Tamoxifen, Radiation Therapy, or Both for Prevention of Ipsilateral Breast Tumor Recurrence After Lumpectomy in Women With Invasive Breast Cancers of One Centimeter or Less

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Purpose: **This trial was prompted by uncertainty about the need for breast irradiation after lumpectomy in node-negative women with invasive breast cancers of ≤ 1 cm, by speculation that tamoxifen (TAM) might be as or more effective than radiation therapy (XRT) in reducing the rate of ipsilateral breast tumor recurrence (IBTR) in such women, and by the thesis that both modalities might be more effective than either alone.**

Patients and Methods: **After lumpectomy, 1,009 women were randomly assigned to TAM (n = 336), XRT and placebo (n = 336), or XRT and TAM (n = 337). Rates of IBTR, distant recurrence, and contralateral breast cancer (CBC) were among the end points for analysis. Cumulative incidence of IBTR and of CBC was computed accounting for competing risks. Results with two-sided *P* values of .05 or less were statistically significant.**

Results: **XRT and placebo resulted in a 49% lower hazard rate of IBTR than did TAM alone; XRT and TAM resulted in a 63% lower rate than did XRT and placebo. When compared with TAM alone, XRT plus TAM resulted in an 81% reduction in hazard rate of IBTR. Cumulative incidence of IBTR through 8 years was 16.5% with TAM, 9.3% with XRT and placebo, and 2.8% with XRT and TAM. XRT reduced IBTR below the level achieved with TAM alone, regardless of estrogen receptor (ER) status. Distant treatment failures were infrequent and not significantly different among the groups (*P* = .28). When TAM-treated women were compared with those who received XRT and placebo, there was a significant reduction in CBC (hazard ratio, 0.45; 95% confidence interval, 0.21 to 0.95; *P* = .039). Survival in the three groups was 93%, 94%, and 93%, respectively (*P* = .93).**

Conclusion: **In women with tumors ≤ 1 cm, IBTR occurs with enough frequency after lumpectomy to justify considering XRT, regardless of tumor ER status, and TAM plus XRT when tumors are ER positive.**

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THREE EVENTS OCCURRED during the 1980s that influenced the diagnosis and treatment of primary breast cancer. Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 randomized trial established the worth of radiation therapy (XRT) in the prevention of ipsilateral breast tumor recurrence (IBTR) after lumpectomy in women with tumors that were associated with either negative or positive axillary nodes;[1] the use of better mammographic screening techniques facilitated the identification of invasive breast cancers that were too small for clinical detection (occult tumors); and findings from trials demonstrated a benefit from tamoxifen (TAM) in women with estrogen receptor (ER)-positive tumors.[2,3]

As lumpectomy and XRT became more common, physicians and women began to question the need for breast irradiation after lumpectomy for occult, invasive cancer. It was also thought that TAM might be just as effective as XRT in reducing the rate of IBTR and, at the same time, might result in a decrease in both the recurrence rate at other sites and the occurrence of cancer in the contralateral breast. In 1989, the NSABP implemented the B-21 study, a randomized trial that had been designed to resolve those uncertainties. This report provides information obtained from that trial about whether treatment with TAM alone is as or more effective than XRT for preventing IBTR after lumpectomy for tumors of ≤ 1 cm. It also addresses the question of whether treatment with TAM and breast irradiation is more effective than either modality alone in preventing IBTR and in reducing both systemic recurrence and contralateral breast cancer (CBC).

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Table 1. NSABP B-21: Patient Entry and Follow-Up Information

	Treatment		
	TAM	XRT + Placebo	XRT + TAM
Randomly assigned, no. of patients	336	336	337
Ineligible	9	16	7
Without follow-up	2	4	3
Included in analysis	334	332	334
Median follow-up time, months	89.2	85.8	86.9

PATIENTS AND METHODS

Study Information

Before they entered the trial, women at NSABP institutions in the United States and Canada who had elected to participate in the study signed a consent form that was in compliance with federal and institutional guidelines. To be eligible, women had to have a primary invasive breast tumor of less than 1 cm in its greatest diameter, as determined by pathologic examination. If a tumor had intraductal, as well as an invasive component, the maximum diameter of both, when measured together, had to be less than 1 cm. If the pathologic size of a tumor was not available, both the clinical and mammographic sizes of the tumor had to be less than 1 cm. In addition, all tumors had to have been removed by lumpectomy and axillary dissection, margins of the resected specimen had to be tumor-free on pathologic examination, and axillary lymph nodes had to be negative on histologic examination.

The trial was opened to enrollment on June 1, 1989. After stratification by age, ie, ≤ 49 or ≥ 50 years, women were randomly assigned to XRT and placebo, XRT and TAM, or TAM alone. On April 6, 1994, when patient accrual was temporarily halted for reasons unrelated to this study, 727 women had been randomly assigned. In an effort to increase the rate of accrual when the trial was reopened in April 1996, women whose largest tumor diameter was, on pathologic examination, reported to be 1.0 cm in size also became eligible for randomization. Between April 1, 1996, and December 31, 1998, when accrual was terminated as a result of recommendations made to an independent data-monitoring committee, an additional 281 women had been entered. Patient entry and follow-up information is listed in Table 1. Thirty-two women (3.2%) were found to be ineligible, and no follow-up information was available for nine women (0.9%).

Patient Characteristics

The distribution of selected patient and tumor characteristics was similar among the three groups (Table 2). Approximately 80% of the women were aged ≥ 50 years. Between 26% and 29% of tumors were T1a ($\leq$ 5 mm) and 70% to 72% were T1b (5.1 to 10 mm). Approximately 6% to 7% of the tumors were 1 cm in size.

Table 2. NSABP B-21: Characteristics of Patients

	Treatment Group					
	TAM (n = 334)		XRT + Placebo (n = 332)		XRT + TAM (n = 334)	
Characteristics	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age at diagnosis						
< 50 years	68	20.4	68	20.5	68	20.4
50-59 years	106	31.7	87	26.2	108	32.3
60+ years	160	47.9	177	53.3	158	47.3
Menopausal status						
Known						
Pre/perimenopausal	71	21.3	81	24.4	74	22.2
Postmenopausal	260	77.8	247	74.4	257	76.9
Unknown	3	0.9	4	1.2	3	0.9
Race						
Known						
White	305	91.3	295	88.9	308	92.2
Black	13	3.9	11	3.3	8	2.4
Other	13	3.9	22	6.6	16	4.8
Unknown	3	0.9	4	1.2	2	0.6
Pathologic tumor size						
Known						
≤ 5 mm	97	29.0	85	25.6	95	28.4
6-10 mm	232	69.5	239	72.0	236	70.7
> 10 mm	1	0.3	4	1.2	1	0.3
Unknown	4	1.2	4	1.2	2	0.6
ER status						
Known						
Negative	43	12.9	45	13.6	45	13.5
Positive	197	59.0	189	56.9	181	54.2
Unknown	94	28.1	98	29.5	108	32.3

Therapy

The techniques of lumpectomy, axillary dissection, pathologic determination of resected specimen margin status, and XRT have been described elsewhere.[4] XRT was usually begun approximately 14 days after surgery, and 50 Gy was administered over a 5-week period. External-beam boosts were not assigned by randomization but were left to the discretion of the investigator. Approximately 25% of the women received a boost; around 75% did not. The median boost dose among those who received a boost was 10 Gy. Any findings that might have resulted from a comparison between women who received a boost and those who did not could have been a result of patient selection bias. Thus, because these results would have been difficult to interpret, they have not been included in this report. TAM or placebo (10 mg tablets bid) was begun within 35 days after lumpectomy and was to be given twice a day for 5 years. Because the placebo and TAM tablets could not be distinguished from each other, neither medical personnel nor patients could determine with certainty which of the pills were being administered. Five percent of women discontinued TAM or placebo because of toxicity, and 11% withdrew for other reasons.

Determination of ER

ER and progesterone-receptor determinations were not required for study entry. Nevertheless, assay information about ER was obtained from reports of 700 of the 1,000 women with follow-up; 530 (76%) of the determinations were carried out by the immunohistochemical method, 18 (3%), by enzyme immunoassay, and 145 (21%), by charcoal binding. The method was not specified in seven (1%) of the women. The methodologies used, as well as the proportion of women with ER-negative or ER-positive tumors, were equally distributed among the groups (Table 2). For immunohistochemical assays, when $\geq$ 10% of cells were stained positive, tumors were classified as ER positive. When the institutional report indicated that the tumors were ER positive, we accepted that value. For charcoal-binding assays, an ER of less than 10 femtomoles per mg of cytosol protein was classified as ER negative, and an ER equal to or greater than 10 femtomoles was classified as ER positive.

Statistical Methods

The primary end point for this analysis was time free from an IBTR as a first event. Both invasive and noninvasive IBTRs were included. The cumulative probabilities of IBTR as a first event were computed for each treatment arm by means of cumulative incidence functions.[5] Hazard rates for IBTR were also summarized for each treatment arm by dividing the number of IBTRs by the total number of woman-years before first event or last follow-up. A global test of equality of hazards across the three treatment arms was performed using the log-rank test. *P* values were obtained by permutation. Follow-up pairwise comparisons were also based on the log-rank test. Hazard ratios (HRs) were estimated using the method of partial maximum likelihood applied to Cox models. Cox models were also used to assess the prognostic effect of patient and tumor characteristics (age, receptor status, and pathologic tumor size) on the incidence of IBTR and to ascertain whether there was differential response to therapy according to these characteristics, ie, treatment-covariate interactions.[6]

Other end points that were compared across treatments included disease-free survival, time to first distant failure, time to CBC, and overall survival. Events used in the determination of disease-free survival included IBTRs, other recurrences, CBC, other second primary cancers, and deaths before treatment failure or second primary cancer. Deaths from all causes were included in the analysis of overall survival. Analyses followed the intent-to-treat principle and so were based on all 1,000 women with follow-up, including two patients who had positive specimen margins. The analyses reflect information received at the NSABP Biostatistical Center through December 31, 2000. The median time on study was 86.9 months.

RESULTS

Type and Location of First Events

Since study entry, 187 (18.7%) of the women have had an event, ie, a tumor recurrence, CBC, other second primary cancer, or death with no evidence of cancer. Nearly two thirds of the first events (n = 120; 64.2%) were breast cancer-related: 77 were IBTRs; 16 were recurrences at other local, regional, or distant sites; and 27 were CBCs (Table 3). Forty-six first events were second primary cancers other than CBC, and 21 first events were deaths unrelated to either breast cancer recurrence or second primary cancer.

Frequency of IBTR

When the hazard rates of IBTR among all women were compared, XRT and placebo resulted in a 49% lower hazard rate than treatment with TAM alone (Table 4). Treatment with XRT and TAM resulted in a 63% reduction in the rate of IBTR when compared with XRT and placebo, and an 81% reduction when compared with TAM alone. Through 8 years, the cumulative incidence of IBTR was 16.5% in TAM-treated women, 9.3% in women who received XRT and placebo, and 2.8% in those treated with XRT and TAM (Fig 1).

IBTRs According to Pathologic Type or to Age of Women at Randomization

Reports from institutional pathologists were available for 76 of 77 IBTRs. Fifty-nine (77.6%) of these were invasive cancer, and 17 (22.4%) were noninvasive cancer, ie, ductal carcinoma-in-situ (DCIS). Thirty-nine (11.7%) of the women in the TAM-treated group had an invasive IBTR, and five (1.5%) had a noninvasive IBTR. There were 14 invasive IBTRs (4.2%) and nine noninvasive IBTRs (2.7%) in the XRT and placebo group. Six women (1.8%) in the XRT and TAM group had invasive IBTRs, and three (0.9%) had noninvasive IBTRs. Pathology reports describing the primary invasive tumors in the 17 women who subsequently developed noninvasive IBTRs showed an extensive DCIS component associated with the invasive cancer in 13.

In women aged $\leq$ 49, 50 to 59, or 60 to 69 years, the rate of IBTR in the XRT and placebo group was lower than the rate in the TAM group (Table 4). IBTR rates were similar in the two groups of women aged $\geq$ 70 years. The greatest rate reduction in all age groups was observed in the XRT and

Table 3. NSABP B-21: Type and Location of First Event(s) Relative to Treatment Regimen

First Event	TAM (n = 334)			XRT + Placebo (n = 332)			XRT + TAM (n = 334)			P† (3-group comparison)
	No. of Patients	%	Rate*	No. of Patients	%	Rate*	No. of Patients	%	Rate*	
Breast cancer recurrence										
IBTR	45	13.5	22.8	23	6.9	11.7	9	2.7	4.39	< .0001
Other local, regional, or distant	7	2.1	3.55	5	1.5	2.54	4	1.2	1.95	.54
CBC	3	0.9	1.52	14	4.2	7.11	10	3.0	4.87	.03
Second primary cancer‡										
Endometrial	1	0.3	0.51	1	0.3	0.51	5	1.5	2.44	.12
Other	14	4.2	7.11	10	3.0	5.08	15	4.5	7.31	.65
Death, NED	4	1.2	2.03	8	2.4	4.06	9	2.7	4.39	.42
Total first events	74	22.2	37.6	61	18.4	31.0	52	15.6	25.3	.08
Alive, event-free	260	77.8		271	81.6		282	84.4		–
Vital status										
Alive	314	94.0		312	94.0		312	93.4		.93
Dead	20	6.0	9.12	20	6.0	9.36	22	6.6	10.1	

Abbreviation: NED, no evidence of disease (breast cancer).

*Per 1,000 woman-years.

†Log-rank test for the equality of cause-specific hazards across the three groups.

‡Other than contralateral breast cancer.

TAM group. A test for continuous age-by-treatment interaction was not significant ($P = .12$).

Treatment of IBTR

Of the women who developed an IBTR, 55.7% had a mastectomy and 44.3% had a second breast-conserving operation; 60.0% of women with an invasive IBTR were treated with mastectomy and 40.0% had breast-conserving surgery. Conversely, 40.0% of the women with a noninvasive IBTR had a mastectomy, and 60.0% were treated with breast-conserving surgery. Type of operation to treat IBTR was not significantly related to initial treatment assignment ($P = .09$).

Time to Distant Treatment Failure

There were 27 distant treatment failures: 11 (3.2%) in the TAM-treated group, 11 (3.3%) in the group that received XRT and placebo, and five (1.5%) in the group that received XRT and TAM ($P = .28$ by log-rank test). Fourteen (six, five, and three in the three groups, respectively) of the 27 failures occurred as first events, and 13 (five, six, and two in the three groups, respectively) were detected after a first event.

CBC

When the rate of CBC in the XRT and placebo group (7.1 per 1,000 women per year) was compared with the rate in

Table 4. NSABP B-21: Rates of IBTR Among Treatment Groups Overall and According to Age or Primary Tumor ER Status

	TAM Events			XRT + Placebo Events			XRT + TAM Events			XRT + Placebo		XRT + TAM		XRT + TAM	
	No. of Patients	Events		No. of Patients	Events		No. of Patients	Events		TAM		XRT + Placebo		TAM	
		No.	Rate*		No.	Rate*		No.	Rate*	HR Ratio	95% CI	HR Ratio	95% CI	HR Ratio	95% CI
Overall	334	45	22.8	332	23	11.7	334	9	4.4	0.51	0.31-0.84	0.37	0.17-0.80	0.19	0.09-0.39
										$P = .008$		$P = .01$		$P < .0001$	
According to age															
≤ 49 years	68	11	24.9	68	7	17.5	68	5	10.2	0.71	0.27-1.83	0.51	0.16-1.65	0.40	0.14-1.17
50-59 years	106	15	25.9	87	6	11.6	108	3	4.8	0.44	0.17-1.15	0.39	0.10-1.58	0.18	0.05-0.63
60-69 years	117	16	22.2	118	5	7.0	101	1	1.6	0.31	0.11-0.85	0.24	0.03-2.04	0.07	0.01-0.57
≥ 70 years	43	3	13.0	59	5	14.9	57	0	0.0	1.06	0.25-4.46	–	–	–	–
According to tumor ER															
Negative	43	14	68.1	45	5	19.1	45	4	14.2	0.29	0.11-0.81	0.56	0.13-2.35	0.21	0.07-0.64
										$P = .018$		$P = .49$		$P = .003$	
Positive	197	19	16.8	189	7	6.9	181	2	2.1	0.41	0.17-0.99	0.30	0.06-1.43	0.12	0.03-0.53
										$P = .049$		$P = .18$		$P = .0007$	
Unknown	94	12	19.0	98	11	15.8	108	3	3.7	0.84	0.37-1.90	0.24	0.07-0.85	0.19	0.06-0.69
										$P = .69$		$P = .017$		$P = .007$	

*Per 1,000 woman-years.

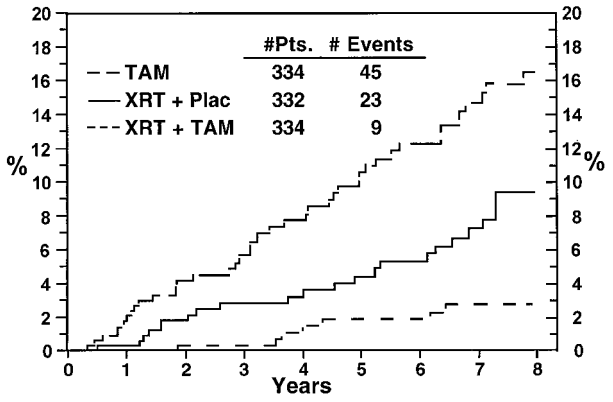

Fig 1. Cumulative incidence of IBTR after treatment with TAM, XRT and placebo, or XRT and TAM. Pairwise comparisons: TAM *v* XRT + placebo: *P* = .008; TAM *v* XRT + TAM: *P* < .0001; XRT + placebo *v* XRT + TAM: *P* = .01.

the two TAM groups combined (3.2 per 1,000 women per year), there was a significant reduction as a result of TAM administration (HR, 0.45; 95% confidence interval [CI], 0.21 to 0.95; $P = .039$). The cumulative incidence of CBC through 8 years was 5.4% in women who received XRT and placebo and 2.2% in those treated with TAM with or without XRT (Fig 2).

Relation of Tumor ER Status to IBTR and to CBC

In women with either ER-negative or ER-positive tumors, the rate of IBTR in the XRT and placebo group was lower than the rate in the TAM-treated group (Table 4). When the XRT and TAM group was compared with the group that received XRT and placebo, there was no significant reduction in the rate of IBTR in women with ER-negative tumors. Women with ER-positive tumors who received XRT and TAM had a nonsignificantly lower rate of IBTR than those who received XRT and placebo. However, a significant reduction in the rate of IBTR was observed with XRT and TAM when that group was compared with the TAM-treated group, regardless of ER status. Tests of a differential benefit from treatment according to ER status did not reveal a statistically significant variation in the relative benefit of the combined treatments over the benefits achieved with TAM alone or with XRT and placebo. However, the number of IBTRs was insufficient to provide adequate power for such tests of interaction.

In women with ER-positive tumors, the rate of occurrence of CBC was significantly less in those who received TAM, either with or without XRT, when this rate was compared with that in the XRT and placebo group (HR, 0.26; 95% CI, 0.09 to 0.78; $P = .013$). There were too few events in either group of women with ER-negative tumors to permit obtaining meaningful findings.

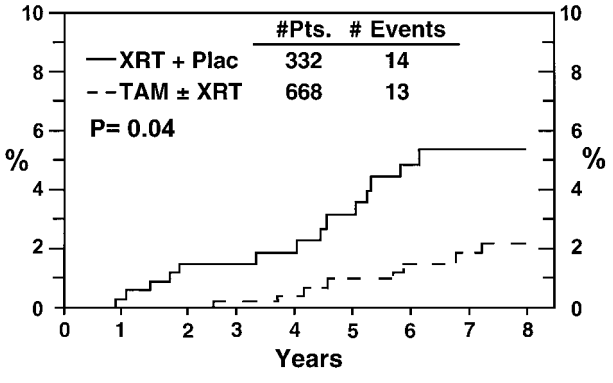

Fig 2. Cumulative incidence of CBC after lumpectomy and treatment with either XRT and placebo or TAM with or without XRT. The two TAM groups were combined.

Size of Primary Tumor and Size as a Prognostic Factor for IBTR

For 984 (98.4%) of the 1,000 women included in these analyses, tumor size was reported to be $\leq$ 10 mm; 0.6% of the women had tumors that were greater than 10 mm, and, in 10 (1.0%), the tumor size was not reported. Of the tumors $\leq$ 10 mm, 28.2% were $\leq$ 5 mm in size and 71.8% were between 6 and 10 mm. Of those tumors that were $\leq$ 10 mm, 6.5% were reported as being exactly 10 mm. To ascertain whether tumor size was a prognostic factor for IBTR, a Cox model was used to estimate HR of IBTR by tumor size ($>$ 5 mm *v* $\leq$ 5 mm), when treatment group was controlled for. Larger tumor size was not related to a worse prognosis; in fact, women with smaller tumors had a somewhat greater risk of IBTR.

Comparison Between Size of Tissue Specimens and Size of Primary Tumor Removed by Lumpectomy in Women With IBTR

To determine whether the occurrence of an IBTR was related to inadequate removal of breast tissue, an estimate of the extent of breast tissue removed around a tumor was compared with the size of the tumor itself. The mean and median of the largest diameters in 66 tissue specimens were 4.99 cm (SD, $\pm$ 2.56) and 4.90 cm, respectively. The mean and median of the smallest diameters in 61 specimens were 2.08 cm (SD, $\pm$ 1.28) and 1.80 cm, respectively. For the 66 tumors, the mean of the largest diameter was 0.61 cm (SD, $\pm$ 0.25), and the median was 0.60 cm.

Survival

Deaths among all women included in the analyses were almost equally distributed among the three groups ($P = .93$;

Table 3). Nine of the deaths in women who received TAM alone were attributable to breast cancer, six were due to other cancers, and five resulted from other causes. Eight of the deaths in the group treated with XRT and placebo were attributable to breast cancer, four were the result of other cancers, and eight occurred for other reasons. Five of the deaths in the XRT and TAM group were attributable to breast cancer, eight resulted from other cancers, and nine resulted from other causes.

Adverse Events

Seven of the women in the study had endometrial cancer (Table 3). A second primary cancer other than cancer of the breast or uterus was diagnosed in 39 women (3.9%). The rate of occurrence of such tumors was 5.1 per 1,000 women per year in the XRT and placebo group and 7.2 in those who received TAM, with or without XRT, after lumpectomy (HR 1.41; 95% CI, 0.69 to 2.89; $P = .40$). In all groups, the number of second primary cancers other than those in the breast and uterus was widely distributed among a large number of sites. There was no indication that the incidence of these cancers differed among treatment groups.

Hot flashes were more frequent in TAM-treated women than in those who received placebo. Nine (1.4%) of the women who received TAM, with or without XRT, had deep vein thrombosis (DVT); five (0.8%) had nonfatal pulmonary embolism (PE); and five (0.8%) had stroke. No DVTs were reported among women in the XRT and placebo group; one patient (0.3%) in this group had PE, and two (0.6%) had stroke. Ten (67%) of the DVTs or PEs in the 15 women who experienced either of those events and five (71%) of the seven strokes occurred in women who were older than 65 years of age at the time of study entry.

DISCUSSION

After we demonstrated that XRT resulted in a decrease in the rate of IBTR after lumpectomy,[1] there was speculation about whether the incidence of IBTR in women with invasive tumors of $\leq$ 1 cm might be low enough to spare them the need for breast irradiation. At that time, no information was available about the frequency of IBTR after removal of such small tumors. Only after the B-21 study was already in progress were there reports of such findings from randomized[2,7-13] and retrospective studies.[14-16] Seventy-two of 572 participants in the NSABP B-06 trial who had tumors of $\leq$ 1 cm were treated with lumpectomy alone; 25% of these women had an IBTR through 8 years of follow-up.[17] In another randomized trial in which 93 women with tumors of $\leq$ 1 cm had been treated with lumpectomy, 22.5% had a local recurrence through 10 years of follow-up.[9] In a nonrandomized study, a similar frequency of IBTR (24% at 10 years) was found in women with tumors of $\leq$ 1 cm who had been treated with lumpectomy.[14] Although the frequency of an IBTR after lumpectomy in approximately 25% of women might be viewed as being too high for such small tumors, the plausibility of that frequency is supported by the findings in our current report, which demonstrate indirectly that there is likely to be a substantial risk of an IBTR after lumpectomy to remove tumors of $\leq$ 1 cm. There is ample reason to believe that the cumulative incidence of IBTR (17% through 8 years of follow-up) in the TAM-treated group in B-21 would have been higher in an untreated control group, had such a group been included in that study. This thesis is supported by the finding that 82% of the tumors in women in the TAM-treated group in B-21 were ER positive, and it has repeatedly been demonstrated that TAM benefits women with all stages of ER-positive invasive breast cancer[2,18-22]; prevents ER-positive invasive cancer in women at increased risk for invasive cancer,[23] including those with a history of DCIS,[13] lobular carcinoma-in-situ, and atypical ductal hyperplasia[23]; and prevents CBC.[24-26] Thus, there is conclusive evidence that the incidence of IBTR after removal of an invasive tumor of $\leq$ 1 cm is high enough to warrant evaluation of the worth of additional therapy after lumpectomy.

The B-21 findings provide information from a randomized clinical trial that was designed a priori for the specific purpose of comparing the worth of TAM and/or XRT in reducing the incidence of IBTR and CBC after lumpectomy in node-negative women with tumors of $\leq$ 1 cm. The B-21 results demonstrate that TAM administration is less effective than XRT in preventing an IBTR after lumpectomy to remove invasive tumors of $\leq$ 1 cm. However, the findings do signify that the use of both XRT and TAM results in a lower rate of IBTR than is observed after the use of either modality alone in women with ER-positive tumors. TAM administration also resulted in a substantial reduction in the rate of occurrence of CBC in ER-positive women. These benefits are in accord with what was observed in two other NSABP studies, one in women with tumors of $\leq$ 1 cm, and the other in women with larger tumors.[22,26]

Information from studies recently published by other investigators with regard to the use of TAM and XRT in older women is relevant to our findings. In one of the studies, axillary node–negative women with T1 and T2 tumors who were over 50 years of age (median age, 68 years) were randomly assigned after lumpectomy to receive either TAM or TAM in addition to XRT.[27] After a median follow-up time of 3.4 years, the investigators concluded that treatment with TAM and XRT resulted in a significantly lower rate of IBTR than did treatment with TAM alone, a

conclusion that was consistent with our findings. However, the findings from a second study, in which TAM with XRT was compared with TAM alone in lumpectomy-treated women aged 70 years or older who had clinical stage I, ER-positive breast cancer, led to a different conclusion.[28] After a median time on study of only 2.8 years, the authors concluded, from a few events, that XRT might not be of clinical benefit in the elderly population that was evaluated. That thesis has been promulgated by several other investigators, who have hypothesized that, in node-negative women over 60 years of age, XRT after breast-conserving surgery might not be necessary.[8,15,29-32] The B-21 findings demonstrated that the rate of IBTR in women of all ages who received XRT and TAM was lower than the rate in women who received TAM alone; thus, they are not in concordance with findings that refute the use of XRT on the basis of age. Because, as we have noted in this report, many of the IBTRs that occurred in women in the B-21 study were diagnosed only after a prolonged time interval, ie, 38% after 5 years, the value of the findings as reported in the two studies previously noted is diminished by the short follow-up time in each.

Some have contended that the higher-than-expected frequency of IBTR after lumpectomy for small, invasive or noninvasive breast cancer is a result of the removal of an insufficient amount of normal breast tissue surrounding a tumor.[30,33,34] It has been suggested that more expansive surgical procedures would achieve better local tumor control and, thus, could preclude the need for XRT. Although the appropriate width of tumor-free breast tissue that should encompass an excised tumor has not yet been determined,[35] it is generally believed that tumor-free specimen margins should be at least 10 mm. In the B-21 study, we demonstrated that the smallest diameter of the resected specimen was generally at least 10 mm greater than the largest diameter of the tumor. Thus, these findings suggest that the frequency of IBTR observed in B-21 is not likely to be due to the removal of an inadequate amount of normal tissue surrounding the tumor.

In 1998, an international consensus panel decided that the size of an invasive tumor was the most important prognostic factor for estimating the risk of relapse in women with node-negative breast cancer.[36] Tumors of $\leq$ 1 cm were classified as being of minimal to low risk. Little or none of that information is germane to the findings from B-21, where tumors varied in size by as little as a millimeter. Within that category, we failed to appreciate correlation between reported tumor sizes and recurrence. In fact, IBTRs were somewhat more frequent in women who had smaller primary tumors, ie, those of $\leq$ 5 mm, than in women who had larger tumors (6 to 10 mm). The lack of correlation may be due to either the difficulty in measuring the size of such tumors with precision[22] or to the presence of a noninvasive component in association with the invasive component of a tumor.

Most investigators have indicated a preference for salvage mastectomy in treating women diagnosed with an IBTR.[37-40] Nearly one half (44.3%) of the women in B-21 who had an IBTR were managed with a second breast-conserving operation. Because almost half of the women with an invasive IBTR who were treated with mastectomy had IBTRs that were $\leq$ 2 cm (many were of $\leq$ 1 cm), on the basis of size alone, it is possible that many women who had a mastectomy could have been candidates for a second breast-conserving operation. These findings suggest that a second lumpectomy to treat women with small, invasive or noninvasive IBTRs may be worthy of consideration.

The B-21 findings and their implications for treatment are likely to be interpreted diversely. Such has been the case after publication of findings from other NSABP trials that have evaluated the prognosis and treatment of women with tumors of $\leq$ 1 cm;[22] subsequent to our report of findings from the NSABP prevention study (P-1), which compared TAM with placebo in women at increased risk for breast cancer[23] and after the publication of the results from two trials that evaluated the worth of XRT, with or without TAM, for the prevention of invasive cancer in women with DCIS.[13,41] Some investigators have viewed the findings from these studies, all of which are linked to the B-21 trial, from a narrow perspective. The results from B-21 should be considered in context with the findings from our studies previously mentioned as part of an overall effort aimed at eradicating breast cancer closer to its phenotypic expression. Paradoxically, although all of those studies have demonstrated benefits from the therapies evaluated, they have resulted in controversy, not with the data themselves, but with the clinical application of the findings. It is apparent that, when a group of women with an increasingly better prognosis is defined and when evidence of a therapeutic benefit among the few in the group who are likely to have a tumor recurrence is demonstrated, treatment decisions become difficult. This is particularly the case when there is no adequate discriminant to indicate with precision who is likely to have a treatment failure and, thus, to require therapy.

We do not suggest that all women with invasive or noninvasive breast cancers of $\leq$ 1 cm should receive chemotherapy, TAM, or XRT after lumpectomy. We do contend, however, that the merits of such therapies should be considered on the basis of the data supporting their value, in conjunction with other characteristics of the individual patient and her tumor, and relative to undesirable effects that might result from the therapy. It is our view that

histopathologic or biologic characteristics, eg, ER status, nuclear grade, tumor type, and a patient's clinical status, in conjunction with tumor size, are likely to be more helpful for making a decision about the treatment of an individual patient than is tumor size alone. Perhaps, before long, gene expression, as identified by means of micro-array technology, will be useful in that regard. It is important to recognize that when therapeutic decisions need to be made about managing women with small tumors, eg, those $\leq$ 1 cm, information used for the process should be that obtained after a longer follow-up period than is usually the case.[42] For example, information obtained after only 5 years of follow-up might be invalid after a more prolonged time because more breast cancer-related events might occur after a longer interval, whereas there might have been little or no change in the number of undesirable events related to the therapy. In addition, in making a decision, the psychologic, cosmetic, and economic consequences that result from IBTR and its management need to be considered.[7,42,43] In conclusion, the use of XRT with or without TAM after breast-conserving surgery in women with tumors of $\leq$ 1 cm to prevent undesirable sequelae deserves serious consideration.

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APPENDIX

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