigned to breast conservation were

From the Radiation Oncology Branch (J.A.J., P.O.), Surgery Branch (D.N.D.), Medicine Branch (K.H.C.), Biostatistics and Data Management Section (S.M.S.), and Cancer Nursing Service (T.D.) of the Clinical Oncology Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.; the Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor (L.P., A.S.L.); Lombardi Cancer Center, Georgetown University Hospital, Washington, D.C. (M.E.L.); and the Department of Radiation Oncology, Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas (E.G.). Address reprint requests to Dr. Jacobson at the Radiation Oncology Branch, National Cancer Institute, Bldg. 10, Rm. B3-B69, Bethesda, MD 20892.

required to have all gross tumor removed but were not required to have negative margins on microscopy. A second excision was permitted when initial surgery was thought to have been incomplete. One patient in the breast-conservation group was thought to have gross tumor remaining after a second excision and underwent a mastectomy. She is analyzed in the breast-conservation group. Patients underwent a complete axillary dissection (level I to III) through a separate axillary incision.

Radiation consisted of an isodose of 4500 to 5040 cGy to the whole breast, given in fractions of 180 cGy five days per week, with treatment plans including at least two off-central axis cuts. In patients with pathologically positive axillary nodes, 4500 to 5040 cGy was also directed to an anterior supraclavicular field at a depth of 3 cm over a period of 5 to 5.5 weeks. An attempt was made to include the internal mammary nodes in patients with positive axillae or medial lesions by extending the tangent field across the midline. The internal mammary nodes were assumed to be covered if the pleurosternal junction was covered. The pleurosternal junction was located with ultrasonography or computed tomography, one of which was used in the planning of all treatment.¹⁰ After 1981, dose plans included correction factors for lung density.¹¹ The axilla was not treated. The tumor bed received a booster dose of radiation (1500 to 2000 cGy) through the use of either iridium-92 implants (81 percent of patients) or an electron beam (19 percent of patients).

All patients with positive nodes received adjuvant chemotherapy consisting of cyclophosphamide (Cytosan) and doxorubicin (Adriamycin). Initially, chemotherapy was given for 1 year in 28-day cycles consisting of doxorubicin at a dose of 30 mg per square meter of body-surface area intravenously on day 1 and cyclophosphamide at a dose of 150 mg per square meter orally on days 3 through 6.¹² The dose of cyclophosphamide was increased to 200 mg per square meter in 1983. In 1985, the dose of doxorubicin was increased to 40 mg per square meter, the cycle length was decreased to 21 days, and the duration of chemotherapy was decreased to 6 months (nine cycles). After 1985, tamoxifen (Nolvadex), at a dose of 20 mg twice per day orally, was given for five years to postmenopausal node-positive patients.

Statistical Analysis

The probability of survival and disease-free survival as a function of time was calculated according to the Kaplan–Meier method.¹³ Overall survival was measured from the date of randomization until death or the last follow-up visit. Disease-free survival and local or regional recurrence were measured from the date of randomization until recurrence or the last follow-up visit; however, patients who had an isolated recurrence of cancer within the breast that was successfully treated by mastectomy were considered to be disease-free as of the date of the last follow-up visit. Cancer in the contralateral breast was not considered an event; however, any distant or local or regional recurrences after the initial treatment for contralateral-breast cancer were ascribed to the initial breast cancer. The significance of differences between pairs of actuarial curves was determined with the Mantel–Haenszel test.¹⁴ All P values are two-tailed.

RESULTS

After a median potential follow-up of 10.1 years (range, 5.9 to 14.3), disease-free survival and overall survival continue to be similar in the two treatment groups (Fig. 1). Overall survival at 10 years was 75 percent for patients assigned to mastectomy and 77 percent for patients assigned to lumpectomy plus radiation ($P=0.89$), yielding a 2 percent difference in survival favoring lumpectomy plus radiation (95 percent confidence interval ranging from 9 percent favoring mastectomy to 14 percent favoring radiation). Disease-free survival at 10 years (Fig. 1B) was 69 percent for patients assigned to mastectomy and 72 percent for patients assigned to lumpectomy plus radiation ($P=0.93$), yielding a 3 percent difference favoring lumpectomy plus radiation (95 percent confidence interval

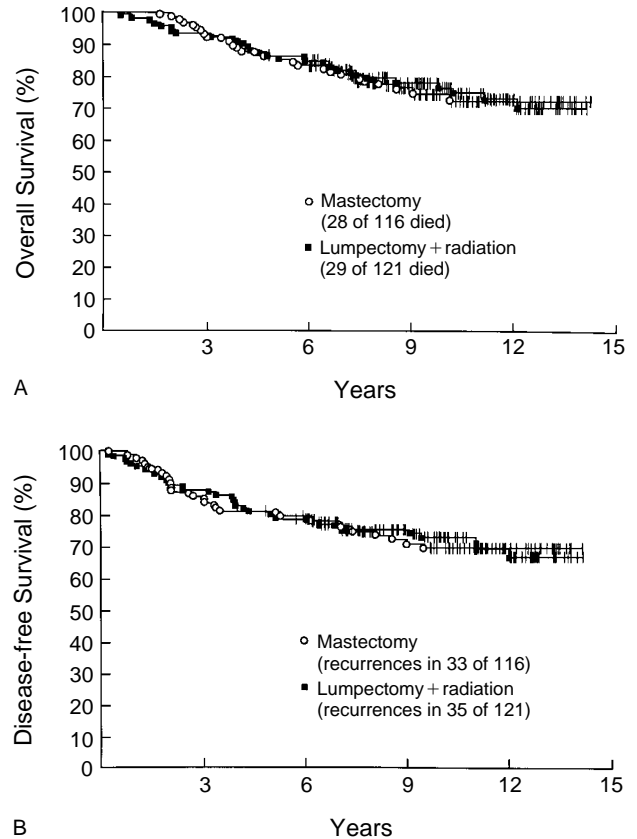


Figure 1. Overall Survival (Panel A) and Disease-free Survival (Panel B) in the Two Groups.

Tick marks indicate the lengths of follow-up for patients who had not died (Panel A) or had a recurrence of disease (Panel B). Wider bars represent overlapping tick marks.

ranging from 9 percent favoring mastectomy to 16 percent favoring radiation). Table 1 shows the cumulative incidence of events in each group.

Local or regional recurrences were defined as recurrences in the ipsilateral supraclavicular, axillary, or internal mammary nodal regions; chest-wall disease; or inoperable recurrence within the breast. Recurrence within the breast that was successfully treated by mastectomy was not considered a local or regional recurrence unless it was followed by a further local or regional event. The rate of local or regional recurrence as an isolated first event was 4 percent for the mastectomy group and 4 percent for the group assigned to lumpectomy plus radiation ($P=0.94$; 95 percent confidence interval ranging from 5 percent favoring radiation to 6 percent favoring mastectomy). However, the rate of local or regional recurrence as any component of a first event, whether isolated or with concomitant distant disease, was 10 percent for the mastectomy group and 5 percent for the group assigned to lumpectomy plus radiation ($P=0.17$; 95 percent confidence interval ranging from 2 percent favoring radiation to 11 percent favoring mastectomy). Figure 2 depicts these results.

In 10 patients in the mastectomy group, local or regional disease, either alone (4 patients) or with distant

Table 1. Incidence of Events in the Two Treatment Groups.

EVENT	MASTECTOMY (N = 116)	LUMPECTOMY + RADIATION (N = 121)
	<i>number</i>	
Initial recurrence		
Local*	0	19
Regional only†	3	0
Local and regional	1	0
Local or regional and distant	6	1
Total local or regional recurrences	10	20
Successful salvage mastectomy	—	15
Successful salvage radiation	0	—
therapy or chemotherapy		
Ultimate local or regional recurrence‡	10	5
Distant recurrence only after salvage mastectomy	—	3
Distant recurrence only	23	27
Contralateral breast cancer	10	7
Second cancer	7	6
Death from intercurrent cause	5	3

*Local recurrence after mastectomy refers to recurrence confined to the chest wall, and local recurrence after radiation therapy refers to recurrence within the breast.

†Regional only refers to recurrence only in a nodal area.

‡Ultimate local or regional recurrence refers only to recurrences that were not successfully treated by salvage therapy.

disease (6 patients), was the first event. In all 10 patients, salvage therapy involving surgery, radiation, or chemotherapy or hormonal treatment was unsuccessful, and distant disease ultimately developed.

At 10 years the actuarial risk of a recurrence confined to the ipsilateral breast in the group that underwent lumpectomy plus radiation was 18 percent (Fig. 3). There were 19 patients with such recurrences, and 1 with concurrent distant metastases. The rate of tumor recurrence within the ipsilateral breast was not significantly associated with any of the stratification factors, including age, tumor stage, and nodal status, or with any of the other factors considered, including the center performing the initial biopsy (National Institutes of Health Clinical Center vs. elsewhere), the need for a second excision, and the estrogen-receptor status. The risk of recurrence within the breast was not higher in patients reported to have had an incomplete initial excision or in patients who required a second excision. The number of patients available for evaluation of any possible recurrence factor was small. Initial salvage mastectomy was possible in 18 of the 19 patients with recurrence confined to the ipsilateral breast. Since mastectomy, no further local or regional disease has occurred in 15 of these 18 patients (83 percent), with additional follow-up ranging from 3 months to 9.9 years. In 3 of the 18, recurrent local or regional disease developed, followed by distant disease. In the 19th patient, who presented with inflammatory disease at the time of recurrence, chemotherapy and hormonal therapy were soon followed by distant metastases. In three patients, distant disease developed after salvage mastectomy without evidence of further local or regional disease 50, 69, and 72 months after salvage mastectomy. One of these three patients also had an intervening node-positive (24 of 24 nodes positive) cancer of the

contralateral breast 18 months after salvage mastectomy and 32 months before the development of distant disease.

Tumor stage and spread to axillary lymph nodes were the only significant prognostic factors for disease-free survival. There were 126 patients with pathological T1 tumors, 103 patients with T2 tumors, and 8 patients whose tumor size was unrecorded. The disease-free survival at 10 years was 81 percent for women with T1 tumors and 58 percent for women with T2 tumors ($P < 0.001$). There were 141 patients with pathologically node-negative breast cancer and 96 with node-positive cancer; in these two subgroups disease-free survival at 10 years was 82 percent and 54 percent, respectively ($P < 0.001$). When the patients were divided according to the tumor stage and nodal status, there were no significant differences in disease-free survival between the two treatment groups.

Patients were stratified according to whether they were younger than 50 years of age or 50 years of age or older. No age-related differences were observed within each treatment group. No significant difference was detected in disease-free survival between the two age groups ($P = 0.64$). The absolute rates of recurrence at 10 years were 27 percent for patients younger than 50 years (30 of 113) and 30 percent for patients 50 years

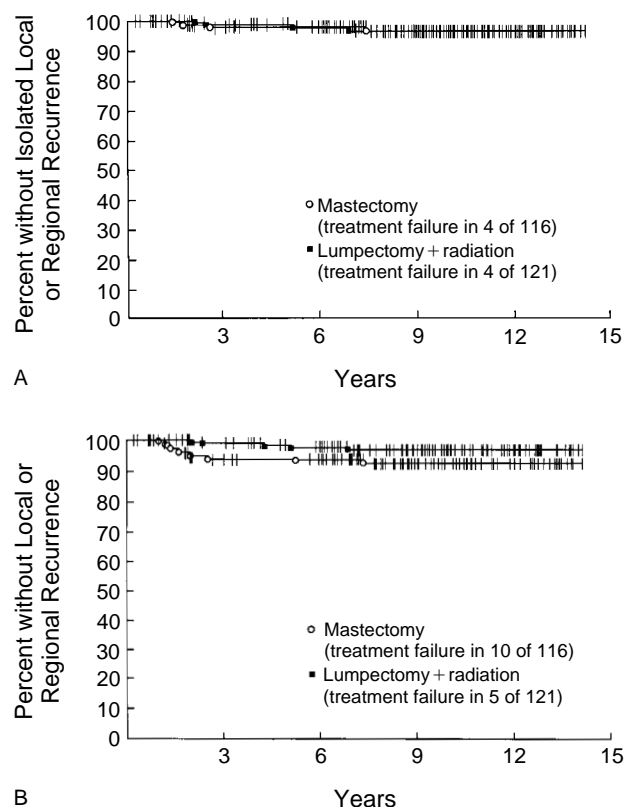


Figure 2. Local or Regional Recurrences as Isolated First Events (Panel A) or as Any Component of a First Event (Panel B) in the Two Treatment Groups.

Data were censored on patients with recurrences confined to the ipsilateral breast and successfully treated. Tick marks indicate follow-up times for patients who had not had recurrences.

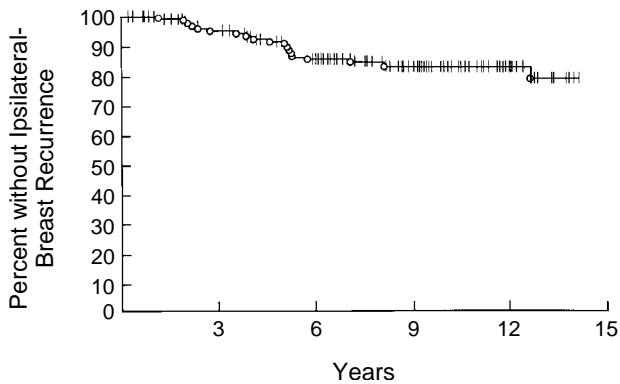


Figure 3. Actuarial Risk of Recurrence Confined to the Ipsilateral Breast among 121 Patients Assigned to Lumpectomy plus Radiation.

Nineteen patients had a recurrence (16 percent). Tick marks indicate follow-up times for patients without recurrences.

or older (37 of 124). Estrogen-receptor status, which was known only for about two thirds of the patients, did not appear to influence disease-free survival, either within treatment groups or overall.

DISCUSSION

The results of this trial after a median potential follow-up of 10.1 years continue to show no difference in the outcome between breast-conservation therapy and mastectomy. This single-institution trial corroborates the results of five other similar randomized trials (Table 2).¹⁻⁵ The follow-up periods in these six trials now range from 6 to 13 years. The criteria for inclusion varied among the trials, as did specific details of treatment, including radiation technique, surgical technique, and chemotherapy regimen. Nevertheless, the results of

all these studies demonstrate the efficacy of breast-sparing surgery plus radiation and the equivalence of survival after either breast-sparing surgery plus radiation or mastectomy. Eligibility criteria in the National Cancer Institute trial were broader than in many of the other trials, including the only other North American trial, the NSABP B-06.^{5,15} All patients with T1 or T2 tumors (tumors up to 5 cm in diameter) were potentially eligible for this trial, in contrast to the NSABP B-06 trial, which excluded women whose tumors measured 4 cm or more, and two of the European trials, which excluded women with tumors measuring 2 cm or more. Eight percent of the patients (10 of 116 in the mastectomy group and 8 of 121 in the group that underwent lumpectomy plus radiation) had tumors that exceeded 4 cm in diameter. Gross tumor resection was required in the National Cancer Institute trial, and a second excision to achieve this was allowed. In only one patient was a second attempt at gross tumor removal unsuccessful. In the NSABP B-06 trial, specimens with initially negative margins on pathological examination were required, and 10 percent of the patients randomly assigned to breast-conservation therapy actually underwent mastectomy because of histologically positive margins.⁵

Recently, concern has been expressed about both the long-term outcome of patients who have undergone salvage mastectomy for recurrences within the breast, and the possible increased risk of development of distant disease.¹⁶⁻¹⁹ The rate of recurrence of cancer confined to the breast in the group assigned to lumpectomy plus radiation in the NSABP B-06 trial was 12 percent at 9 years²⁰ and has ranged from 8 to 20 percent at 10 to 15 years in other studies.²¹⁻²³ In our trial, the actuarial rate of recurrence of cancer con-

Table 2. Comparison of Randomized Trials of Breast-Conservation Therapy.*

TRIAL	FOLLOW-UP yr	ELIGIBILITY CRITERIA	NO. OF PATIENTS	DFS	OS	LOCAL OR REGIONAL RECURRENCE	RECURRENCE WITHIN THE BREAST	
						percent		
NSABP B-06 ^{5†}	8	Stage I or II; T<4 cm; N0-1	Mastectomy	590	58	71	8	NA
			Breast conservation	629	59	71	8	10
Gustave-Roussy ³	10	Stage I; T<2 cm; N0-1	Mastectomy	91	58	80	10	NA
			Breast conservation	88	66	79	5‡	—
Milan ²	13	Stage I; T<2 cm; N0-1	Mastectomy	349		69	2	NA
			Breast conservation	352		71	3‡	—
EORTC ¹	8	Stage I or II	Mastectomy	426		63§	9	NA
			Breast conservation	456		58§	13‡	—
Danish Breast Cancer Group ⁴	6	Stage I or II	Mastectomy	429	66	82	6	NA
			Breast conservation	430	70	79	5	3
Present study	10	Stage I or II	Mastectomy	116	69	75	10	NA
			Breast conservation	121	72	77	5	18

*DFS denotes disease-free survival, OS overall survival, NA not applicable, and EORTC European Organization for Research and Treatment of Cancer.

†There was an episode of misconduct⁶ in the NSABP B-06 trial. The reanalysis of the study, after completion of an audit, has yet to be published.

‡The rate of recurrence within the breast is included in the value.

§The value was obtained from the survival curve.

fined to the ipsilateral breast at 10 years was 18 percent. Three months to 9.9 years after salvage mastectomy, 12 of the 19 patients with such recurrences had no further evidence of disease. The projected rate of disease-free survival at 10 years for these 19 patients is 67 percent — a rate that is not significantly different from that for all women assigned to lumpectomy plus radiation. Moreover, the risk of local or regional failure at 10 years in the group that underwent mastectomy was 10 percent. All 10 of the patients in this group with local or regional failure had either concurrent or subsequent distant disease and none underwent successful salvage therapy, whereas distant metastases developed in only 8 of the 20 patients with a recurrence of cancer within the breast after breast-conservation therapy.

The 10-year follow-up of the National Cancer Institute trial confirms that the outcome of treatment for women with stage I or II breast cancer does not depend on the nature of the local treatment of the breast, provided the treatment is adequate. Mastectomy and lumpectomy plus radiation are both excellent local therapies, with equivalent survival rates. An important corollary of these results is that no new putative predictor of increased rates of local recurrence, whether it be a biologic marker or a new sensitive imaging technology, if used to alter decisions regarding local treatment, can be expected to affect the risk of distant disease or the likelihood of survival. After careful evaluation and discussion with her surgeon, radiation oncologist, and medical oncologist, it is the patient who must decide which of the two local therapies to receive. We believe that improvements in survival can only arise from improvements in the early detection of breast cancer before dissemination has occurred or from improvements in adjuvant therapy.

We are indebted to Drs. Bruce Chabner and Dwight Kaufman for their critical comments and many helpful suggestions.

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