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Tamoxifen with or without Breast Irradiation in Women 50 Years of Age or Older with Early Breast Cancer

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ABSTRACT

BACKGROUND

We determined the effect of breast irradiation plus tamoxifen on disease-free survival and local relapse in women 50 years of age or older who had T1 or T2 node-negative breast cancer.

METHODS

Between December 1992 and June 2000, 769 women with early breast cancer (tumor diameter, 5 cm or less) were randomly assigned to receive breast irradiation plus tamoxifen (386 women) or tamoxifen alone (383 women). The median follow-up was 5.6 years.

RESULTS

The rate of local relapse at five years was 7.7 percent in the tamoxifen group and 0.6 percent in the group given tamoxifen plus irradiation (hazard ratio, 8.3; 95 percent confidence interval, 3.3 to 21.2; $P < 0.001$), with corresponding five-year disease-free survival rates of 84 percent and 91 percent ($P = 0.004$). A planned subgroup analysis of 611 women with T1, receptor-positive tumors indicated a benefit from radiotherapy (five-year rates of local relapse, 0.4 percent with tamoxifen plus radiotherapy and 5.9 percent with tamoxifen alone; $P < 0.001$). Overall, there was a significant difference in the rate of axillary relapse at five years (2.5 percent in the tamoxifen group and 0.5 percent in the group given tamoxifen plus irradiation, $P = 0.049$), but no significant difference in the rates of distant relapse or overall survival.

CONCLUSIONS

As compared with tamoxifen alone, radiotherapy plus tamoxifen significantly reduces the risk of breast and axillary recurrence after lumpectomy in women with small, node-negative, hormone-receptor-positive breast cancers.

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IN MOST WOMEN WITH BREAST CANCER, breast-conserving surgery plus local radiotherapy reduces the risk of recurrence in the ipsilateral breast and results in long-term survival similar to that after mastectomy.¹⁻⁴ Adjuvant treatment with tamoxifen also reduces the risk of local relapse.^{5,6} Since mammographic screening is capable of detecting relatively small tumors and salvage therapy is successful in many women who have a relapse in the breast,^{3,7} there is interest in identifying patients at low risk who could avoid radiotherapy. They are likely to have a small tumor and negative axillary nodes.⁸ Postmenopausal patients have a lower risk of relapse than premenopausal women.⁸⁻¹² The findings of Study B-06 of the National Surgical Adjuvant Breast and Bowel Project (NSABP) suggest that the risk of local relapse decreases after the age of 50 years among women who have undergone lumpectomy and irradiation.¹³ We aimed to define the role of adjuvant treatment with radiotherapy in women 50 years of age or older who had early breast cancer by comparing treatment with tamoxifen plus breast irradiation with tamoxifen alone.

METHODS

STUDY DESIGN AND POPULATION

Women 50 years of age or older at the time of diagnosis who had undergone breast-conserving surgery for an invasive adenocarcinoma 5 cm or less in diameter (pathological stage T1 or T2) were eligible. Additional eligibility criteria included a finding of pathologically negative resection margins for both invasive and in situ cancer at the time of initial or repeated resection (defined as no tumor at the inked pathological margin) and pathologically negative axillary lymph nodes except in patients 65 years of age or older, who were eligible if they were node-negative on the basis of either clinical or pathological criteria. Sentinel-node biopsy was not routinely performed.

Consenting patients were randomly assigned to receive breast irradiation plus concurrent tamoxifen (20 mg daily for five years) or tamoxifen alone. Patients were excluded for the following reasons: a history of cancer (other than treated nonmelanoma skin cancer or carcinoma in situ of the cervix), with fewer than 5 years of disease-free survival, or previous breast cancer (including in situ disease), with fewer than 10 years of disease-free survival; bi-

lateral breast cancer or multifocal primary breast tumors; unsuitability for radiation therapy for technical or other reasons; concurrent illness that would preclude the use of tamoxifen; lack of informed consent or lack of availability for follow-up; metastatic disease at initial assessment; or planned adjuvant chemotherapy or tamoxifen therapy before breast cancer was diagnosed (e.g., as chemoprevention).

Participating centers included the Princess Margaret Hospital, the Women's College Campus of the Sunnybrook and Women's College Health Sciences Centre in Toronto, and the British Columbia Cancer Agency centers in Vancouver and Victoria. The institutional review boards of all participating centers approved the study protocol, and written informed consent was obtained from all participants before entry.

RANDOMIZATION

Women were randomly assigned to receive tamoxifen plus breast irradiation or tamoxifen alone according to a computer-generated table of random numbers. Stratification was performed for the following factors: tumor size (2 cm or less vs. more than 2 cm), estrogen-receptor status (negative vs. positive or unknown), method of determining the status of axillary lymph nodes in women 65 years of age or older (clinical vs. pathological), and participating center. The statistical coordinator kept a separate randomization list in a location away from the clinic in order to prevent possible bias. Randomization was performed by means of a telephone call, fax, or both from the clinical-trials coordinator to the Biostatistics Department at the Princess Margaret Hospital.

INTERVENTIONS

Radiotherapy to the involved breast was to be administered within 12 weeks after the most recent surgery. The prescribed dose was 40 Gy, given in 16 daily fractions to the breast and underlying chest wall over a period of three to four weeks, followed by a boost of 12.5 Gy, given in 5 daily fractions to the primary site. Each field was treated daily, Monday through Friday, with a parallel-opposed pair of tangential fields that used 4- or 6-MV photons (320 women) or cobalt-60 gamma rays (in 66 women). The dose to the breast was to be given at a point two thirds of the distance from the skin to the base of the tangential fields or to an isodose that most ac-

curately encompassed the target volume. Partial wedging was used to improve the homogeneity of the dose (± 7 percent).

The boost was administered with the use of a direct appositional beam with cobalt-60 photons, electrons of 9 to 12 MeV, or a mixed beam of electrons and 4- or 6-MV photons prescribed at the depth of maximal absorption. The volume was determined on the basis of the preoperative mammogram, operative notes, clinical assessment, and location of the clips (if they had been placed). Typically, the field encompassed the tumor bed with margins of 1 to 2 cm.

Tamoxifen was given orally at a dose of 20 mg per day for five years. Side effects were documented and compliance was assessed by means of an interview at each follow-up visit.

FOLLOW-UP AND OUTCOME MEASURES

Patients were seen every three months for the first three years, every six months for the next two years, and yearly thereafter. Mammography was performed annually, and chest radiography was performed every two years.

The primary outcome was disease-free survival, defined as the time from randomization to the first treatment failure (in the ipsilateral breast, in the axillary nodes, or at a distant site) or death (if no recurrence had been noted). Secondary outcome measures were the incidence of relapse in the breast and axillae and overall survival.

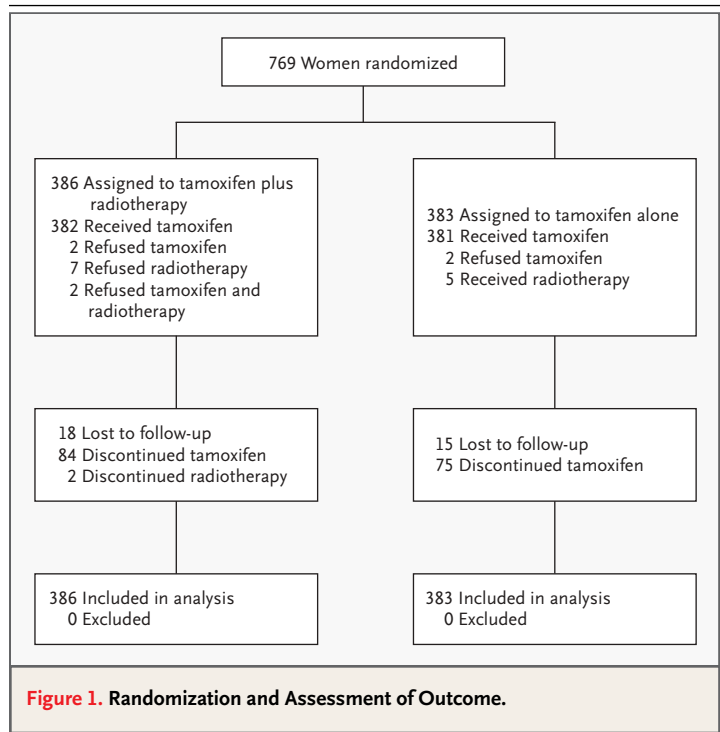
STATISTICAL ANALYSIS

A noninferiority design was used to test the hypothesis that for women 50 years of age or older who had node-negative breast cancer of pathological stage T1 or T2, lumpectomy plus adjuvant tamoxifen is equivalent to lumpectomy, breast irradiation, and adjuvant tamoxifen. The treatment groups were considered to be equivalent if the upper limit of the 95 percent confidence interval of the difference in disease-free survival at five years was no more than 7 percent.¹⁴ We estimated that a sample of 800 patients was required, with a one-sided alpha of 0.05 and a statistical power of 90 percent or greater, assuming a 5 percent loss to follow-up. Kaplan–Meier methods were used to estimate the rates of disease-free survival and overall survival.¹⁵ Differences between the groups were evaluated by means of the log-rank test. The Cox proportional-hazards model was used to evaluate

the possible differences in rates of relapse and survival between the groups after adjustment for other clinical factors. The probability of local relapse was calculated with the use of a cumulative-incidence approach. All randomized patients were included in the assessment of the primary outcome (an intention-to-treat analysis).

RESULTS

Between December 1992 and June 2000, 769 eligible women were enrolled (Fig. 1); 386 were randomly assigned to receive tamoxifen plus breast irradiation, and 383 to receive tamoxifen alone. Of these 769 women, 641 were enrolled at the Princess Margaret Hospital and 128 at the British Columbia Cancer Agency. Data were collected at the Princess Margaret Hospital on eligible women who were not enrolled. Of 1572 eligible women, 899 (57.2 percent) declined to participate and 32 (2.0 percent) were not enrolled for other reasons. Accrual was stopped before the planned 800 women were enrolled because only 9 women were enrolled in the last year of the study, largely because of the increasing use of adjuvant chemotherapy in such women. Only 18 patients did not receive the allocated inter-



vention. In the tamoxifen group, two women did not receive tamoxifen and five were treated with irradiation; in the group assigned to tamoxifen plus irradiation, seven patients did not receive irradiation, two did not receive tamoxifen, and two declined both irradiation and tamoxifen. Tamoxifen was discontinued in 159 women before the planned five years of administration (84 women in the group given tamoxifen plus irradiation, after a median of 3.2 years of use, and 75 in the tamoxifen group, after a median of 4.1 years of use), predominantly as a result of adverse events. The median duration of follow-up was 5.6 years, and 33 women were lost to follow-up, with more than 4 years having elapsed since the last follow-up visit.

CLINICAL AND PATHOLOGICAL CHARACTERISTICS

The baseline characteristics of the two groups were similar (Table 1). In both groups, the median age at

the time of diagnosis was 68 years and the median tumor size was 1.4 cm. Seventy-four women (9.6 percent) required a second excision to obtain clear pathological margins. Estrogen or progesterone receptors were positive in the tumors from 621 women (80.8 percent), both types of receptors were negative in 46 women (6.0 percent), and the status was unknown in 102 women (13.3 percent), most frequently owing to the presence of small or "microinvasive" tumors for which biochemical assays were not possible. Women with tumors of unknown receptor status were analyzed together with women with receptor-positive tumors, because both groups had similar outcomes (disease-free survival at five years was 88.6 percent among women with receptor-positive tumors and 89.7 percent among women with unknown receptor status). Among the women, 734 (95.4 percent) had had a natural or surgical menopause, 22 (2.9 percent) were premenopausal, and 13 (1.7 percent) had an unknown menopausal status.

OUTCOMES

At the time of the analysis in April 2003, 34 women had died without having a relapse and 81 had relapsed, including 43 with local relapses. The disease-free survival rate at five years was 84 percent in the tamoxifen group and 91 percent in the group given tamoxifen plus irradiation (hazard ratio for relapse, 1.7; 95 percent confidence interval, 1.2 to 2.5; $P=0.004$) (Fig. 2). The upper limit of the 95.8 percent confidence interval of this 7 percent difference was 11.9 percent. Therefore, we concluded that tamoxifen plus breast irradiation resulted in a significantly better disease-free survival rate at five years than did tamoxifen alone. The overall survival rate at five years was 93.2 percent in the tamoxifen group and 92.8 percent in the group given tamoxifen and irradiation ($P=0.83$).

There were 54 relapses in the tamoxifen group and 27 among the women in the group given tamoxifen plus irradiation. The rate of relapse in the ipsilateral breast at five years was 7.7 percent in the group given tamoxifen alone, as compared with 0.6 percent in the group given tamoxifen plus irradiation (hazard ratio, 8.3; 95 percent confidence interval, 3.3 to 21.2; $P<0.001$) (Fig. 3). At eight years, with 86 women at risk, the rate of local relapse increased to 17.6 percent and 3.5 percent, respectively.

There was a significant difference in the five-year rates of relapse in the ipsilateral axilla (0.5 per-

Table 1. Characteristics of the Women.

Characteristic	Tamoxifen + Radiotherapy (N=386)	Tamoxifen (N=383)
	<i>no. of women (%)</i>	
Age at diagnosis		
50–59 yr	98 (25.4)	85 (22.2)
60–69 yr	117 (30.3)	144 (37.6)
≥70 yr	171 (44.3)	154 (40.2)
Tumor size*		
≤1 cm	128 (33.2)	139 (36.3)
>1–2 cm	193 (50.0)	179 (46.7)
>2–5 cm	64 (16.6)	64 (16.7)
Hormone receptor status†		
Positive	313 (81.1)	308 (80.4)
Negative	25 (6.5)	21 (5.5)
Unknown	48 (12.4)	54 (14.1)
Pathological grade		
1	84 (21.8)	81 (21.1)
2	179 (46.4)	181 (47.3)
3	57 (14.8)	67 (17.5)
Unknown	66 (17.1)	54 (14.1)
Nodal assessment		
Pathological	320 (82.9)	316 (82.5)
Clinical	66 (17.1)	67 (17.5)

* The tumor size was unknown for one patient in each group.

† Positive status was defined by positive results for estrogen receptors, progesterone receptors, or both; negative status was defined by negative results for both estrogen and progesterone receptors.

cent in the group given tamoxifen plus irradiation, as compared with 2.5 percent in the tamoxifen group; $P=0.049$). Among the 476 women who were 65 years of age or older at the time of diagnosis, there was a trend to an increased rate of axillary relapse when dissection was omitted (3.3 percent at five years in the tamoxifen group, as compared with 0.6 percent in the group given tamoxifen plus irradiation; $P=0.07$).

There was no significant difference in the rate of distant relapse between the two groups (4.5 percent in the group given tamoxifen plus irradiation and 4.0 percent in the tamoxifen group, $P=0.69$). There was also no significant difference between the two groups in the number of deaths overall (31 in the group given tamoxifen plus irradiation and 29 in the tamoxifen group) or in the number of deaths that were due to breast cancer (10 in each group).

PROGNOSTIC FEATURES

A univariate analysis showed that the adverse prognostic factors for local relapse and disease-free survival were a larger tumor size (T2 tumors), negative hormone-receptor status, treatment with tamoxifen alone, and a higher pathological grade (Table 2). The age at diagnosis was not significant overall, but the greatest risk of local relapse was among women who were 50 to 59 years of age at diagnosis. As compared with women 60 years of age or older, women who were 50 to 59 years of age at the time of diagnosis had a higher rate of local relapse (6.0 percent vs 3.5 percent, $P=0.02$). Multivariate analysis demonstrated that the only factors that remained significant for local relapse were the treatment group (hazard ratio for local relapse in the tamoxifen group as compared with the group given tamoxifen plus irradiation, 9.0; 95 percent confidence interval, 3.5 to 22.9; $P<0.001$), negative hormone-receptor status (hazard ratio, 3.8; 95 percent confidence interval, 1.7 to 8.4; $P<0.001$), and a larger tumor size (hazard ratio, 1.7; 95 percent confidence interval, 1.2 to 2.3; $P=0.001$). There were no significant interactions between treatment and either tumor size ($P=0.67$) or hormone-receptor status ($P=0.77$).

A planned subgroup analysis of 611 women with T1 tumors (2 cm or less in diameter) and positive hormone receptors demonstrated an overall rate of local relapse at five years of 3.2 percent, as compared with 7.8 percent for the 157 women whose tumors did not have estrogen or progesterone receptors or with T2 tumors ($P=0.002$). How-

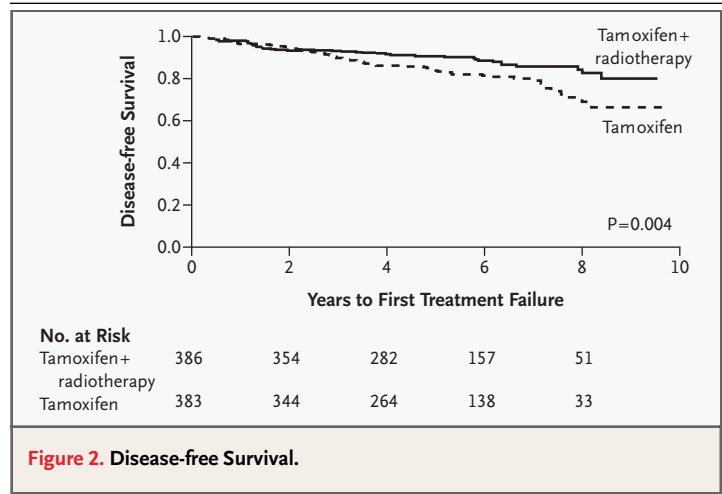


Figure 2. Disease-free Survival.

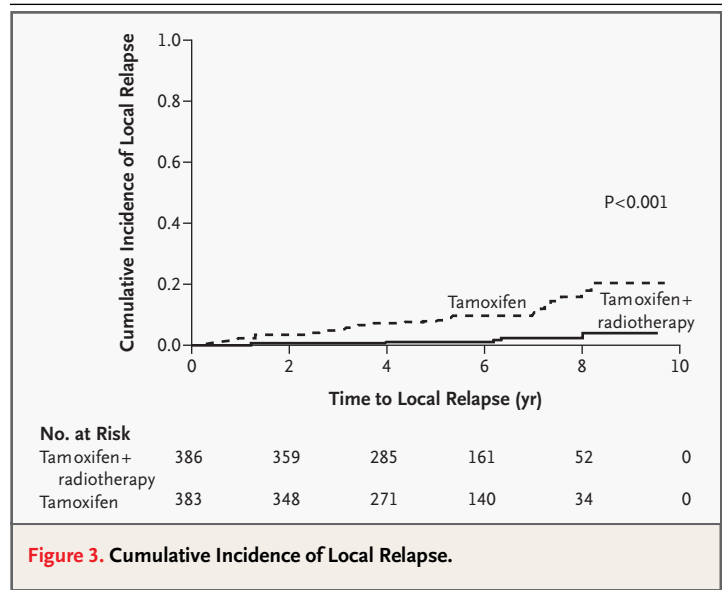


Figure 3. Cumulative Incidence of Local Relapse.

ever, in this group of women with a good prognosis, the rate of local relapse at five years was only 0.4 percent in the group given tamoxifen plus irradiation and 5.9 percent in the tamoxifen group ($P<0.001$) (Fig. 4). As Figure 4 also shows, the rate of breast relapse at eight years increased to 3.6 percent and 15.2 percent, respectively.

We also performed an unplanned subgroup analysis of women who had tumors that were 1 cm or less in diameter with positive hormone receptors. The risk of local relapse at five years was 2.6 percent in the tamoxifen group (139 women) and 0 percent in the group given tamoxifen plus irradiation (124 women, $P=0.02$). When the analysis was

Table 2. Univariate Analysis of Five-Year Estimates of Local Relapse and Disease-free Survival According to Treatment and Tumor Characteristics.

Characteristic	Total No. of Women	Local Relapse %	P Value	Disease-free Survival %	P Value
Overall	769	4.1		87	
Randomized treatment*					
Tamoxifen + radiotherapy	386	0.6		91	
Tamoxifen	383	7.7	<0.001	84	0.004
Tumor size†					
T1	639	3.5		90	
≤1 cm	267	1.4		95	
>1–2 cm	372	5.1		86	
T2	128	7.1	0.004	75	<0.001
Hormone-receptor status*					
Positive or unknown	723	3.4		89	
Negative	46	15.4	<0.001	67	<0.001
Pathological grade					
1	165	1.3		94	
2	360	4.0		91	
3	124	9.3	0.005	67	0.003
Age at diagnosis					
50–59 yr	183	6.0		86	
60–69 yr	261	3.8		91	
≥70 yr	325	3.2	0.06	85	0.08

* This feature was also significant on multivariate analysis.

† The tumor size was unknown for one woman in each group.

further restricted to women who were 60 years of age or older at the time of diagnosis, there was no significant difference in the rate of local relapse (1.2 percent in the tamoxifen group, as compared with 0 percent in the group given tamoxifen plus irradiation; $P=0.16$), but the small number of women (193) and the likelihood of further local relapses with longer follow-up call for caution in evaluating these results.

ADVERSE EVENTS

Adverse events related to treatment with tamoxifen plus irradiation were assessed with the use of the Common Toxicity Criteria of the National Cancer Institute. One woman in the group given tamoxifen plus irradiation had a stroke. Grade 3 events occurred in 39 women in the group given tamoxifen plus irradiation and in 30 women in the tamoxifen group ($P=0.33$). Hot flashes were the most common adverse events (30 and 23 events, respec-

tively), followed by fatigue (4 and 0, respectively), skin erythema due to radiation (4 and 0, respectively), fluid retention (2 and 1, respectively), and depression (2 and 1, respectively). Second cancers occurred in 31 women in the group given tamoxifen plus irradiation and in 41 women in the tamoxifen group ($P=0.22$): cancers of the contralateral breast were the most frequent (10 women in each group), followed by lung tumors (2 women in the group given tamoxifen plus irradiation and 7 women in the tamoxifen group) and uterine tumors (4 and 5, respectively). The results of an assessment of subjective breast and arm symptoms in relation to treatment have been reported previously.^{16,17}

DISCUSSION

This trial demonstrated that the addition of radiation therapy to tamoxifen significantly decreased the rate of local relapse in women 50 years of age or

older who had T1 or T2 node-negative breast cancer. At five years, only 0.6 percent of the women in the group given tamoxifen plus irradiation had had a local relapse, whereas 7.7 percent of the women in the group given tamoxifen alone had had a recurrence in the breast. The unexpectedly low rate of relapse in the combined-therapy group can be explained by the enrollment of patients with good prognostic features: older age and negative tumor margins. Women with tumors of 2 cm or less that were receptor-positive had a low risk of relapse but still had recurrences beyond five years, particularly those in the tamoxifen group (3.6 percent with tamoxifen plus irradiation and 15.2 percent with tamoxifen alone at eight years). There was no interaction between treatment group and clinical or pathological features, as is consistent with the demonstration of a reduced rate of local relapse in all patients with the use of radiation therapy. There was no difference in overall survival between groups, although the trial was underpowered to detect small differences in survival.

We observed a significantly greater risk of axillary recurrence in women who were treated with tamoxifen alone, although the magnitude of the difference was small. This result suggests that breast irradiation may reduce the risk of axillary relapse as well as that of breast relapse. Studies have shown that breast tangents frequently include nodes contained within an axillary dissection.^{18,19}

Our results are similar to those from the NSABP B-21 study of treatment with breast irradiation, tamoxifen, or both in low-risk patients with tumors of 1 cm or less. The NSABP study, however, included patients younger than 50 years of age, who would be expected to have a greater risk of treatment failure.⁶ The B-21 trial demonstrated a risk of local relapse at eight years of 16.5 percent among 336 women given tamoxifen alone, 2.8 percent among 337 women given irradiation plus tamoxifen, and 9.3 percent among 336 women given irradiation plus placebo. The similar relapse rates at eight years in our trial (17.6 percent for tamoxifen alone and 3.5 percent for tamoxifen plus irradiation), despite the use of different entry criteria, suggest that the omission of breast irradiation may be best suited to older patients with small tumors. Our exploratory subgroup analysis suggested that women 60 years of age or older who have tumors 1 cm or less in size and positive or unknown hormone-receptor status have a low risk of breast re-

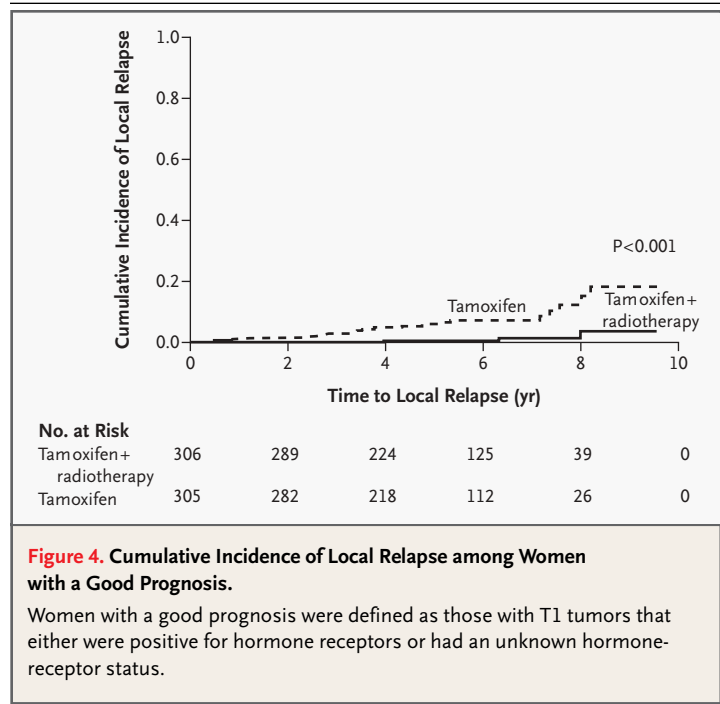


Figure 4. Cumulative Incidence of Local Relapse among Women with a Good Prognosis.

Women with a good prognosis were defined as those with T1 tumors that either were positive for hormone receptors or had an unknown hormone-receptor status.

lapse at five years. However, the number of events in this subgroup was small, and the lack of benefit of irradiation may be due to the low power of the study to detect a treatment effect. The observation of late breast relapses in women 50 years of age or older who had early cancer in this trial makes tamoxifen plus breast irradiation the preferred treatment for such patients, particularly given its minimal toxicity. Data from the Surveillance, Epidemiology, and End-Results Program suggest there has been a trend toward avoidance of the use of breast irradiation in recent years,²⁰ but the validity of this trend is not supported by the data from this and other trials. Nevertheless, a thorough discussion of the risks and benefits of treatment will allow women to make an appropriate decision on the basis of their individual circumstances and tolerance of the risks of relapse and adverse effects.

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