The Effects of Postradiation Treatment with Tamoxifen on Local Control and Cosmetic Outcome in the Conservatively Treated Breast

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BACKGROUND. The aim of this study was to evaluate the impact on disease recurrence and cosmetic outcome of tamoxifen treatment initiated after breast-conserving therapy (BCT).

METHODS. Between 1982 and 1994, 498 women (509 breasts) were treated with BCT in accordance with a highly standardized institutional protocol. Adjuvant tamoxifen was administered to 130 patients (134 breasts), beginning 1–6 weeks after irradiation. The median ages and duration of follow-up for groups who received tamoxifen (TAM+) and no tamoxifen (TAM−) were 62.5 years/56 months and 53 years/60 months, respectively. The members of the TAM+ group were significantly older ($P = 0.0001$) and had increased incidences of positive axillary lymph nodes or undissected axilla ($P = 0.001$). There was a significant ($P = 0.001$) difference between the TAM+ and TAM− groups in the distribution of histopathologic subtypes; this reflected an increased proportion of associated ductal carcinoma in situ in the TAM− group. More extensive regional lymphatic irradiation was administered to the TAM+ group. Chemotherapy was administered to 15% of TAM+ and 28% ($P = 0.003$) of TAM− patients. There were no significant differences between the groups with respect to tumor size, reexcision, total excised tissue volume, final margin status, total radiation dose, or use of interstitial implant boost.

RESULTS. There was no significant difference between the TAM+ and TAM− groups in the overall distribution of cosmetic scores ($P = 0.18$). The 5-, 7-, and 10-year actuarial local failure rates for TAM+ versus TAM− patients were 0% versus 3.1%, 1.9% versus 5.4%, and 1.9% versus 8.4%, respectively. Multivariate regression analyses of potentially confounding variables revealed no significant associations between tamoxifen and either cosmetic outcome or local failure.

CONCLUSIONS. Radiotherapy followed by tamoxifen has no adverse interactive effect on cosmesis, and tamoxifen is associated with a trend toward enhanced 5-year local control probability. ***Cancer* 1997;80:732–40.**
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KEYWORDS: tamoxifen, radiotherapy, breast conservation, cosmesis, local control.

In 1992, we reported on an analysis of 234 patients for factors influencing cosmetic outcome in women given breast-conserving therapy (BCT).[1] We found that of 24 patients who received tamoxifen, there was a borderline significant ($P = 0.06$) association with adverse cosmesis due primarily to an increase in breast fibrosis. We postulated that there may be an interactive effect on normal tissue recovery caused by tamoxifen-enhanced secretion of TGF-beta, resulting in exaggerated postradiation fibrosis. To evaluate further this initial observation and assess for a possible influence of tamoxifen on tumor

control in the irradiated breast, we have updated our analysis with an expanded patient cohort.

PATIENTS AND METHODS

Patient Evaluation

Between 1982 and 1994, 498 women (509 breasts) received BCT for American Joint Committee on Cancer Stage I/II breast carcinoma. Adjuvant tamoxifen was administered to 130 patients (134 breasts). For purposes of comparison, patients were categorized as those who received tamoxifen and those who did not. Table 1 summarizes the distribution of these two groups according to the patients' presenting features, including age at diagnosis.

The details regarding patient selection and therapy have been described previously.[1–3] Briefly, all tumor excisions were performed with the aim of complete tumor removal, with a macroscopically normal tissue margin of 0.5–1.0 cm. With the exception of cases in which initial surgery was performed at an outside institution, all excision specimens were coated with india ink, and the margins at all surfaces of the specimen were measured at multiple levels.[4] For each tumor, the histopathologic subtype was categorized as invasive ductal carcinoma (IDC), invasive ductal with associated ductal carcinoma in situ (ID/DCIS), DCIS with $\leq$1 mm microinvasion (DCIS/micro), and invasive lobular carcinoma (ILC). Due to variations in the amount of material available for archival review, it was not possible to recategorize retrospectively all specimens according to the quantitative definition of extensive intraductal component (EIC) as defined by others,[5] because the proportion of DCIS varied substantially in the multiple sections evaluated for each tumor.

For operational purposes, margins were prospectively defined as follows: greater than 5 mm, low risk; 2–5 mm, intermediate risk; less than 2 mm, high risk. A re-excision of the tumor bed was performed if a margin was assessed as high risk and the re-excision was deemed cosmetically feasible.

Irradiation

At minimum, all patients received irradiation through parallel opposed tangential portals to the whole breast. Until 1983, treatment was administered with a cobalt-60 unit (12 patients); thereafter, a 6-MV linear accelerator was used. The whole breast was treated with a dose of 50–50.4 gray (Gy) at 1.8–2.0 Gy per fraction, and wedges were used to improve dose homogeneity. The number of radiation fields was classified as follows: tangents only, 2 fields; tangents plus medial supraclavicular field, 3 fields; tangents, supraclavicular field, and posterior axillary supplement, 4 fields; tangents, supraclavicular field, internal mammary field (electrons), and posterior axillary supplement, 5 fields. Multilevel planning with lung correction was performed for all cases after 1989. The following scheme for boost irradiation to the tumor bed as a function of final margin status was strictly observed (98.4% full compliance):

1. Minimal risk = no tumor found on re-excision. No boost was performed.
2. Low risk = margin greater than 5 mm. Electron boost of 10 Gy.
3. Intermediate risk = margin 2–5 mm. Electron boost of 14 Gy.
4. High risk = margin $<$2 mm. Boost to 20 Gy with reduced tangential photons, appositional electrons, or an interstitial iridium-192 implant.

When electrons were used, the energy was selected to encompass the volume to the anterior chest wall within the 80–90% isodose line. The photon compression boost (administered to 12 patients) was delivered through parallel opposed tangential portals limited to the soft tissues of the breast. The dose was prescribed to midplane, providing significant skin sparing. Interstitial implantation (administered to 127 patients) involved a technique designed to achieve a high level of dose homogeneity and has previously been described in detail.[6]

Systemic Adjuvant Treatment

Patients with appropriate risk of systemic micrometastases received six to eight cycles of chemotherapy with cyclophosphamide, 5-flourouracil, and either methotrexate or doxorubicin. Typically, patients received one or two cycles of chemotherapy followed by irradiation. After completion of radiotherapy, the remaining chemotherapy was administered. No patients in this series received concurrent chemotherapy and irradiation.

Postmenopausal women with tumors $\geq$2 cm and/or positive axillary lymph nodes who were shown to have evidence of hormonally responsive tumors by dextran-coated charcoal assay ($>$10 fmol/mg protein) or immunohistochemistry ($>$10% positive staining) were prescribed 20 mg of tamoxifen daily. In all cases, tamoxifen therapy was initiated 1– 6 weeks (median, 2.7 weeks) after completion of breast radiotherapy. The duration of tamoxifen therapy was variably recorded in the treatment record and was estimated in some cases after a retrospective review of clinical follow-up notes. Therefore, a calculated mean duration of 3.8 $\pm$ 0.6 years was considered a crude approximation for this cohort.

Follow-Up

All patients were evaluated for tumor control and cosmesis at 3- to 6-month intervals after completion of therapy. Cosmesis scoring was performed by at least two separate examiners on each visit, and the lowest score was retained for analysis. A previously published rating scale was employed.[1] Radiographic or clinical evidence of tumor recurrence was confirmed by biopsy.

The median follow-up was 56 months (range, 10–133 months) for patients who received tamoxifen and 60 months (range, 9–151 months) for patients who did not receive tamoxifen.

Statistical Analyses

The cosmetic outcomes for tamoxifen and no tamoxifen groups were compared by the Pearson chi-square test, and their results were categorized as excellent, good, fair, and poor. To maximize statistical power, we combined the last three categories to compare with excellent cosmesis as a binary outcome and calculated the odds ratio for the effect of tamoxifen. Local failure rates were computed at 5, 7, and 10 years by the actuarial method. Distributions of the potential confounders of the tamoxifen effect on cosmesis and local failure were compared between the tamoxifen and no tamoxifen cases. Student's *t* test was used to compare means, or, in the case of highly skewed distributions, the Kruskal–Wallis test was used to compare medians of continuous variables between groups. Proportions for categoric variables were compared by the Pearson chi-square test. Variables that significantly differed at the $P \leq 0.05$ level between tamoxifen and no tamoxifen cases were analyzed as covariates by logistic regression for cosmesis and Cox proportional hazards regression for local failure. Interactions between tamoxifen and covariates were also tested in the cosmesis analysis. The validity of the proportional hazards assumption in the Cox regression analysis was tested by including centered log time as a time-dependent covariate and testing its significance in an interaction with tamoxifen treatment. All analyses were performed using the SAS software package (versions 6.10/6.11).

RESULTS

The clinical, histopathologic, and therapy-related features of the tamoxifen and no tamoxifen cases are summarized in Tables 1 and 2. There was a highly significant difference ($P = 0.0001$) in the ages of the patients in the two groups; when median ages were compared, patients who received tamoxifen were nearly 10 years older than patients who did not. Furthermore, patients who received tamoxifen were significantly more likely (25% vs. 15%) to have had pathologically positive axillary lymph nodes.

TABLE 1
Distribution of Cases According to Age, Tumor Size, and Lymph Node Status

Variable	Tamoxifen (n = 134)	No tamoxifen (n = 375)	*P* value
Age (yrs)			
Mean (SD)	62.5 (10.1)	54.6 (12.8)	0.0001[a]
Median	62.5	53	
Range	35–84	25–86	
Tumor size (mm)			
<10	21 (16%)	90 (24%)	
11–20	63 (47%)	162 (43%)	
21–30	32 (24%)	73 (20%)	
>31	17 (13%)	49 (13%)	0.22[b]
indeterminate	1	1	
Axillary lymph nodes			
Negative	58 (43%)	238 (63%)	
Positive	34 (25%)	58 (15%)	
Undissected	42 (31%)	79 (21%)	0.001[b]

SD: standard deviation.
[a] From 2 sample Student's *t* tests with unequal variances.
[b] From the chi-square test.

Prior to 1992, a common practice at our clinic in the treatment of elderly (age >65 years) or medically infirm patients with a clinically negative axilla was to omit lymph node dissection and treat the draining lymphatics presumptively with irradiation.[7] Therefore, an undissected axilla was present in 31% of patients receiving tamoxifen, as compared with 21% in the no tamoxifen group.

There was no significant difference between the two groups with respect to the overall distribution of tumor size or the final measurement of the margin. However, the overall distribution of histopathologic subtypes between the groups was significantly different ($P = 0.001$); this primarily reflected a decreased proportion of IDC and an increased proportion of DCIS/micro histopathologies among the no tamoxifen cases.

The distribution of cases is presented in Table 2, according to the details of surgery and radiation therapy. The extent of surgery applied to both groups was similar. There were no significant differences in the incidence of re-excision or the total volume of excised tissue. The intensity of the radiotherapy administered to the two groups was similar in that there was no significant difference in the total dose of radiation or the incidence of interstitial implant boost. However, there was a significant difference ($P = 0.001$) in the distribution of cases according to the number of radiation treatment fields, due primarily to an increased

TABLE 2
Distribution of Treatment-Related Variables

Variable	Tamoxifen (n = 134)	No tamoxifen (n = 375)	*P* value
Re-excision	70 (52.2%)	213 (56.8%)	0.36[a]
Total excision volume (cc)			
Mean (SD)	126.8 (136.4)	115.3 (116.7)	0.50[b]
Median	90	77	
Range	7–863	1–700	
Sample size	74	281	
Histopathology			
IDC	81 (60%)	192 (51%)	
ID/DCIS	40 (30%)	99 (26%)	
DCIS/micro	2 (1%)	57 (15%)	
ILC	11 (8%)	26 (7%)	0.001[a]
Other	0	1	
Final excision margin (mm)			
Positive	25 (19%)	80 (22%)	
≤2	29 (22%)	70 (19%)	
2.1–5	22 (17%)	62 (17%)	
≥5	18 (14%)	51 (14%)	
No residual tumor[c]	39 (29%)	98 (27%)	0.91[a]
Indeterminate	1	14	
No. of radiation fields:			
2	57 (43%)	174 (47%)	
3	25 (19%)	119 (32%)	
4	51 (38%)	71 (19%)	
5	1 (1%)	10 (3%)	0.001[a]
Indeterminate	0	1	
Total radiation dose (Gy)			
Mean (SD)	62.1 (8.1)	62.5 (8.0)	0.67[b]
Median	65	65	
Range	50–70	50–70	
Interstitial implant boost	27 (20.2%)	100 (26.7%)	0.14[a]
Chemotherapy	20 (15%)	104 (28%)	0.003[a]

SD: standard deviation; IDC: invasive ductal carcinoma; ID/DCIS: invasive ductal with ductal carcinoma in situ; DCIS/micro: DCIS with ≤1 mm microinvasion; ILC: invasive lobular carcinoma; Gy: gray.

[a] From the chi-square test.

[b] From the Kruskal–Wallis test.

[c] After re-excision.

prevalence of 3 fields (32% vs. 19%) and a decreased prevalence of 4 fields (19% vs. 38%) in the no tamoxifen group. Finally, the administration of chemotherapy was nearly twice as common for patients who did not receive tamoxifen (28% vs. 15%; $P = 0.003$).

The distribution of cases according to cosmetic outcome is presented in Table 3. Overall, there was no significant difference in cosmetic score between patients who received tamoxifen and those who did not. However, due to the imbalance of some factors between the two groups, a more detailed evaluation was undertaken. Results of logistic regression analysis of the binary outcome (excellent cosmesis vs. good/fair/poor) are presented in Table 4. Tamoxifen, unadjusted for any covariates, was not significantly associated with cosmetic outcome. Furthermore, when the tamoxifen effect was adjusted for each of the covariates that were statistically different between the tamoxifen and no tamoxifen groups (age, histology, chemotherapy, lymph node status, and number of radiation fields), there remained no significant association between tamoxifen and cosmetic outcome.

A number of specific features related to the technical delivery of breast-conserving surgery and radiation therapy have previously been shown to affect cosmesis.[1] To assure that potentially important factors were adequately accounted for in examining the influence of tamoxifen on cosmesis, we used a stepwise selection process to add covariates significantly associated with cosmesis into a multivariable model. The only significant covariate was the number of radiation fields, which had an adverse effect on cosmesis. As shown in

TABLE 3
Distribution of Cases According to Cosmetic Outcome

Cosmesis score	Tamoxifen (n = 134)	No tamoxifen (n = 375)	*P* value
Excellent	48 (36%)	157 (42%)	
Good	66 (49%)	161 (43%)	
Fair	17 (13%)	48 (13%)	
Poor	3 (2%)	9 (2%)	0.62[a]

[a] From the chi-square test.

TABLE 4
Unadjusted and Adjusted Odds Ratios of Tamoxifen as a Determinant of Excellent versus Good/Fair/Poor Cosmesis from Logistic Regression Analyses

Variable	Sample size	OR	95% CI	*P* value
Tamoxifen (unadjusted)	509	0.78	0.51–1.17	0.23
Tamoxifen adjusted for:				
Age	509	0.87	0.56–1.33	0.51
DCIS histology[a]	509	0.77	0.51–1.17	0.22
Chemotherapy	509	0.75	0.49–1.14	0.18
Lymph node status[b]	509	0.86	0.56–1.31	0.49
No. of radiation fields	508	0.85	0.55–1.29	0.45

OR: odds ratio: CI: confidence interval; DCIS: ductal carcinoma in situ; ID/DCIS: invasive ductal with DCIS; DCIS/micro: DCIS with ≤1 mm microinvasion; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.

[a] ID/DCIS and DCIS/micro vs. IDC and ILC.

[b] Positive vs. negative vs. undissected.

Table 4, after adjustments were made for the number of radiation fields, tamoxifen was still not significantly related to cosmesis. We also looked at interaction effects of all variables with tamoxifen (including those for which there were no significantly different distributions between the tamoxifen and no tamoxifen groups: re-excision, total excision volume, total radiation dose, and interstitial implant boost) and found only one to be significant. An adverse interactive effect on cosmesis was suggested by the combination of tamoxifen and re-excision ($P < 0.05$). However, after adjustments were made for the number of radiation fields, this interaction was no longer statistically significant and therefore was not included in a multivariable model.

The analyses just described were also performed with cosmesis as a three-level ordinal outcome (excellent vs. good vs. fair/poor). The results (not shown) were not substantively different from those observed with cosmesis as a binary outcome.

A time-to-local-failure analysis for tamoxifen versus no tamoxifen cases showed no significant difference ($P = 0.18$), with a relative risk of 0.25 (95% CI = 0.03,1.90). The actuarial rates of local failure at 5, 7, and 10 years in cases treated with and without tamoxifen are presented in Table 5, and Kaplan–Meier survival curves are shown in Figure 1. This analysis, which includes all margin categories, indicates a trend in favor of tamoxifen, although the test was not powerful enough to achieve statistical significance due to the small number of cases with long term follow-up and the small number of local failure outcomes.

Subset analyses for local failure, according to margin status <2 mm or positive, are also presented in Table 5 and Figures 2 and 3. Again, although a trend in favor of tamoxifen was observed for cases with close or positive margins, these differences were not significant.

The effect of tamoxifen on local failure was further analyzed by adjusting the tamoxifen effect for other variables, as shown in Table 6. Accounting for these variables did not change the nonsignificant effect of tamoxifen on local failure. Because of the limited number (n = 16) of local failures in this series, we concluded that there was not adequate power to construct larger multivariable models reliably.

DISCUSSION

The clinical interaction of tamoxifen and radiation remains poorly defined. The cellular mechanisms affected by tamoxifen are not completely understood, but they include a number of hormonal as well as nonhormonal effects. Tamoxifen appears to exert its cytostatic activity at least partly through competitive inhibition at the estrogen receptor, resulting in segregation of cells into the G0/G1 phase of the cell cycle.[8] Tamoxifen-induced cell cycle redistribution has been shown in vitro to reduce the sensitivity of hormonally responsive breast carcinoma cells to some cell cycle specific chemotherapeutic agents.[9] Because radiosensitivity varies throughout the cell cycle, with relative radioresistance observed in early G1,[10] a hypothetical concern was raised early in our clinical experience with tamoxifen that its combination with breast radiotherapy might result in radioprotection of tumor clonogens. This was supported by preliminary work in our laboratory, which showed a modest increase in colony-forming efficiency after acute radiation exposure of hormonally responsive MCF-7 breast carcinoma cells preincubated with growth-arresting concentrations of tamoxifen.[11] On the basis of this concern, a policy was established in our clinic in 1983 whereby tamoxifen therapy was not initiated until after completion of breast irradiation.

Subsequent in vitro studies by our group and others have revealed that the interaction of tamoxifen and irradiation is more complex than is suggested by sim-

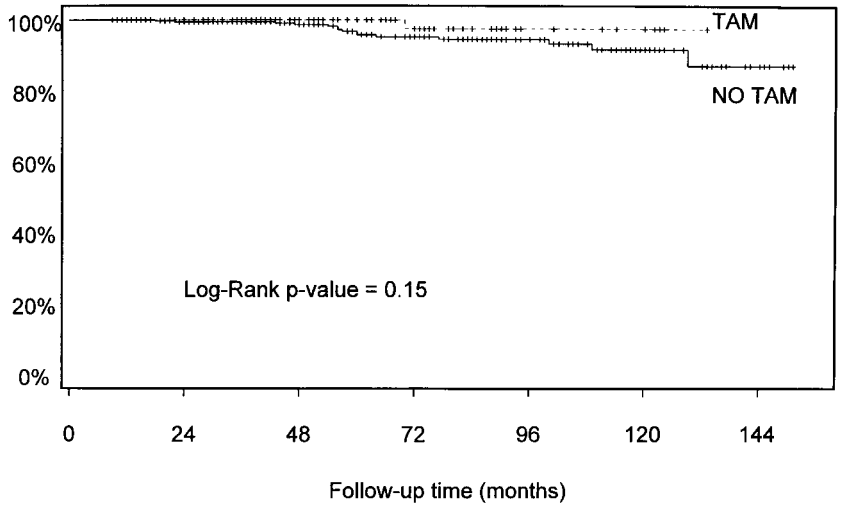

FIGURE 1. Freedom from local failure is shown for all cases. TAM: patients who received tamoxifen; NO TAM: patients who received no tamoxifen.

TABLE 5
Actuarial Rates of Local Failure in Cases Treated with and without Tamoxifen

	Actuarial rates (no. of cases at risk)	
Follow-up Time	**Tamoxifen (n = 134)**	**No tamoxifen (n = 375)**
All cases		
5 yrs	0% (75)	3.1% (222)
7 yrs	1.9% (28)	5.4% (142)
10 yrs	1.9% (6)	8.4% (51)
Final margin <2mm or positive	(n = 54)	(n = 150)
5 yrs	0% (34)	5.4% (86)
7 yrs	3.9% (16)	9.9% (53)
10 yrs	3.9% (5)	13.2% (20)
Final margin positive	(n = 25)	(n = 80)
5 yrs	0% (16)	5.9% (51)
7 yrs	7.7% (8)	12.8% (35)
10 yrs	7.7% (4)	17.8% (11)

ple single fraction clonogenic survival curves. We demonstrated more recently that when MCF-7 cells were exposed to multiple radiation fractions, tamoxifen had no adverse effect on cytotoxicity, suggesting that sublethal damage repair was unaltered.[12] Furthermore, the results of acute cell survival experiments may exhibit some heterogeneity. Blazek and Graybill,[13] after using a different MCF-7 cell strain, reported that preincubation of hormonally responsive breast carcinoma cells with tamoxifen increased radiation-induced DNA double-strand breaks with an overall enhancement of classically defined radiosensitivity. In contrast to our early assumptions, these more recent data would be consistent with overall favorable effects of tamoxifen and radiotherapy on tumor control, which would perhaps be related to cell repair mechanisms or blunted repopulation.

A broader understanding of the cellular effects of tamoxifen has begun to emerge, suggesting mechanisms of action beyond competitive inhibition at the estrogen receptor. Tamoxifen can induce the cellular secretion of the cytokine transforming growth factor-β (TGF-β)[14] and has been shown in patients to result in increased levels of TGF-β in breast stromal fibroblasts.[14] A number of biologic effects are associated with TGF-β, including the regulation of other growth factors. The effect of TGF-β appears to be tissue specific in that it generally inhibits the growth of epithelial cells but causes chemotaxis of fibroblasts.[15] The association of TGF-β with the growth inhibition of epithelial cells has been proposed as a possible mode of action of tamoxifen,[16] whereas the chemotactic stimulation of fibroblasts may explain the importance of TGF-β in the pathogenesis of fibrosis.[17] This may be relevant to the clinical interaction of tamoxifen and radiotherapy, as there is accumulating experimental evidence that TGF-β likely plays a critical role in mediating radiation-induced fibrosis in a number of organ systems,[18–21] including the breast.[22]

Several retrospective studies of patients subjected to BCT have assessed the influence of tamoxifen on local control.[23–26] Although the timing and sequencing of tamoxifen administration relative to irradiation in these studies was either highly variable or simply not reported, all showed that tamoxifen was associated with either no difference or possibly a modest enhancement of local control.

The National Surgical Adjuvant Breast Project (NSABP) conducted a prospective study in which the effects of tamoxifen on local control in women treated

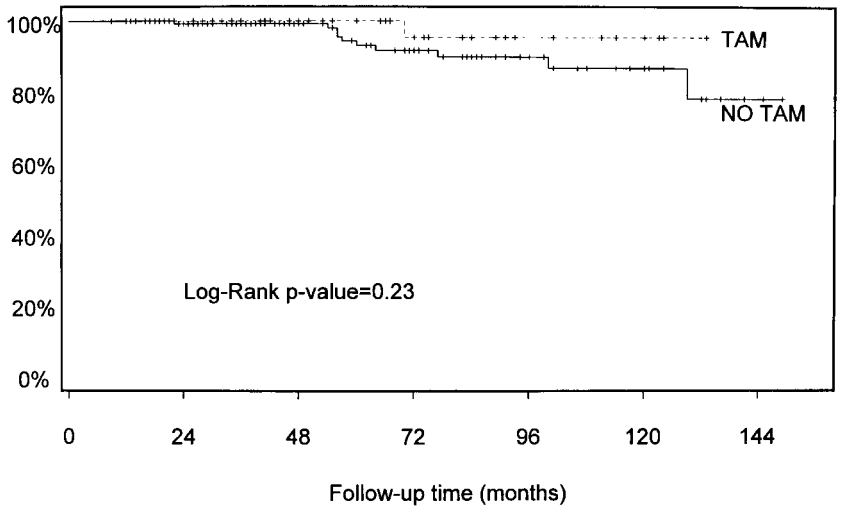

FIGURE 2. Freedom from local failure is shown for cases in which the final margin was <2 mm or positive. TAM: patients who received tamoxifen; NO TAM: patients who received no tamoxifen.

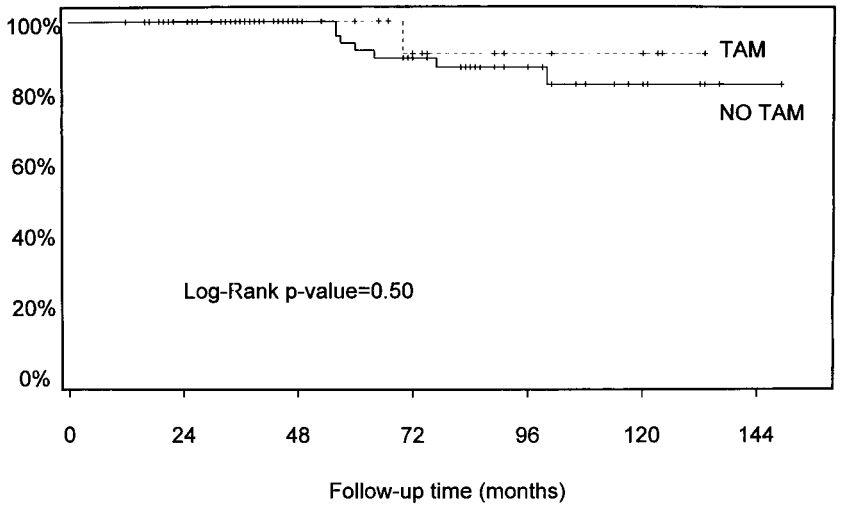

FIGURE 3. Freedom from local failure is shown for cases in which the final margin was positive. TAM: patients who received tamoxifen; NO TAM: patients who received no tamoxifen.

with BCT could be at least partly evaluated. In the B14 trial,[27] 2644 patients with negative axillary lymph nodes were randomized to tamoxifen (20 mg/day for 5 years) or observation. Breast-conserving surgery and radiotherapy were performed for 1072 patients, with tamoxifen administered after surgery and during radiotherapy. There was a significant decrease in the breast relapse rate at 5 years with tamoxifen (5.5% vs. 2.2%, $P = 0.002$).

More recently, Bartelink et al.[28] reported the long term follow-up of a trial in which 410 patients with locally advanced breast carcinoma were randomized between radiotherapy alone, radiotherapy plus chemotherapy, radiotherapy plus hormonal therapy (initiated after radiotherapy), and radiotherapy plus hormonal therapy and chemotherapy. It was found that both chemotherapy and hormonal therapy significantly delayed the time to locoregional recurrence, with the combined treatment group experiencing the greatest therapeutic effect. The locoregional recurrence rate at 6 years in patients treated with radiotherapy and hormonal therapy was reduced from 61% to 47%.

Although our data show a trend toward improved local control at 5 years with postradiation tamoxifen, this did not achieve statistical significance. The failure to show a difference in our patients may be related to the timing of tamoxifen administration, as the NSABP-B14 data would suggest that concurrent tamoxifen and irradiation may confer a local control advantage. Alternatively, the small number of local failures in our patient cohort may simply lack sufficient statistical power to allow the detection of a difference.

Our earlier preliminary finding[1] of an adverse in-

TABLE 6
Unadjusted and Adjusted Relative Risks of Tamoxifen Therapy on Local Failure, Based on Cox Proportional Hazards Survival Models

Variable	Sample size	RR	95% CI	*P* value
Tamoxifen (unadjusted)	509	0.25	0.03–1.90	0.18
Tamoxifen adjusted for:				
Age	509	0.45	0.05–3.64	0.46
DCIS histology[a]	509	0.25	0.03–1.93	0.19
Chemotherapy	509	0.25	0.03–1.93	0.19
Lymph node status[b]	509	0.33	0.04–2.62	0.30
No. of radiation fields	508	0.27	0.03–2.05	0.21
Final margin status	494	0.23	0.03–1.18	0.16

RR: relative risk; CI; confidence interval; DCIS: ductal carcinoma in situ; ID/DCIS: invasive ductal with DCIS; DCIS/micro: DCIS with ≤1 mm microinvasion; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.

[a] ID/DCIS and DCIS/micro vs. IDC and ILC.

[b] Positive vs. negative vs. undissected.

fluence of tamoxifen on cosmetic outcome was not supported by the results of the current study. Tamoxifen did not significantly alter cosmesis even when we controlled for other potentially important variables.

Fowble et al.[23] recently reported on 154 patients treated with tamoxifen (with variable or unknown sequencing relative to radiotherapy) and found no major effect on cosmetic outcome except when the breast and regional lymph nodes were irradiated. In such cases, 86% of the patients who received tamoxifen had good or excellent outcome, as compared with 92% of the patients who did not receive tamoxifen. In addition, breast edema was more common in patients who received tamoxifen (49% vs. 31%). Taylor et al.[29] found no overall adverse effect of tamoxifen on cosmesis irrespective of whether it was administered concurrently or sequentially with radiotherapy.

With breast cosmesis as an endpoint, these and other[30] data indicate that tamoxifen therapy results in little, if any, potentiation of postradiation normal tissue reactions. However, a recent report by Bentzen et al.[31] suggests that caution must be exercised in drawing any final conclusions as to the potential for tamoxifen-radiotherapy interactions in other organ systems. In an analysis of normal tissue effects of postmastectomy radiotherapy in women enrolled on the DBCG 77C trial, 84 patients were evaluated who had been randomly assigned to receive tamoxifen (30 mg/day, begun prior to radiotherapy) or not. This study showed a significant association of tamoxifen with postradiotherapy lung fibrosis.

We conclude that postradiation tamoxifen administration does not compromise local control or cosmetic outcome in the conservatively treated breast. In fact, tamoxifen administered after irradiation may confer a modest enhancement of local conrol after 5 years. Future studies may seek to assess whether local control can be further improved through concurrent tamoxifen therapy during radiotherapy.

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