Lumpectomy and Radiation Therapy for the Treatment of Intraductal Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-17

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Purpose: In 1993, findings from a National Surgical Adjuvant Breast and Bowel Project (NSABP) trial to evaluate the worth of radiation therapy after lumpectomy concluded that the combination was more beneficial than lumpectomy alone for localized intraductal carcinoma-in-situ (DCIS). This report extends those findings.

Patients and Methods: Women (N = 818) with localized DCIS were randomly assigned to lumpectomy or lumpectomy plus radiation (50 Gy). Tissue was removed so that resected specimen margins were histologically tumor-free. Mean follow-up time was 90 months (range, 67 to 130). Size and method of tumor detection were determined by central clinical, mammographic, and pathologic assessment. Life-table estimates of event-free survival and survival, average annual rates of occurrence for specific events, relative risks for event-specific end points, and cumulative probability of specific events comprising event-free survival are presented.

Results: The benefit of lumpectomy plus radiation was virtually unchanged between 5 and 8 years of follow-up and was due to a reduction in invasive and noninvasive ipsilateral breast tumors (IBTs). Incidence of locoregional and distant events remained similar in both treatment groups; deaths were only infrequently related to breast cancer. Incidence of noninvasive IBT was reduced from 13.4% to 8.2% (P = .007), and of invasive IBT, from 13.4% to 3.9% (P < .0001). All cohorts benefited from radiation regardless of clinical or mammographic tumor characteristics.

Conclusion: Through 8 years of follow-up, our findings continue to indicate that lumpectomy plus radiation is more beneficial than lumpectomy alone for women with localized, mammographically detected DCIS. When evaluated according to the mammographic characteristics of their DCIS, all groups benefited from radiation.

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THE MORE FREQUENT USE of mammography has resulted in an increase in the incidence of clinically nondetectable intraductal carcinoma-in-situ (DCIS) free of an invasive component.[1-4] Knowledge about DCIS that was diagnosed before the use of mammography was derived mainly from patients who had large palpable tumors with undetected concurrent invasive cancer. The information obtained provided little insight into the natural history, biologic significance, or clinical management of the type of DCIS that is now being recognized.

The uncertainty about what represented appropriate treatment for women with small localized DCIS detected by mammography prompted the National Surgical Adjuvant Breast and Bowel Project (NSABP) to initiate the B-17 trial in 1985. The aim of that study was to test the hypothesis that excision of DCIS with tumor-free specimen margins (referred to as a lumpectomy, despite the fact that most women did not have a palpable mass) followed by radiation therapy was more effective than lumpectomy alone in preventing the occurrence of a second tumor in the ipsilateral breast (IBT). The B-17 findings, which were obtained from 818 randomized patients and first reported in 1993, indicated that the overall 5-year event-free survival was significantly better for women who underwent lumpectomy followed by radiation therapy and that the improvement was the result of a reduction in the incidence of both invasive and noninvasive IBTs.[5] Those findings led us to conclude that lumpectomy and breast irradiation is more appropriate than lumpectomy alone for preventing an IBT. Despite the recent appearance of reports derived from retrospectively collected data often obtained from diverse small patient populations, our findings provide the only information about DCIS that has been obtained from a prospective randomized clinical trial.

This report is an update of the B-17 trial through 8 years of follow-up. It provides data with regard to mammographically detected DCIS, indicates the frequency of occurrence of contralateral breast tumors (CBTs) in women with the disease, and presents additional information about certain

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aspects of our first report. The B-17 findings confirm our original conclusion and provide the basis for rational consideration of the type of treatment that should be considered appropriate for DCIS.

PATIENTS AND METHODS

A detailed description of patient eligibility requirements, study design, surgery and radiation therapy used, follow-up, study end points, and statistical analyses is included in our initial report of B-17.[5] Patients with DCIS detected by either physical examination or mammography were eligible for the study. Women underwent a lumpectomy with removal of the tumor and a sufficient amount of normal breast tissue so that specimen margins were histologically tumor-free. Women with a histologic diagnosis of DCIS whose mammograms showed diffuse calcifications were eligible if no tumor was demonstrated upon histologic examination of tissue that contained the calcifications.

After they had undergone lumpectomy and had given written consent, women were randomly assigned to receive either ipsilateral breast irradiation or no radiation therapy. To avoid an imbalance in treatment assignment, randomization was performed with a stratification scheme using age (≤ 49 or > 49 years), tumor type (DCIS or DCIS plus lobular carcinoma-in-situ), method of detection (mammography, clinical examination, or both), and axillary dissection (performed or not performed). Axillary dissection was obligatory at the onset of the study, but subsequently became optional on the basis of evidence, indicating that it was not necessary in the treatment of DCIS.[6]

The protocol stipulated that radiation therapy (50 Gy) be started no later than 8 weeks after surgery. The technique used was similar to that which has been described in previous NSABP studies.[7,8] Patients had semiannual follow-up examinations, and mammography was performed annually. A tumor detected at a local or regional site after the initial operation was considered an event only when a tissue biopsy of the lesion was positive. A tumor detected at a distant site was considered an event when clinical, radiographic, or pathologic findings indicated that tumor was present. The presence of IBT or CBT, regional or distant metastasis, a second primary tumor other than a breast tumor occurring as a first event after the operation, or the patient's death in the absence of evidence of recurrent breast cancer was used to determine event-free survival.

The location of primary tumors and postoperative IBTs was determined from mammographic, operative, and pathologic reports submitted to the NSABP Biostatistical Center. Tumors were classified as being (1) in a specific quadrant; (2) on the border between two quadrants; (3) central, ie, in a subareolar position or at the border of a quadrant and the areola; or (4) diffuse, ie, in more than one of the preceding locations.

Findings in the two treatment groups were compared for all randomized patients with follow-up data. A total of 818 women were entered onto the trial between October 1, 1985 and December 31, 1990 (Table 1): 405 women were treated by lumpectomy alone and 413 by lumpectomy followed by radiation therapy. Six patients in the group treated by lumpectomy alone and 12 in the group treated by lumpectomy and radiation therapy (N = 18; 2.2%) were considered ineligible because they failed to meet entry criteria. Reasons for ineligibility for 16 of the 18 ineligible patients have been outlined in our first report.[5] Two additional patients in the group treated by lumpectomy and radiation therapy have since been declared ineligible: one because of inadequate consent to participate and the other because tumor was found at the margin of resected specimens. All women for whom follow-up information was available, including those who failed to meet the entry criteria, were included in the analyses. As stated in our previous report, information from 24 patients at one institution was omitted due to concerns about data quality. The results of a subsequent audit of these patient records demonstrated no data irregularities. Consequently, data from all of these patients have been included in this report. Two women in each group (N = 4; 0.49%) had no follow-up data. Thus, 814 (99.5%) of the 818 patients randomized have been included in the current analyses: 403 women in the lumpectomy group and 411 in the group treated with lumpectomy followed by radiation therapy. The mean follow-up duration was 90 months (range, 67 to 130). In our first report, we presented information to indicate that there were no differences between treatment groups in the distribution of selected patient and tumor characteristics.[5] The tumor sizes listed in that report were those submitted to the NSABP Biostatistical Center by the investigators who had enrolled the patients. In some instances, tumor size had been obtained from a mammogram; in others, gross pathologic tumor size had been obtained from the surgically resected tissue. In still other cases, tumor size had been obtained from clinical examination. Because there has been increased emphasis on the use of tumor size for therapeutic decision making with regard to DCIS, an extensive review by NSABP Headquarters personnel of the tumor sizes that had been submitted was performed in preparation for this report. Tumor sizes determined from clinical, pathologic, and mammographic examinations were reviewed separately, and many of the patients contributed to each of the three assessments. The mammograms from 730 (89.7%) of the patients used for the current analysis were reviewed by one NSABP Headquarters radiologist (William Poller, MD), who was unaware of either clinical or pathologic tumor size or of any other patient or tumor characteristics. Size of tumor mass was recorded in all mammograms in which such a mass was demonstrated. All measurements were taken using routine views. Where no mass was evident, size of the cluster of calcifications was noted. Radiology reports submitted to the NSABP Biostatistical Center were used to obtain such information for 84 patients whose films were unavailable for central review. Information about mammographic findings was obtained from 60 of those patients.

The percentage of women who remained event-free was determined by the Kaplan-Meier life-table estimate,[9] and the two treatment groups were compared by the use of a two-sided log-rank test.[10] Comparisons adjusted for stratification variables were computed using the Cox proportional hazards model[11]; findings did not differ from those obtained using the unstratified analysis. The Cox model was also used to evaluate interactions among treatment and covariates. Average annual rates of occurrence for specific events were computed and compared by exact binomial tests. Relative risks (RRs) and 95% confidence intervals (CIs) were derived from the Cox model for the event-specific end points.[12] The cumulative probability of specific events comprising disease-free survival was determined using cumulative incidence functions.[13] Results in this report have been derived from data reported through June 30, 1996.

Table 1. Study Information

Variable	Lumpectomy	Lumpectomy + XRT	All Patients
Randomized	405	413	818
Ineligible	6	12	18
No follow-up	2	2	4
Patients included in analysis	403	411	814

Abbreviation: XRT, radiation therapy.

RESULTS

Tumor Size

Clinical assessment. Headquarters review of the clinical information submitted during the study was performed for 809 of 814 patients in the current analyses. No tumor was palpable in 670 (83%) of the women. A total of 139 (17%) of the women were reported to have tumors that were clinically palpable; 6.6% of these were ≤ 1 cm in size (half were < 1 cm and half were 1.0 cm), 6.1% were 1.1 to 2.0 cm, and 4.6% were ≥ 2 cm.

Pathologic assessment. No gross tumor was found in 431 (54.1%) of 797 resected specimens, all of which contained DCIS. Measurements of an additional 261 (32.7%) specimens indicated that tumors were ≤ 1 cm. In 10.6% of the resected specimens, tumor size was 1.1 to 2.0 cm, and in 2.4%, it was ≥ 2 cm.

Mammographic assessment. A total of 730 mammograms (89.7% of all patients included in the analyses) were centrally reviewed. A tumor mass was identified in 15.6% of these (Table 2). Fewer than one third (30.8%) of the masses had associated calcifications, and 43.9% of the masses (6.8% of the 730 mammograms evaluated) were ≤ 1.0 cm in size. A tumor mass greater than 2.0 cm was identified in only 2.3% of mammograms. Nearly 80% of mammograms demonstrated either scattered (7.4%) or clustered (70.4%) microcalcifications, but no mass. In 73.0% of mammograms that demonstrated clustered calcifications, the size of the cluster was ≤ 1.0 cm. An additional 2.7% of mammograms demonstrated architectural distortion with no mass or calcifications. There were no mammographic abnormalities in 4.0% of cases. The mammographic characteristics were distributed uniformly among the two treatment groups. Reports from 60 of 84 mammograms unavailable for central review showed similar characteristics; approximately 20% indicated the presence of a tumor mass and 80% showed microcalcifications. The majority of the masses and microcalcifications were small.

Event-Free Survival

Women treated by lumpectomy followed by ipsilateral breast irradiation had a significantly better event-free survival at 8 years of follow-up than women treated by lumpectomy alone (75% *v* 62%, respectively; P = .00003) (Fig 1). There was a 43% reduction in the average annual incidence rate (per 100 women) for all first events as a result of radiation therapy (6.40 for the group treated by lumpectomy alone *v* 3.68 for the group treated by lumpectomy plus breast irradiation; P = .00004; Table 3). A RR of failure of 1.74 (95% CI, 1.34 to 2.26; Fig 1) for patients who received lumpectomy alone as compared with those who received lumpectomy and radiation confirmed the beneficial effect of radiation therapy.

IBTs as First Events Following Primary Tumor Removal

Rate, RR, and cumulative incidence of IBT. One hundred four of 143 first events (73%) in the group treated by

Table 2. Mammographic Characteristics

Characteristic	Lumpectomy		Lumpectomy + XRT		Overall	
	No.	%*	No.	%*	No.	%*
Patients in analyses	403	—	411	—	814	—
Mammograms						
Not centrally reviewed	42	10.4	42	10.2	84	10.3
Centrally reviewed	361	89.6	369	89.8	730	89.7
Tumor mass	51	14.1	63	17.1	114	15.6
Without calcifications	40	11.1	39	10.6	79	10.8
With calcifications	11	3.0	24	6.5	35	4.8
Tumor size (cm)						
≤1.0	22	6.1	28	7.6	50	6.8
1.1-2.0	24	6.6	23	6.2	47	6.4
2.1-3.0	3	0.8	10	2.7	13	1.8
3.1+	2	0.6	2	0.5	4	0.5
Calcifications (no mass)	283	78.4	284	77.0	567	77.7
Scattered	27	7.5	26	7.0	53	7.4
Clustered	256	70.9	258	69.9	514	70.4
Size of cluster (cm)						
≤1.0	194	53.7	181	49.1	375	51.4
>1.0	62	17.2	77	20.9	139	19.0
Architectural distortion	12	3.3	8	2.2	20	2.7
No abnormality	15	4.2	14	3.8	29	4.0

*Percent for mammogram characteristics are for those with central review.

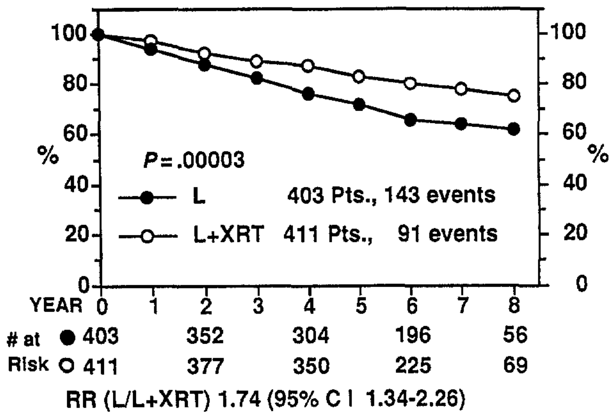

Fig 1. Event-free survival of women treated by lumpectomy alone (L) or by lumpectomy and radiation therapy (L+XRT).

lumpectomy alone were IBTs, as compared with 47 of 91 first events (52%) in the group treated by lumpectomy and radiation therapy (Table 3). The average annual incidence rate of IBT was reduced by 59% as a consequence of radiation therapy (4.65 in the lumpectomy group and 1.90 in the group treated by lumpectomy and radiation therapy; $P < .000005$). The rate of noninvasive cancer was reduced by 47% (2.28 and 1.21 in the two treatment groups, respectively; $P = .007$) and the rate of invasive cancer, by 71% (2.37 and 0.69, respectively; $P < .000005$). At 8 years of follow-up, the cumulative incidence of an IBT of any type occurring in women whose primary tumor was treated by lumpectomy alone was 26.8%; in women treated by lumpectomy followed by radiation therapy, it was 12.1% (Fig 2). The cumulative incidence of a noninvasive IBT was 13.4% in women treated by lumpectomy alone and 8.2% in women treated by lumpectomy and radiation therapy; the cumulative incidence of an invasive IBT was 13.4% in the former group and 3.9% in the latter group.

Treatment and outcome of patients with IBT. The schema outlined in Fig 3 is presented as an aid in tracking the outcome of patients with IBT and other events. One hundred four patients whose primary DCIS was treated by lumpectomy alone subsequently developed an IBT. Fifty-four (51.9%) of these women were treated by a second lumpectomy; 14 were reported to have received radiation therapy. Fifty of the 104 patients (47.2%) were treated by mastectomy. Fifty-one percent of patients whose IBT was noninvasive (DCIS) were treated by a lumpectomy; 52.8% of those with an invasive IBT were similarly treated. Three of 54 women who had a second lumpectomy developed a second IBT. All of these were in the group whose first IBT was DCIS. One of those patients developed distant disease and is still alive. Subsequent locoregional disease occurred in one patient whose noninvasive IBT had been treated by mastectomy. Another locoregional event occurred in a patient who had an invasive IBT; this was also treated by mastectomy. She developed distant disease and subsequently died. None of the 54 women whose first IBT was treated by lumpectomy have developed locoregional disease (other than an IBT) or died.

Eighteen of 47 IBTs (36.2%) that occurred in patients treated by lumpectomy and breast irradiation were treated by a second lumpectomy (15 of 30 [50.0%] women with a noninvasive IBT and three of 17 [17.7%] of those with an invasive IBT). After they had undergone a second lumpectomy, four women with a noninvasive IBT developed a second IBT. One woman who had undergone a second lumpectomy for treatment of a noninvasive IBT developed distant disease and subsequently died. Another patient who had undergone a mastectomy for a noninvasive IBT also developed distant disease, but remains alive. Two patients treated by mastectomy for invasive IBT developed distant metastases; one of them has died.

Table 3. Site, Rate, and RR of First Events According to Treatment Group

Type of Event	Lumpectomy (403) No.	Lumpectomy (403) Rate*	Lumpectomy + XRT (411) No.	Lumpectomy + XRT (411) Rate*	RR†	95% CI	Exact *P*
IBT	104	4.65	47	1.90	.41	.29-.58	<.000005
Noninvasive	51	2.28	30	1.21	.53	.34-.83	.007
Invasive	53	2.37	17	0.69	.29	.17-.50	<.000005
Other locoregional	2	0.09	4	0.16	1.81	.33-9.86	.79
Distant	3	0.13	3	0.12	.90	.18-4.47	.99
CBT	13	0.58	19	0.77	1.32	.65-2.67	.55
Second primary cancers‡	10	0.45	14	0.57	1.26	.56-2.85	.72
Deaths from causes other than breast cancer	11	0.49	4	0.16	0.33	.10-1.03	.08
All events	143	6.40	91	3.68	0.57	.44-.75	.00004

*Rate per 100 patients per year.

†Rate in group treated by lumpectomy and radiation therapy/rate in group treated by lumpectomy alone.

‡Excluding cancer in the opposite breast.

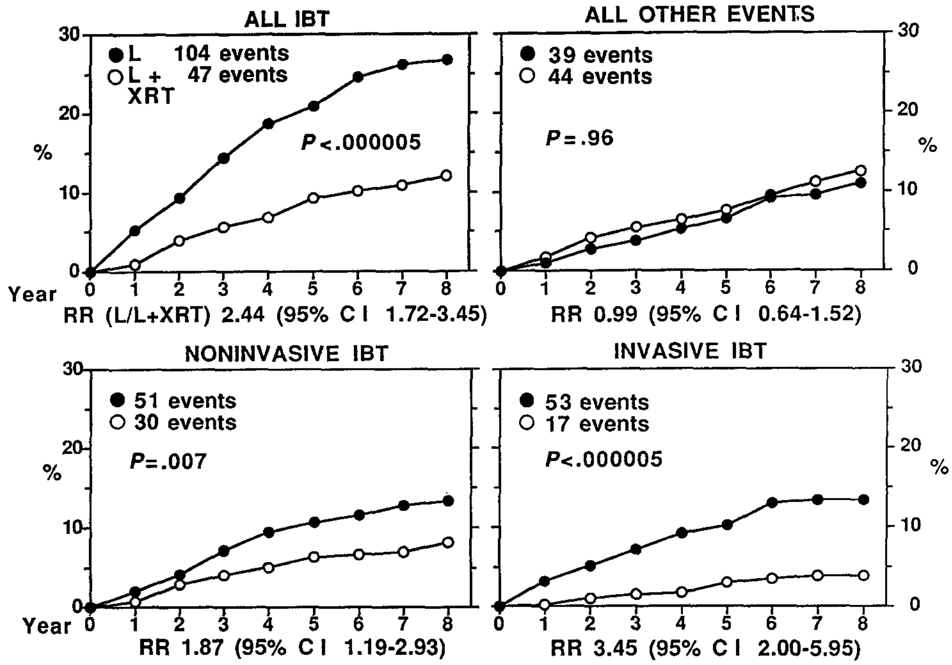

Fig 2. Cumulative incidence of all IBTs, of noninvasive and invasive IBTs, and of all other first events in women treated by L or L+XRT. *P* values are comparisons of average annual rates of failure.

Location of IBT. There was concordance in the location within the breast of both primary DCIS and IBT in 84.1% of 126 women in whom the site of these tumors was known. When the frequency with which the primary DCIS and IBT were reported to have occurred in the same quadrant was determined in these women according to whether their IBT was invasive or DCIS, the concordance was greater in the latter group (51.7% *v* 80.3%). This discordance in location between an invasive IBT and its primary tumor was observed in both treatment groups (not shown).

First Events Other Than IBT

The use of radiation therapy after lumpectomy resulted in no significant reductions in the average annual incidence rates of first events at sites other than in the ipsilateral breast (Table 3). At 8 years of follow-up, the cumulative incidence of all first events other than an IBT was not significantly different in the two treatment groups: 11.0% in the group treated by lumpectomy alone and 12.5% in the group treated by lumpectomy and radiation therapy (*P* = .96; Fig 2).

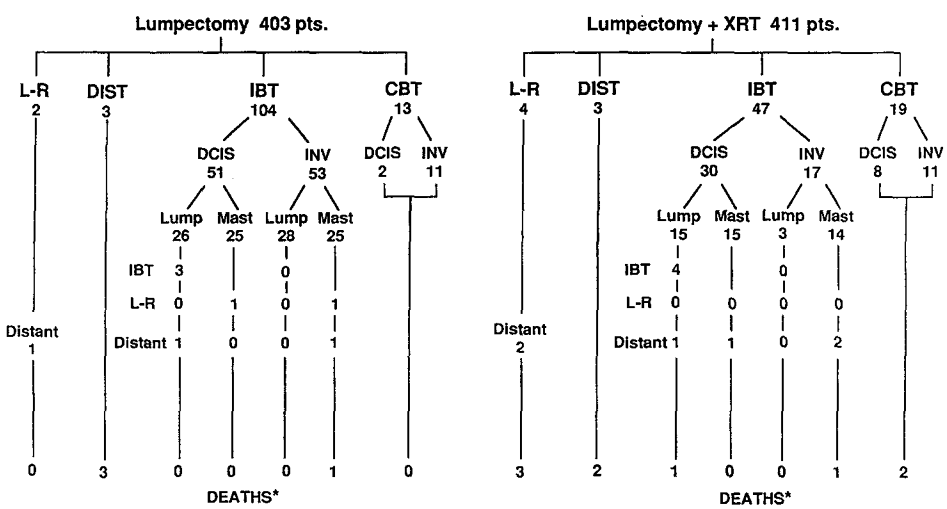

Fig 3. Schema of treatment and outcome of patients treated by L or L+XRT. L-R, locoregional; DIST, distant; INV, invasive; Lump, lumpectomy; Mast, mastectomy. Numbers refer to events; >1 event could have occurred in the same patient. *Due to breast cancer.

Locoregional or distant first events. Only 12 locoregional or distant first events occurred in the 814 randomized patients with follow-up data (Table 3 and Fig 3). Two patients in the group whose initial tumors were treated by lumpectomy had only regional recurrences: one in the intramammary lymph nodes and the other in the axillary lymph nodes. Three women developed distant metastatic disease. Four patients in the group initially treated by lumpectomy and radiation therapy had first events at local or regional sites (on the scar and chest wall in one patient, in the ipsilateral axillary nodes in another, and in the ipsilateral supraclavicular nodes in two others). Metastatic disease occurred at distant sites in three patients. Only one of five patients initially treated by lumpectomy alone had a concurrent invasive IBT at the time of detection of locoregional or distant first events. The initial tumors of three of those five patients demonstrated mammographic microcalcifications ≤ 1 cm in size; in the other two patients, the calcifications were greater than 1 cm. Three of seven patients in the group treated by lumpectomy and radiation therapy who developed locoregional or distant metastases had concomitant second IBTs, all of which were invasive. As in the lumpectomy group, most of these had been mammographically detected and contained small foci of calcifications. No distinct pathologic characteristics of the primary DCIS seemed to be related to the 12 events; for example, in some of these patients, comedo necrosis was either absent or slight, whereas it was more marked in others. For the most part, specimen margins were tumor-free.

CBT. The overall cumulative incidence of CBTs that occurred as a first event through 8 years of follow-up in the 814 randomized patients with follow-up data was 4.5%. Overall cumulative incidence at any time before death was 5.7% (Table 4). In the 403 patients whose primary tumors were managed by lumpectomy alone, 13 CBTs (3.3%) occurred as first events at 8 years (Fig 3). Two of these were DCIS and 11 were invasive cancers. There were 19 CBTs (5.7%) among 411 women who received radiation therapy following lumpectomy: eight of these were DCIS and 11 were invasive cancers. The average annual incidence rates in each of the two treatment groups were 0.58 and 0.77, respectively ($P = .55$; Table 3). When CBTs were evaluated according to pathologic tumor type, the cumulative incidence of invasive and noninvasive CBTs occurring as a first event in all 814 patients was 3.0% and 1.5%, respectively. The cumulative incidence of invasive and noninvasive CBTs in both treatment groups, whether as first or any events or before death, while small, was always slightly greater for the invasive than for the noninvasive tumor type.

Table 4. Cumulative Incidence of CBT as a First Event or at Any Time Before Death

Type of CBT and Time of Event	Lumpectomy (N = 403) No.	Lumpectomy (N = 403) %	Lumpectomy + XRT (N = 411) No.	Lumpectomy + XRT (N = 411) %	Both Groups (N = 814) No.	Both Groups (N = 814) %
Any tumor type						
As first event	13	3.3	19	5.7	32	4.5
Before death	19	5.4	20	6.0	39	5.7
Invasive						
As first event	11	2.8	11	3.3	22	3.0
Before death	16	4.9	12	3.6	28	4.2
Noninvasive						
As first event	2	0.5	8	2.4	10	1.5
Before death	3	0.5	8	2.4	11	1.5

Treatment of Primary DCIS

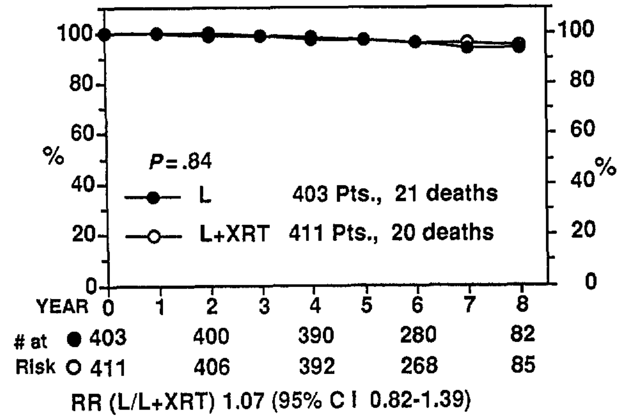

Fig 4. Survival of women treated by L or L+XRT.

Second primary tumors. There was no significant difference between the two treatment groups in the rate of second primary cancer ($P = .72$; Table 3). Ten second cancers, exclusive of cancer in the contralateral breast, occurred as first events in women treated by lumpectomy alone: two of these occurred in the colon, one in the pancreas, two in the lung, one on the skin of the arm, two in the uterus and cervix, and one each in the thyroid and lymph nodes. Fourteen second cancers occurred in women who received radiation therapy: four occurred in the colon, two in the uterus, and one each in the tonsil, esophagus, bone, lung, bladder, skin of the arm, lymph nodes, and soft tissue.

Survival and causes of death. Through 8 years of follow-up, the overall survival rate was 94% for women treated by lumpectomy alone and 95% for women who received radiation therapy following lumpectomy (RR = 1.07; 95% CI, 0.82 to 1.39; $P = .84$; Fig 4). Deaths from causes unrelated to breast cancer occurred as a first event in 11 women in the group treated by lumpectomy alone and in four women in the group treated by lumpectomy and radiation therapy (Table 3). Two deaths in the former group were due to complications from diabetes, two to aneurysm, three to myocardial infarction, two to chronic pulmonary disease, and one to tachycardia. In one patient, the cause of death was unknown. Deaths in the latter group were the result of accident, suicide, posthemorrhagic anemia, and myocardial infarction.

Fourteen deaths were attributable to breast cancer: four of these occurred in the group treated by lumpectomy alone and 10 occurred in the group treated by lumpectomy and radiation therapy. Three of the 14 deaths occurred in patients who received radiation therapy and who experienced locoregional failures as first events. Five patients who died had distant failures as a first event; three in the group treated by lumpectomy alone and two in the group that received lumpectomy and breast irradiation. Three deaths occurred subsequent to distant metastatic disease among the 151 women who had an IBT. One of these occurred in a patient in the lumpectomy group subsequent to removal of an invasive IBT and two in patients who received radiation therapy—one following removal of a noninvasive IBT and the other after mastectomy for an invasive IBT. Two of the 19 women with a CBT in the group treated by lumpectomy and breast irradiation have died. Both of these deaths occurred in women who had an invasive CBT. One additional patient died of widespread metastases thought to have arisen from second primary (lung) cancer. Re-review failed to determine with certainty whether the cause of death was due to breast cancer or to a second primary tumor. At no time did the patient have an IBT recurrence.

Rate and RR of IBT according to selected mammographic and clinical characteristics at time of diagnosis of primary DCIS. The size of a mammographically detected tumor was not a significant predictor of an IBT (Table 5). The rate of IBT in either treatment group was not significantly different (RR = .86; 95% CI, 0.31 to 2.36), regardless of whether the detected tumor was ≤ 1 cm or greater than 1 cm in size. There was a reduction in the rate of IBT following radiation therapy in both tumor-size categories. Among women in both treatment groups whose mammograms showed microcalcifications and no tumor mass, those whose mammograms demonstrated either clustered calcifications greater than 1.0 cm in their maximum diameter or scattered calcifications had a significantly greater rate of IBT than did those whose mammograms showed clustered calcifications ≤1.0 cm in size (RR = 2.06; 95% CI, 1.36 to 3.10 in the former, and RR = 2.41; 95% CI, 1.40 to 4.16 in the latter). The RR of a noninvasive IBT was greater in women whose mammograms demonstrated clustered calcifications greater than 1.0 cm in size or scattered calcifications than in women whose mammograms showed microcalcifications ≤1.0 cm; RR = 2.91 (95% CI, 1.65 to 5.01) in the former and 3.01 (95% CI, 1.45 to 6.25) in the latter (not shown). There was no evidence of such a trend in women with invasive IBT. There was a reduction in the rate of IBT after radiation therapy in each of the groups found to have microcalcifications. This decrease occurred regardless of whether the IBTs were invasive or noninvasive. The rate of IBT was less after radiation therapy in women whose mammograms demon-

Table 5. Rates and RRs of IBT According to Selected Mammographic and Clinical Characteristics at Diagnosis of the Primary DCIS

Characteristics	Lumpectomy			Lumpectomy + XRT				
	No. of Patients	No. of IBTs	Rate	No. of Patients	No. of IBTs	Rate	RR*	95% CI
All patients	403	104	4.65	411	47	1.90		
Mammographic characteristics								
Tumor mass (cm)	51	11	3.60	63	4	0.98		
≤ 1.0	22	4	3.04	28	3	1.86	1.0	
> 1.0	29	7	4.01	35	1	0.41	0.86	0.31-2.36
Calcifications (no mass)	283	76	4.84	284	36	2.13		
Clustered (cm)								
≤ 1.0	194	39	3.52	181	17	1.57	1.0	
> 1.0	62	27	8.15	77	12	2.59	2.06	1.36-3.10
Scattered	27	10	7.58	26	7	4.88	2.41	1.40-4.16
Architectural distortion	12	2	2.90	8	1	1.85		
No abnormality or other	15	4	4.92	14	3	3.92		
Not centrally reviewed	42	11	5.31	42	3	1.21		
Method of detection								
Mammogram only	324	86	4.75	330	33	1.66	1.0	
Mammogram and clinical examination	78	18	4.30	81	14	2.91	1.15	0.78-1.70
Age at diagnosis (years)								
≤ 49	137	36	4.79	137	21	2.65	1.0	
50-59	115	33	5.15	131	12	1.48	0.87	0.88-2.44
≥ 60	151	35	4.16	143	14	1.60	0.77	0.53-1.13

*RRs for covariate strata group *v* first group; adjusted for treatment.

strated only architectural distortion but no mass or calcifications (Table 5). There was also a slight reduction in the rate of IBT after radiation therapy in those women with normal mammograms or other findings.

No significant correlation was noted between the method of detection of the primary DCIS, ie, by mammography only or by mammography and clinical examination, and the rate of IBT (Table 5). No difference in rates of IBT was noted in those women whose DCIS was detected only by mammography and those whose tumors were detected by mammography and clinical examination (RR = 1.15; 95% CI, 0.78 to 1.70). There was a reduction in IBT in women in both groups who received radiation therapy. Age at diagnosis was not a significant predictor for IBT. Rates of IBT and RRs did not differ across age groups. A reduction in the rate of IBT among patients who received radiation therapy was evident in all age groups.

DISCUSSION

The findings in this report continue to indicate, through 8 years of follow-up, that, as we first reported in 1993,[5] the cumulative incidence of both invasive and noninvasive IBTs is significantly decreased as a result of radiation therapy administered after lumpectomy in women with localized DCIS detected primarily by mammography. These findings are supported by the fact that the cumulative incidence of an invasive IBT was only 3.9% in patients treated by lumpectomy and radiation therapy, as compared with 13.4% in women treated by lumpectomy alone, and that there was a significant decrease in the cumulative incidence of noninvasive IBTs (13.4% *v* 8.2%, respectively). Our current findings also refute the contention that, although radiation therapy may result in a short-term advantage, the benefit is apt to decrease with greater follow-up.[14] Retrospective studies have demonstrated that the incidence of IBT doubles between 5 and 8 years of follow-up in women who receive radiation therapy after lumpectomy.[15-18] Our findings indicate that there was also only a slight increase in the cumulative incidence of both invasive (from 3.0% to 3.9%) and noninvasive (from 6.4% to 8.2%) IBTs in the group treated by radiation therapy. The percent reduction in cumulative incidence of both invasive and noninvasive IBTs continues to be large for radiation-treated patients.

Following our original report, there was concern regarding the lack of information provided to identify a cohort of patients who could safely be treated by lumpectomy alone.[14,17,19-25] The intent of our original report was to present only those findings that addressed the hypothesis that had given rise to our study, ie, the thesis that radiation therapy following lumpectomy is appropriate treatment for DCIS. When we obtained information to support that thesis and estimated the extent of the benefit, we believed the data sufficiently compelling to warrant an initial publication, to be followed by a second report that would provide not only a detailed evaluation of the pathologic features of tumors from B-17 patients, but also a description of our efforts aimed at identifying both those patients at risk for an IBT and those patients who either did or did not benefit from radiation therapy. Publication of that second report was delayed by unanticipated circumstances that interrupted the activities of the NSABP.

In our second report,[26,27] the outcome of patients with DCIS was examined relative to each of nine pathologic characteristics. In each of the nine, the average annual hazard rate of IBT was lower in the group that received radiation therapy than in the group treated by lumpectomy alone. When the two treatment groups were compared relative to the rate of IBT in each subcategory of each tumor characteristic, eg, good or poor nuclear grade, comedo necrosis moderate/marked or absent/slight, an overall benefit from the use of radiation therapy was observed. Univariate proportional hazard modeling indicated that, of the nine pathologic features evaluated individually, only nuclear grade, comedo necrosis, specimen margin status, and histologic tumor type were significant prognostic variables for an IBT. However, when these variables were examined by multivariate analysis, only moderate/marked comedo necrosis and uncertain/involved tumor margin status were independent predictors of IBT. Most important, the findings indicated that, when comedo necrosis and tumor margin status were examined together, patients with tumor-free specimen margins and with slight comedo necrosis had less chance of developing an IBT than did patients whose margins were involved with tumor and demonstrated moderate to marked comedo necrosis. However, after the use of radiation therapy, not only did both good- and poor-risk patients benefit from radiation therapy, but their outcomes also became similar subsequent to the therapy. Those pathologic findings supported our original conclusion, ie, that lumpectomy and radiation therapy was more appropriate than lumpectomy alone for the treatment of women with localized DCIS. They also failed to provide evidence of a discriminant that identified DCIS patients who should not receive postoperative radiation therapy. That contention continues to be supported by our current finding that size of a mammographically detected tumor mass, method of detection of a DCIS, and patient age do not affect the RR for an IBT. On the other hand, the risk of an IBT increased with the size of mammographically identified clustered microcalcifications and with the presence of scattered calcifications. Nonetheless, as we noted in our report that evaluated pathologic variables, when the treatment groups were compared relative to the rate of IBT in each subcategory of each characteristic, radiation therapy resulted in a benefit. When tumors were measured histologically, the same conclusion was reached, ie, for tumors less than 1 cm or ≥1 cm.

There is universal agreement about the need to continue the search for discriminants to identify patients who either should or should not receive a particular treatment. None have yet been identified that clearly indicate which patients should or should not receive radiation therapy following lumpectomy. One such attempt to do so has been the development of the Van Nuys Prognostic Index (VNPI). In that schema, histologic type of DCIS, width of surgical excision margin, and tumor size are incorporated into a scoring scheme that is purported to identify which patients should be treated by local excision alone, by local excision and radiation therapy, or by mastectomy.[14,17,24] At present, the VNPI has not been sufficiently validated and has shortcomings that preclude its use as part of a strategy for the treatment of DCIS.[28,29] Moreover, the VNPI cannot be applied to DCIS patients in the B-17 study because it was derived from patients with all sizes of DCIS, including tumors ≥ 4.1 cm. Our study provides no information with regard to the treatment of large, clinically determined DCIS. Information about the treatment of DCIS larger than that demonstrated in this study should be forthcoming from another study, ie, NSABP B-24, in which the worth of tamoxifen for the management of such patients is currently being evaluated. Nonetheless, the likelihood of identifying a single biologic marker, or a combination of markers, that can identify with precision the 13% of women with focal, mammographically detected DCIS who will develop an invasive breast cancer after lumpectomy, let alone identify the small number (4%) who may not benefit from radiation therapy, seems remote.

In our initial report of B-17, the tumor sizes noted were those obtained by the NSABP Biostatistical Center from participating institutions. Investigators were required to complete a special data form indicating whether there was a clinically palpable tumor mass and, if so, to record the size. When no mass was palpable, the size submitted to the NSABP Biostatistical Center was to be that obtained from the submitted mammogram report. However, in numerous instances, when there was no palpable mass, the tumor size was reported by the institution as "zero," an indication that there was no clinically detected tumor. Approximately 45% of tumors were listed in our original report as having a size of less than 0.1 cm instead of zero (no palpable mass). An additional 30% of patients had tumors of a size that is determined most often by mammogram (0.1 to 1.0 cm). Another 13% to 15% of tumors were recorded as being 1.1 to 2.0 cm in size. There was justifiable concern that tumors "less than 0.1 cm or 0.1 cm" could not be either clinically or mammographically measured. Those sizes, which were used by investigators to indicate DCIS that was not clinically measurable, were troublesome. Nonetheless, from the information presented in our initial report, it was evident that the types of DCIS found in women entered onto our study were, for the most part, small lesions that had been mammographically detected. The careful clinical, pathologic, and mammographic re-review of tumor size performed in preparation for the current report confirms that conclusion. Clinical assessment showed that 90% of tumors were ≤1 cm, gross pathologic assessment indicated that 87% were ≤1 cm, and mammographic findings demonstrated that approximately 90% of tumors had been mammographically detected. Thus, the population of patients in the B-17 study is unique in that almost all of them had DCIS that was localized and had been mammographically detected. When a tumor was designated grossly as being ≤1 cm, that size was found to be concordant with the size determined histologically. However, there was less concordance when tumor size was greater than 1 cm.[30]

Because 33% of patients in the B-17 study were ≤ 49 years of age, our findings have relevance to the current issues regarding the use of mammography in younger women. They indicate that DCIS can be detected in younger women. It is of interest that, in this study, DCIS occurred with the same frequency in younger women as in women aged 50 to 59 years (30%) or ≥ 60 years (36%). Although the detection of DCIS in such patients may not be reflected in enhancement of overall survival of younger patients as a result of mammography, the efficacy of mammography should be assessed not only by its impact on the reduction of mortality but also by its contribution to quality of life attained through breast preservation.

Some physicians still consider mastectomy the standard against which other proposed therapeutic modalities for DCIS should be compared,[25] and it has been suggested that such a treatment group should have been included for comparison in the B-17 study. Although no randomized trial has yet been conducted to compare the outcome of patients treated by mastectomy with those treated by breast-conserving surgery, no clear scientific or clinical rationale exists for doing so. Moreover, our current findings indicate that, in view of the nature of DCIS present in the women who were entered onto B-17, we would have been ill-advised to have included in that study a group treated by mastectomy. The low incidence of locoregional recurrence (exclusive of IBT), of distant events, and of deaths from breast cancer observed after breast-conserving surgery in B-17 makes the conduct of such a trial moot. In addition, reviews of reports based on heterogeneous information that has been retrospectively accumulated indicate that locoregional treatment failures, distant disease, and deaths do occur after mastectomy performed for DCIS.[25,31,32] Although the magnitude of those events in patients with mammographically detected DCIS treated by mastectomy remains obscure, it is generally accepted that mastectomy for DCIS does not guarantee either freedom from invasive breast cancer or survival in all patients. Consequently, as was observed in our current study, some patients treated by lumpectomy, either with or without radiation therapy, demonstrated local, regional, and distant metastatic disease and died of breast cancer. These events are likely to have occurred even if those women had been treated by mastectomy. Of particular interest was the observation that those metastatic events occurred most often in women whose DCIS was mammographically detected and who failed to demonstrate an IBT when the events were discovered. Moreover, in several of the patients, locoregional disease was identified only 7 and 15 months after removal of the primary tumor, and two patients who experienced distant disease died within 12 months after treatment of their primary tumor. The fact that the frequency of metastatic disease and deaths was similar in both treatment groups was not surprising, because radiation therapy would not have been expected to influence the occurrence of distant metastatic disease and death.

Thus, given the findings from this study, the physical and emotional morbidity associated with mastectomy, and the lack of any tangible benefit from it, there is no reasonable justification for treating small, localized DCIS with such an operation. The fact that any argument about how such patients should be treated relates to whether they should receive radiation therapy indicates that lumpectomy has been accepted as the preferred surgical treatment for the type of disease encountered in the B-17 study.

There is little information available from retrospective studies about the occurrence of CBTs subsequent to the removal of a DCIS.[33] Despite this deficit, it is often speculated that, because women with DCIS are at sufficient risk for a CBT, prophylactic mastectomy of the contralateral breast could be a worthy consideration for at least some patients. Our current findings do not support that view. Through 8 years of follow-up, the cumulative incidence of invasive CBT occurring at any time before death (not only as a first event, but also as an event at any time) was only 4.2%. Such information should be provided to women with DCIS in whom prophylactic mastectomy of the contralateral breast is being considered. The fact that about 19 of every 20 breasts would be removed despite the absence of invasive tumor raises serious questions about the merit of mastectomy. Moreover, the finding that women treated by lumpectomy and radiation therapy have about the same likelihood of subsequently developing an invasive CBT (3.6%) or an invasive IBT (3.9%) should also be taken into account when a prophylactic mastectomy is contemplated.

In NSABP B-06, radiation therapy following lumpectomy for the treatment of invasive cancer was found to significantly decrease the incidence of IBT recurrence from approximately 40% to 10% through 12 years of follow-up. A similar reduction was noted after removal of DCIS in B-17 (from 27% to 12% at 8 years). Although there were too few locoregional and distant events in each of the two B-17 treatment groups for statistical analysis, there was no evidence to suggest that a reduction of IBT in patients with DCIS was associated with either better or worse distant disease-free survival or survival. These findings are in keeping with the findings from B-06, which were obtained from patients with invasive cancer. Thus, in both studies, the advantage from radiation therapy relates solely to the significant decrease in the incidence of IBT. Consequently, any further consideration of the use of radiation therapy must relate to its effect on IBT.

Of particular interest is information in this report relative to the location of a DCIS and of an IBT occurring subsequent to removal of the DCIS. We initially reported[5] that the overall concordance in location of the two was high. However, our recent findings suggest that the degree of concordance, ie, the occurrence of both tumors in the same quadrant, was higher among women whose IBT was noninvasive and that the incidence of an invasive IBT was greater than that of a noninvasive IBT at sites different from the primary DCIS. These findings provoke speculation relative to certain biologic considerations with regard to DCIS. Although the discordance in location of a primary DCIS and a subsequent invasive IBT does not prove or disprove the commonly held thesis that DCIS is a precursor of invasive breast cancer, it does suggest that, at least in some, if not many, instances, that might not be so. Confirmation of these findings could be of particular value in understanding the natural history of DCIS.

The current findings have relevance to the issue of whether postlumpectomy radiation should be used for the treatment of invasive tumors of less than 1 cm that are detected by mammography or incidental to the removal of another lesion, eg, DCIS. The findings seem to indicate the appropriateness of radiation therapy in patients with such tumors, particularly if these are associated with an intraductal component. NSABP B-21, which is currently being conducted, should provide information to support or reject the thesis that radiation can be replaced by tamoxifen therapy for the treatment of invasive tumors less than 1 cm.

In conclusion, the findings from this study indicate that radiation therapy should be used following lumpectomy in women with localized, mammographically detected DCIS. No data are yet available to identify which patients with the kind of DCIS observed in this study do not need to be treated with radiation therapy because they will not have an IBT recurrence. Further, there are, as yet, no pathologic, mammographic, or biologic discriminants to indicate which patients will not benefit from such therapy. Consequently, based on the data from B-17, the use of radiation therapy for all patients with the type of DCIS such as that encountered in that study seems appropriate to ensure that all women who can benefit from the therapy receive the opportunity to do so. Given the low frequency of the occurrence of invasive IBT and locoregional events following lumpectomy plus radiation therapy, mastectomy is not warranted in this group of patients.

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