

ORIGINAL ARTICLE

Lumpectomy plus Tamoxifen with or without Irradiation in Women 70 Years of Age or Older with Early Breast Cancer

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ABSTRACT

BACKGROUND

In women 70 years of age or older who have early breast cancer, it is unclear whether lumpectomy plus tamoxifen is as effective as lumpectomy followed by tamoxifen plus radiation therapy.

METHODS

Between July 1994 and February 1999, we randomly assigned 636 women who were 70 years of age or older and who had clinical stage I (T1N0M0 according to the tumor–node–metastasis classification), estrogen-receptor–positive breast carcinoma treated by lumpectomy to receive tamoxifen plus radiation therapy (317 women) or tamoxifen alone (319 women). Primary end points were the time to local or regional recurrence, the frequency of mastectomy for recurrence, breast-cancer–specific survival, the time to distant metastasis, and overall survival.

RESULTS

The only significant difference between the two groups was in the rate of local or regional recurrence at five years (1 percent in the group given tamoxifen plus irradiation and 4 percent in the group given tamoxifen alone, $P < 0.001$). There were no significant differences between the two groups with regard to the rates of mastectomy for local recurrence, distant metastases, or five-year rates of overall survival (87 percent in the group given tamoxifen plus irradiation and 86 percent in the tamoxifen group, $P = 0.94$). Assessment by physicians and patients of cosmetic results and adverse events uniformly rated tamoxifen plus irradiation inferior to tamoxifen alone.

CONCLUSIONS

Lumpectomy plus adjuvant therapy with tamoxifen alone is a realistic choice for the treatment of women 70 years of age or older who have early, estrogen-receptor–positive breast cancer.

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MULTIPLE TRIALS OF BREAST-CONSERVING surgery for breast cancer¹⁻⁵ have shown that postoperative irradiation decreases the rate of ipsilateral recurrence but offers no survival benefit. However, the high rate of recurrence with surgery alone (10 to 40 percent) has suggested that the only two appropriate treatments are modified radical mastectomy and breast-conserving surgery plus adjuvant radiation therapy. Since tamoxifen, with³ or without⁴ radiation therapy, decreases the risk of recurrence, and given the cost and adverse effects of breast irradiation⁵⁻¹² and its negative effect on the quality of life,^{6,7} we designed a trial to determine whether women 70 years of age or older who have early, estrogen-receptor-positive breast cancer can be safely treated with tamoxifen alone instead of irradiation plus tamoxifen. Such women were selected for the trial because they have a lower rate of recurrence⁸⁻¹⁶ and a shorter time at risk for recurrence than younger women.

METHODS

The study (C9343) was designed by the Cancer and Leukemia Group B (CALGB) in cooperation with the Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG). The protocol was approved by each local institutional review board and complied with the Declaration of Helsinki. Written informed consent was obtained from all participants with the use of consent forms approved by each local institutional review board. Study oversight was provided by an independent data and safety monitoring committee.

Data collection was managed by the CALGB Statistical Center. Data quality was ensured by review of data by staff members of the CALGB Statistical Center and by the study chairperson. CALGB statisticians performed the statistical analyses.

Under the CALGB quality-assurance program, members of the data audit committee visit all participating institutions at least every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements. Such on-site review of medical records was performed for 105 patients (16 percent) enrolled in this study.

PATIENT SELECTION

Eligible subjects were women 70 years of age or older who had clinical stage I breast cancer (T1N0M0

according to the tumor-node-metastasis classification system) and no history of cancer other than in situ cervical cancer or nonmelanoma skin cancer within five years before randomization. When the trial began in July 1994, the eligibility criteria included a tumor with a diameter of no more than 4 cm (T1 or T2), regardless of estrogen-receptor status. In August 1996, in an attempt to broaden participation by physicians concerned about the upper size limit, the eligible tumor size was reduced to 2 cm or less (T1) and estrogen-receptor status was required to be positive or unknown. Patients had to have undergone a lumpectomy with negative margins (defined by the absence of tumor at the inked pathological margins) and to have been node-negative on clinical assessment.

TREATMENT

At study entry patients were randomly assigned, in a 1:1 ratio, to receive tamoxifen alone or with radiation therapy. Randomization was performed by the CALGB Statistical Center with the use of a shuffling algorithm by Knuth.¹⁴ Patients were stratified according to age (less than 75 years vs. 75 years or more) and whether axillary dissection was performed (yes vs. no). Randomization of the CALGB and RTOG patients was handled by the CALGB Statistical Center, and randomization of the ECOG patients was handled by the ECOG Randomization Desk with the use of the same algorithm and stratification scheme. Patients were followed every four months for five years, then yearly thereafter.

Local Therapy

All women underwent lumpectomy (i.e., partial mastectomy or a wide local excision) with a clear margin, defined by the absence of tumor on the inked pathological margins. Axillary-node dissection was allowed but was discouraged.

Among the women who were randomly assigned to receive radiation therapy, the entire ipsilateral breast was treated, with tangential fields. The 45-Gy dose was given in 25 daily fractions of 1.8 Gy, delivered by means of either cobalt-60 gamma rays or a linear accelerator with a maximal energy of 6-MV photons. The planning volume included a 1-cm margin to allow for motion and included the area of lower axillary lymph nodes (levels I and II). Corner blocks were permitted only at the inferior deep border. The maximal width of the lung in the tangential fields was 3 cm. Breast irradiation was followed by an electron boost to the primary

site of up to 14 Gy, given in seven fractions of 2 Gy per day. The electron boost was given to a shaped field that included the area of the tumor bed with a 2-cm margin in all directions. The dose was not adjusted for the heterogeneity of tissue. Wedge compensators were used to achieve a uniform dose.

Tamoxifen

All women received 20 mg of tamoxifen per day for five years.^{9,10} Tamoxifen was begun during or after radiation therapy at the discretion of the treating physician.

STUDY END POINTS

The primary study end points were the time to local or regional recurrence, the frequency of mastectomy for recurrence, breast-cancer-specific survival, the time to distant metastasis, and overall survival. Local or regional recurrence was defined as any recurrence in the supraclavicular, infraclavicular, and ipsilateral axillary nodes, as well as any recurrence in the ipsilateral breast.

Secondary end points were the cosmetic result and adverse effects and were assessed at baseline and at the four-month, one-year, two-year, and four-year follow-up visits. Both physicians and patients compared the affected and unaffected breasts with regard to the range of motion of the arm and shoulder, arm and breast swelling, breast and chest-wall pain, skin-color changes, fibrosis or retraction, and cosmesis. Cosmesis was scored on a four-point scale, with 1 indicating excellent results and 4 poor results. The other adverse effects (breast pain, shoulder pain, arm or shoulder stiffness, arm edema, breast edema, skin-color changes, and fibrosis and retraction of the breast) were rated on a four-point scale, with 1 indicating no difference between the affected and unaffected breasts and 4 indicating that the affected breast was much worse than the unaffected breast.

STATISTICAL ANALYSIS

To determine sample size when the study was planned, we used the results of the two large published randomized trials that were available (National Surgical Adjuvant Breast and Bowel Project Study B-04 for axillary recurrence¹¹ and Study B-06 for breast recurrence), knowing that both had excluded women over the age of 70 years (we could not assume that the risk of local or regional recurrence would be lower in older women, since there were no definitive data to support this assumption).

Table 1. Baseline Characteristics of the 636 Women.

| Characteristic | Tamoxifen + Irradiation (N=317) | Tamoxifen (N=319) |
|-------------------------------------|------------------------------------|----------------------|
| | <i>no. of women (%)</i> | |
| Stratification | | |
| Age | | |
| 70–74 yr | 139 (44) | 146 (46) |
| ≥75 yr | 178 (56) | 173 (54) |
| Axillary dissection | | |
| No | 200 (63) | 204 (64) |
| Yes | 117 (37) | 115 (36) |
| Demographic | | |
| Race or ethnic group* | | |
| White | 287 (91) | 287 (90) |
| Hispanic | 5 (2) | 8 (2) |
| Black | 23 (7) | 22 (7) |
| Asian | 0 | 2 (1) |
| Other | 1 (<1) | 0 |
| Unknown | 1 (<1) | 0 |
| Estrogen-receptor status | | |
| Negative | 6 (2) | 4 (1) |
| Positive | 308 (97) | 310 (97) |
| Unknown | 3 (1) | 5 (2) |
| Progesterone-receptor status | | |
| Negative | 56 (18) | 67 (21) |
| Positive | 251 (79) | 245 (77) |
| Unknown | 10 (3) | 7 (2) |
| Size of primary tumor | | |
| ≤2 cm | 312 (98) | 310 (97) |
| >2 cm | 5 (2) | 9 (3) |

* Race or ethnic group was reported by the investigators.

tion). Power calculations were based on the time to local or regional recurrence. The three-year rate of local or regional recurrence was expected to be 16 percent among women treated with tamoxifen alone and 9 percent among women treated with tamoxifen plus irradiation. The enrollment of 572 women over a period of 38 months was required for the study to have a statistical power of 90 percent to detect this difference, assuming a one-sided significance level of 5 percent and assuming that follow-up continued for 4 years after enrollment ended. P values and confidence intervals were determined with use of O'Brien–Fleming boundaries with a Lan–DeMets spending function on the basis of these four analysis points.¹²

Distributions of time-to-event variables were estimated according to the Kaplan–Meier method¹⁵ and distributions were compared between treatment groups by means of the log-rank test.¹⁶ For cosmetic and adverse-effect end points, at each assessment, patients' ratings in the two groups

were compared with the use of the t-test for independent samples. The process was repeated for physicians' ratings. All P values are two-sided and unadjusted for multiplicity.

According to standard CALGB policy, formal monitoring reports, including analysis of all study end points, were submitted every six months to an independent data and safety monitoring board. The study was allowed to exceed its accrual goals because of the smaller than expected number of events. In October 2000, the data and safety monitoring board released the results for publication when it became apparent that the event rate was markedly lower than expected and that further delay would have little effect on the ultimate differences in survival or breast recurrence.

Data are current as of September 2003. The median follow-up as of that date was five years.

RESULTS

The study was initiated by the CALGB in July 1994 and by the RTOG and ECOG in December 1996. Enrollment ended in February 1999. A total of 647 women were enrolled: 307 by the CALGB, 112 by the ECOG, and 228 by the RTOG. Eleven patients (2 percent) never received the treatment outlined in the protocol. Four patients (1 percent) were found to be ineligible. Statistical analyses included 636 patients: 317 were randomly assigned to receive tamoxifen plus irradiation and 319 to receive tamoxifen alone. Before the change in eligibility, 129 patients were enrolled; 10 of these 129 had estrogen-receptor-negative tumors, and 14 had tumors that

were more than 2 cm in diameter. The baseline characteristics of the women were similar in the two groups (Table 1).

TIME TO LOCAL OR REGIONAL RECURRENCE

As compared with the tamoxifen group, the group given tamoxifen plus irradiation had a significantly longer time to local or regional recurrence (breast plus axilla) ($P < 0.001$) (Fig. 1). Sixteen women in the tamoxifen group had had a local or regional recurrence (actuarial rate at five years, 4 percent); of these, 13 had an ipsilateral recurrence only, 1 had an ipsilateral recurrence with distant spread, and 2 had an axillary recurrence only (Table 2). Two women in the group given tamoxifen plus irradiation had had a local or regional recurrence (actuarial rate at five years, 1 percent); both were ipsilateral recurrences. The five-year probability of freedom from local or regional recurrence was 99 percent (95 percent confidence interval, 98 to 100 percent) in the group given tamoxifen plus irradiation and 96 percent (95 percent confidence interval, 93 to 98 percent) in the tamoxifen group.

TIME TO MASTECTOMY

The time to mastectomy after a recurrence did not differ significantly between the two treatment groups ($P = 0.15$). After a recurrence in the ipsilateral breast, two women in the group given tamoxifen plus irradiation and six women in the tamoxifen group underwent mastectomy. Eight women in the tamoxifen group who had a recurrence in the breast underwent lumpectomy (in seven it was followed by breast irradiation), whereas the two women with an axillary recurrence in this group underwent axillary dissection. The five-year probability of not undergoing mastectomy was 99 percent (95 percent confidence interval, 98 to 100 percent) in the group given tamoxifen plus irradiation and 98 percent (95 percent confidence interval, 97 to 100 percent) in the tamoxifen group.

TIME TO DISTANT METASTASIS

The time to distant metastasis did not differ significantly between the two treatment groups ($P = 0.97$); distant relapse occurred in seven patients in each group. The five-year probability of freedom from distant recurrence was 99 percent (95 percent confidence interval, 97 to 100 percent) in the group given tamoxifen plus irradiation and 98 percent (95 percent confidence interval, 97 to 100 percent) in the tamoxifen group.

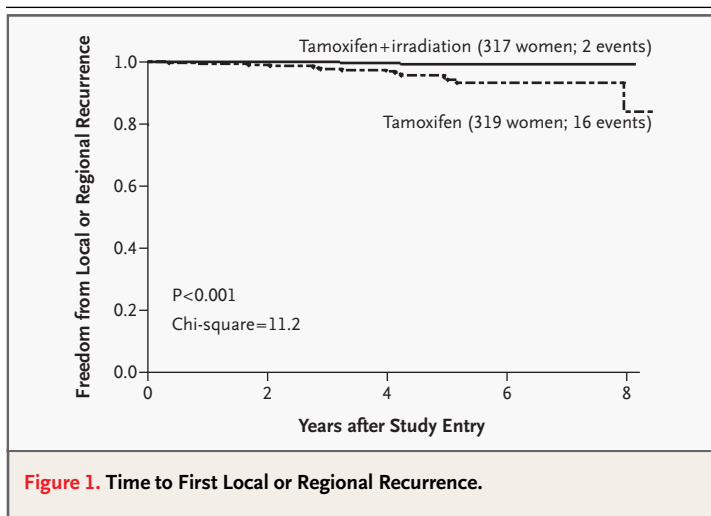


Figure 1. Time to First Local or Regional Recurrence.

OVERALL SURVIVAL

Treatment was not significantly related to overall survival ($P=0.94$): 54 women died in the group given tamoxifen plus radiation therapy, as compared with 53 in the tamoxifen group (Table 2). Among these 107 women, 6 died of breast cancer (3 in each group). The probability of being alive at five years was 87 percent (95 percent confidence interval, 84 to 91 percent) in the group given tamoxifen plus irradiation and 86 percent (95 percent confidence interval, 82 to 90 percent) in the tamoxifen group (Fig. 2).

RATINGS OF COSMETIC RESULTS AND ADVERSE EFFECTS

Table 3 shows comparisons of cosmetic results and adverse effects between the two treatment groups as rated by physicians and patients. Physicians rated overall cosmesis, breast pain, breast edema, and skin-color changes as significantly worse during the first two years of follow-up in the group given tamoxifen plus irradiation than in the tamoxifen group; however, by the four-year assessment, the differences were no longer significant. Physicians also rated fibrosis or retraction as significantly worse in the group given tamoxifen plus irradiation than in the tamoxifen group one year and two years after treatment; by four years after treatment, however, the ratings in the two groups did not differ significantly.

As compared with the women in the tamoxifen group, women in the group given tamoxifen plus irradiation consistently rated breast pain as worse. The women in this group also judged fibrosis and retraction to be significantly worse during the first two years after treatment; this difference had resolved by the four-year assessment.

DISCUSSION

Several large trials have shown that survival among women with breast cancer is not influenced by the addition of irradiation to partial mastectomy, although irradiation does decrease the incidence of ipsilateral recurrence.¹⁻⁵ A meta-analysis of radiation after lumpectomy or mastectomy has suggested that there may be an advantage in terms of breast-cancer-specific survival; however, it found no significant difference in overall mortality.²

Breast cancer tends to be less aggressive and more indolent in women who are 70 years of age or older than in younger women. The rate of ipsilateral

Table 2. Outcome.

| Outcome | Tamoxifen + Irradiation (N=317) | Tamoxifen (N=319) | Total (N=636) |
|------------------------------|---------------------------------|-------------------|---------------|
| | <i>no. of women</i> | | |
| Recurrence | | | |
| Any local or regional | 2 | 16 | 18 |
| Axilla | 0 | 2 | 2 |
| Ipsilateral breast alone | 2 | 13 | 15 |
| Ipsilateral breast + distant | 0 | 1 | 1 |
| Distant alone | 7 | 6 | 13 |
| Death from any cause | 54 | 53 | 107 |
| Death from breast cancer | 3 | 3 | 6 |

recurrence decreases with age, an effect likely to be enhanced by tamoxifen.⁹ In addition, the presence of coexisting conditions¹⁷ and the fact that these women have fewer years to live than younger women¹⁸ shorten the time during which women 70 years of age or older are at risk for a recurrence.

Our results confirm earlier observations that radiation therapy significantly improves local control but not overall survival among women with breast cancer. Although it is true that 99 percent of the group given tamoxifen plus irradiation, as compared with 96 percent of the tamoxifen group, were free from local or regional recurrence at five years ($P<0.001$), the clinical significance of this absolute decrease of 3 percent must be considered critically.

Previous studies have suggested that lumpectomy is an option after local recurrence if irradiation

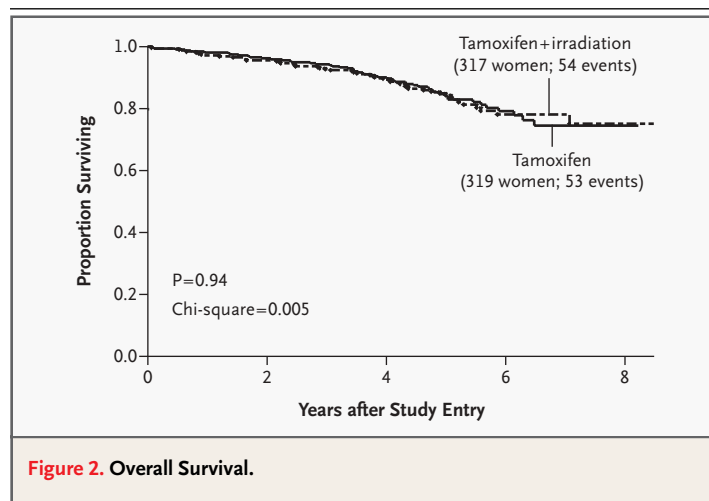


Table 3. Evaluation of Treatment Effects by Physicians and Patients.*

| Variable | At 4 Mo (N=603) | At 1 Yr (N=477) | At 2 Yr (N=437) | At 4 Yr (N=241) |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| <i>P</i> value | | | | |
| Physicians' ratings | | | | |
| Overall cosmesis | 0.01–0.05 | 0.01–0.05 | ≤0.01 | NS |
| Breast pain | 0.01–0.05 | 0.01–0.05 | NS | NS |
| Chest-wall or shoulder pain | NS | NS | NS | NS |
| Arm or shoulder stiffness | NS | NS | NS | NS |
| Breast edema | 0.01–0.05 | 0.01–0.05 | 0.01–0.05 | NS |
| Skin-color changes | 0.01–0.05 | 0.01–0.05 | 0.01–0.05 | NS |
| Fibrosis or retraction | NS | 0.01–0.05 | ≤0.01 | NS |
| Arm edema | NS | NS | NS | NS |
| <i>P</i> value | | | | |
| Patients' ratings | | | | |
| Overall cosmesis | NS | NS | ≤0.01 | NS |
| Breast pain | 0.01–0.05 | ≤0.01 | ≤0.01 | ≤0.01 |
| Chest-wall or shoulder pain | NS | NS | NS | NS |
| Arm or shoulder stiffness | 0.01–0.05 | NS | NS | <0.01 |
| Breast edema | NS | NS | NS | NS |
| Skin-color changes | NS | NS | NS | NS |
| Fibrosis or retraction | 0.01–0.05 | 0.01–0.05 | 0.01–0.05 | NS |
| Arm edema | NS | NS | NS | NS |

* P values of 0.05 or less indicate significantly worse adverse effects in the group given tamoxifen plus irradiation than in the tamoxifen group. NS denotes a P value greater than 0.05.

was not used in the initial therapy.¹⁹ Eight of the 14 women with breast recurrence in the tamoxifen group underwent breast-conserving therapy. In the group given irradiation plus tamoxifen, both women with a local recurrence required a mastectomy. There was no discernible difference between the groups in the likelihood of mastectomy after recurrence.

None of the women in the group given tamoxifen plus irradiation had an axillary recurrence, and there were no axillary recurrences among the 115 women in the tamoxifen group who had undergone axillary dissection. There were only 2 women with axillary recurrences among the 204 women in this group who had not undergone axillary dissection; in both, salvage therapy with axillary dissection was successful. These findings suggest that axillary evaluation (by means of dissection or sentinel-node biopsy) has little value in women 70 years

of age or older who are receiving tamoxifen for clinical stage I, estrogen-receptor–positive breast cancer (an exception would be women for whom chemotherapy is being considered on the basis of the axillary status).

There was no significant difference in the rate of distant recurrence between the two treatment groups. As of September 2003, there had been only 14 distant recurrences, 7 in each group. There was also no significant difference in survival between the two groups. After a median follow-up of five years, 107 women had died. It should be emphasized that only six deaths (6 percent of all deaths) were caused by breast cancer, reinforcing the notion that older women die from causes other than cancer.

Although breast irradiation is relatively well tolerated, it is not without adverse effects. In this study, breast pain and skin fibrosis or retraction were worse in women who had undergone breast irradiation. In addition, physicians considered cosmesis, edema, and skin color worse among patients who received irradiation than among women who did not, and women who received irradiation reported significantly worse shoulder and arm stiffness. These results are consistent with previous reports.^{20,21}

In summary, among women 70 years of age or older who have early, estrogen-receptor–positive breast cancer, the addition of adjuvant radiation therapy to tamoxifen does not significantly decrease the rate of mastectomy for local recurrence, increase the survival rate, or increase the rate of freedom from distant metastases. For these reasons, tamoxifen alone is a reasonable choice for adjuvant treatment in such women. Patients and their physicians should weigh the slightly increased risk of local recurrence against the cost, inconvenience, and adverse effects of irradiation. The choice of treatment should take into account the needs of the patient. Both options appear to be appropriate for women who are 70 years of age or older and who have clinical stage I, estrogen-receptor–positive cancers.

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APPENDIX

The following institutions and persons participated in the study: CALGB Statistical Center, Durham, N.C. — S. George; Dana-Farber Cancer Institute, Boston — G.P. Canellos; Dartmouth Medical School-Norris Cotton Cancer Center, Lebanon, N.H. — M.S. Ernstoff; Duke University Medical Center, Durham, N.C. — J. Crawford; Massachusetts General Hospital, Boston — M.L. Grossbard; Medical University of South Carolina, Charleston — M. Green; Memorial Sloan-Kettering Cancer Center, New York — C. Hudis; Mount Sinai School of Medicine, New York — L.R. Silverman; North Shore-Long Island Jewish Medical Center, Manhasset, N.Y. — D.R. Budman; Rhode Island Hospital, Providence — W. Sikov; Roswell Park Cancer Institute, Buffalo, N.Y. — E. Levine; SUNY Upstate Medical University, Syracuse, N.Y. — S.L. Graziano; Ohio State University Medical Center, Columbus — C.D. Bloomfield; University of Alabama Birmingham, Birmingham — R. Diasio; University of California at San Diego, San Diego — S.L. Seagren; University of California at San Francisco, San Francisco — A.P. Venook; University of Chicago Medical Center, Chicago — G. Fleming; University of Illinois Community Clinical Oncology Program, Chicago — T. Lad; University of Maryland Greenebaum Cancer Center, Baltimore — M. Edelman; University of Massachusetts Medical Center, Worcester — P. Bhargava; University of Missouri/Ellis Fischel Cancer Center, Columbia — M.C. Perry; University of Nebraska Medical Center, Omaha — A. Kessinger; University of North Carolina at Chapel Hill, Chapel Hill — T.C. Shea; University of Tennessee, Memphis — H.B. Niell; Vermont Cancer Center, Burlington — H.B. Muss; Wake Forest University School of Medicine, Winston-Salem, N.C. — D.D. Hurd; Walter Reed Army Medical Center, Washington, D.C. — J.J. Drabek; Washington University School of Medicine, St. Louis — N. Bartlett; and Weill Medical College of Cornell University, New York — S. Wadler.

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