Background: The effectiveness of routine postoperative irradiation following breast-conserving treatment of breast cancer has not previously been assessed in randomized clinical trials that have taken place in settings where mammography has been a major pathway to diagnosis or that have followed patients treated surgically by sector resection. Purpose: The aim of this study was to determine if treatment of stage I breast cancer by strictly standardized surgical technique with meticulous confirmation of a complete excision can reduce the local recurrence rate to an acceptable level without routine adjuvant radiotherapy. Methods: In this trial conducted in Sweden, 381 women with stage I breast cancer were surgically treated by sector resection plus axillary dissection; then 184 women were randomly selected to receive postoperative radiotherapy to the breast (XRT group), and 197 women received no further treatment (non-XRT group). Patient accrual started in October 1981 and ended in September 1988. Criteria for eligibility were a unifocal cancer 20 mm or less in diameter (visible on mammogram) and radical excision and patient selection should be improved. The benefits of reduced cost and patient inconvenience that would result from the elimination of postoperative radiotherapy must be carefully weighed against the disadvantages of local recurrence. Longer term follow-up must be done to estimate the risk of cancer recurrence in these women 10 and 15 years later, and methods must be developed to identify those women who have a higher risk of recurrence. Finally, economic analyses of this and similar trials are needed to give empirical underpinnings for optimal use of radiotherapy. [J Natl Cancer Inst 86:717-722, 1994] The effectiveness of routine postoperative irradiation following breast-conserving treatment of breast cancer has not previously been assessed in randomized clinical trials that have taken place in settings where mammography has been a major pathway to diagnosis or that have followed patients treated surgically by sector resection.

Breast irradiation after conservative surgery has not been shown to influence survival (1,2). Rather, the aim of such treatment is to enhance local tumor control, presumably by destroying cancer cells in the surgical field and by eradicating the remaining multifocal lesions. The relative importance of these two effects is not well understood. After a lumpectomy, the eradication of remnants of the primary tumor might be the most important effect inasmuch as multifocal lesions appear to play a minor role in tumor recurrence (2).

The aim of this study was to determine whether a strictly standardized surgical technique, with meticulous confirmation of a complete excision but without routine adjuvant radiotherapy, could reduce the local tumor recurrence rate. Substantial reductions in the cost of breast-conserving treatment as well as a more tolerable treatment for the patients might then be possible.

We report results after a median 5-year follow-up in a population-based, prospective, randomized trial of sector resection (3) and axillary lymph node dissection with or without postoperative radiotherapy to the breast in patients with histopathologic stage I^2 disease and tumors 20 mm or smaller on the mammogram.

Patients and Methods

Study Design

The study design has been described previously in detail (4). Women below the age of 80 years with unifocal breast cancer and a maximum tumor diameter of 20 mm or less on the preoperative mammogram were eligible. All patients were subjected to a standardized sector resection, as described previously (3). In short, the mammary gland was dissected free to its periphery in the plane of Scarpa’s fascia down to the pectoralis muscle, and the pectoral fascia was included in the specimen. A sector was excised with bidigital control of the palpable or localized tumor. Nonpalpable lesions were localized by the wire-hook technique (5) or by the stereotactic application of dye (coal or methylene blue) (6). To ensure complete tumor excision, the protocol stipulated peroperative radiography of the specimen. The axillary content from the vein down to the axillary tail of the breast, going back to latissimus dorsi, was excised.

Patients were eligible for randomization, provided that the specimen was histopathologically free of multifocal in situ and invasive lesions outside 20 mm from the border of the primary tumor. The axillary content from the vein down to the axillary tail of the breast, going back to latissimus dorsi, was excised.
lary lymph nodes were to be histopathologically free from metastases. Patients were ineligible for randomization if the tumor was transacted during surgery. Full informed consent was given by all participating subjects. The study was approved by the regional ethics committee.

**Randomization**

After surgery and stratification for participating center, mode of detection (screening or clinical diagnosis), and tumor size (≤10 mm or >10 mm), patients were randomly allocated to one of two treatment groups: postoperative radiotherapy (XRT group) or no postoperative radiotherapy (non-XRT group). Randomization was done by telephone contact with the study secretariat. Allocation to a treatment group was stratified in blocks of four within each center and stratum. The participating investigators did not know the size of the blocks.

**Radiotherapy**

The breast parenchyma plus 1 cm of the surrounding tissue was defined as the target volume. The contour was determined through the mamilary plane. Two opposing tangential fields with an open angle of 185° were used. Radiotherapy was delivered by photons from a 4- to 10-MV linear accelerator or from a 60Co radiotherapy unit. A total dose of 54 Gy (CRE [cumulative radiation effect], 16.4) in 27 fractions (five fractions per week) without a booster dose was applied to the target. The isodose, representing the minimum target-absorbed dose, was defined as 95% of the planned dose. With this definition, the target dose varies by ±5%.

**Patient Accrual**

Patient accrual started in October 1981. Six central county hospitals in Sweden enrolled patients for the study (see Table 2). The last center entered the trial in May 1985. Patient accrual was terminated in September 1988, with a total of 389 patients. However, after a complete evaluation, eight women were ineligible to participate. Thus, the trial included 381 patients. Of the 381 women in the study, 184 were randomly assigned to the XRT group, and 197 were randomly assigned to the non-XRT group. Eleven women who refused postoperative irradiation were analyzed according to the assigned treatment, as were four women who had never begun this treatment because of complications or death (postoperative infection, two; cerebrovascular incident, one; and suicide, one).

We reviewed the records for all patients with invasive breast cancer of histopathologic stage I diagnosed at the participating centers from October 1981 through October 1986 (4). Records for all patients were reviewed only through 1986 as a careful check of the patient flow during the first years of the trial; the detailed scrutiny of the randomization into the trial was not done for the entire trial period. From October 1981 through October 1986, 611 patients with stage I breast cancer had been treated at the participating centers. Of the 611, 314 (51%) were eligible for the trial, and 232 (74% of the eligible patients) were finally randomly assigned. Reasons for ineligibility among the remaining 297 patients were the following: multiple tumors (107 patients [36%]), undefinable tumor size on mammography (92 patients [31%]), and other reasons such as not willing to participate, contraindications to irradiation, and mental disorders (98 patients [33%]). There was no evidence of selection bias with regard to age or tumor characteristics.

**Evaluation Procedures**

The follow-up procedures consisted of (a) a minimum of two visits per year with a physician participating in the study, (b) mammography performed annually or more often if indicated by clinical findings, and (c) a chest x-ray performed 1 year after diagnosis. Further investigations were undertaken only when distant metastases were suspected. The closing date of follow-up for this analysis was April 30, 1992. The median follow-up time was 63 months in the non-XRT group and 65 months in the XRT group. A local tumor recurrence in the breast was defined as any cytologically or histopathologically confirmed invasive or in situ cancer in the ipsilateral breast. Local recurrences were classified as (a) recurrence in the surgical field, (b) new primary cancer in quadrants outside the surgical field, (c) metastases in an intramammary lymph node, or (d) recurrence in the cuticular tissue. Recurrence in the ipsilateral axilla was classified as a regional recurrence.

Estimates of disease-free survival took into account all types of regional and distant metastases (including regional recurrences in the axilla). Every patient contributed with person-years to the date of the type of recurrence analyzed, regardless of whether another type of event preceded; e.g., if a local recurrence developed first, the patient was still eligible for the analysis of distant metastases after that. In two patients, death from disseminated breast cancer was the first sign of relapse.

**Statistical Analyses**

We assumed that approximately 5% of the XRT group would develop a local tumor recurrence on the basis of previously reported results (7,2). We wanted to be able to detect a local recurrence rate in the non-XRT group that would be 15% or higher at a 5% level of significance (two-sided test) and 90% power. With these considerations, the predetermined sample size was 360 patients. The probabilities of disease-free survival and overall survival were estimated with the life-table method. The differences between the curves were tested with the logrank test (7). Determinants of local recurrence rate were analyzed in a Cox multivariate model (8), and age and tumor diameter were the continuous variables. Center and year of inclusion were analyzed with a set of dummy variables. The first 3 years of inclusion and the hospital at which most patients were treated were reference categories in the multivariate modeling.

According to the study protocol, two reports were to be presented— one at the termination of patient accrual (4) and one when all the women had a minimum of 3 years of follow-up (the present report).

**Results**

Table 1 shows the similar distribution of selected clinical variables in the two treatment groups—patients treated with surgery plus postoperative radiotherapy (XRT group) and patients treated with surgery alone (non-XRT group).

**Local Tumor Recurrences**

During the follow-up period, a local recurrence developed in 43 patients, six of whom were in the XRT group. Of these six women, one had not received her treatment because of postoperative infection and another because of noncompliance. A third woman developed a local relapse during radiotherapy, at which time her therapy was discontinued.

After 5 years, the local recurrence rate was 2.3% (95% confidence interval [CI] = 0.1%-4.3%) in the XRT group and 18.4% (95% CI = 12.5%-24.2%) in the non-XRT group (Fig. 1, A). The life-table curves were significantly different (P = .0001). The estimated difference between the recurrence rates in the two groups at 5 years was 16.1% (95% CI = 8.2%-24.7%).

Thirty-three (77%) of all local recurrences occurred in the surgical field. One was in the cuticular scar, and two were in the skin overlying the surgical field. Seven tumor recurrences developed in the breast parenchyma outside the field of surgery, and one was in an intramammary lymph node. Three recurring tumors were multifocal, and two were in situ carcinomas.

In the XRT group, four of six women with local recurrences were treated with mastectomy. In the non-XRT group, 11 women with local recurrences were treated with a second breast-conserving procedure (postoperative radiotherapy was given to six); the remaining 26 women underwent a mastectomy. Systemic treatment was administered to three women (XRT group) and five women (non-XRT group) with a local recurrence. Only one (from the XRT group) of these women received CMF combination chemotherapy (i.e., intravenous cyclophosphamide, methotrexate, and fluorouracil) in nine courses given at 3-week intervals; the others were treated with tamoxifen (20 mg/d) for 2 years.

**Survival Free From Regional and/or Distant Tumor Recurrence**

In 19 patients assigned to the XRT group and in 27 assigned to the non-XRT
group, regional and/or distant metastatic disease was the first sign of relapse. Five women in the XRT group and two women in the non-XRT group had both regional and distant recurrences. After 5 years, the estimated survival free from regional and distant recurrences was 90.0% (95% CI = 85.3%-94.5%) in the XRT group and 87.1% (95% CI = 82.3%-92.0%) in the non-XRT group (Fig. 1, B). The probabilities of remaining free from regional and distant disease did not differ significantly between the treatment groups (P = .23).

Survival

During the study period, a total of 51 patients died. Breast cancer was responsible for 25 (50%) of the deaths, and of these, 12 were among women in the non-XRT group. At 5 years, the life-table estimates of overall survival were 90.0% (95% CI = 85.3%-94.5%) in the XRT group and 87.1% (95% CI = 82.3%-92.0%) in the non-XRT group (Fig. 1, C). The life-table curves did not differ significantly (P = .44).

Cox Multivariate Regression Analysis of Local Tumor Recurrences

The 5-year local recurrence rate in the non-XRT group was markedly higher in this analysis (18.4%) than estimated in our earlier report (10.7%) (4). We explored the reasons for this finding in a multivariate analysis (Table 2).

The relative hazard of developing local recurrence was about seven times higher in the non-XRT group than in the XRT group. Tumor size was not significantly associated with risk of local recurrence, whereas increasing age entailed a decreased risk of 3% per year of increased age (P = .02). The local recurrence rate showed notable variation between hospitals; however, the statistical power to ascertain such differences was low, as indicated by the wide CIs that included unity in all instances.

An explanation for the increasing 5-year local recurrence rate in the present analysis was revealed when year of entry was analyzed as a determinant. A marked fourfold to fivefold increase occurred as early as 1984, and a further rise was seen about 2 years later. The trend was statistically significant (P = .003).

Discussion

When this trial started in 1981, experimental (9) and clinical (10,11) data indicated that the rate of distant tumor recurrence and death was similar after different ablative surgical procedures in patients with breast cancer. Postoperative radiation therapy had been shown to improve local tumor control in most instances, but it had no evident impact on survival (10,12). During the 1980s, this information was applied to breast-conserving therapy (2). Our study confirms these conclusions in a population-based setting, including about 74% of all eligible patients where overall survival and disease-free survival are similar in patients with and without radiotherapy after a sector resection. Likewise, our results confirm that breast conservation followed by radiotherapy in patients with stage I breast cancer results in local tumor control in 90% or more of all patients (1,2). In contrast, markedly higher local recurrence rates were found after breast-conserving surgery alone. In two other studies (2,13), an even larger difference in local recurrence rate between irradiated and nonirradiated patients did not influence the overall survival.

Our trial was designed to show whether a meticulous surgical technique can replace postoperative adjuvant radiotherapy to obtain local control of tumor after breast-conserving surgery. We found a lower local recurrence rate in both treatment arms than in trials using lumpectomy rather than sector resection (2,13). Thus, the surgical technique may influence local recurrence rate independent of radiotherapy (14). However, differences in the local recurrence rates between trials may also reflect the method of patient selection. A substantial proportion (45%) of the participants in our study were recruited from mammography screening. All of these participants were examined mammographically before they were included so that we could determine tumor size and could look for multicentric lesions. In addition, all specimens underwent perioperative x-ray. No other trials (2,13) have stipulated such a rigorous evaluation.

The markedly higher risk of local recurrence among patients included later in our study was unexpected. This significant (P = .003) trend may be due to changes in patient selection, to impaired surgical technique over time, or to both. As more centers and doctors participated, inclusion criteria might have become less strictly followed. Conceivable explanations include overlooked multifocality on the preoperative mammogram, margins of the surgical excision that were too narrow, and less extensive histopathologic examination of the specimen that resulted in incomplete surgical removal of multicentric lesions. All of these factors have been associated with a higher rate of local recurrence (15-19), as have large tumor size (20,21) and young age (22-25).

In our study, tumor size was not a statistically significant determinant of risk. Each year of increasing age was, however, associated with an estimate of 3% diminishing risk. The 95% CI, however, goes from only fractions of a percent to as much as 10% (Table 2). On the basis of our estimate, a 60-year-old woman would have a 48% (95% CI = 37%-65%) lower risk of developing a local recurrence than a 40-year-old woman.
woman. This estimate does not reflect differences in time at risk, since the Cox proportional hazards model takes censoring into consideration and since competing events were rare in the trial as a whole. The possible confounding effect of age on the evaluation of radiotherapy was eliminated in the multivariate analysis (Table 2).

Fig. 1. A) Probability of remaining free from local tumor recurrence. B) Probability of remaining free from regional or distant metastases. C) Probability of overall survival. XRT = postoperative radiotherapy. For Fig. 1, A, B, and C, P value was calculated by logrank test.
The results of a recent study by Veronesi et al. (26) on quadrantectomy with or without postoperative radiotherapy. These authors reported that women older than 55 years had a lower incidence of local recurrence than younger women during the first 3 years of follow-up.

Our data suggest that radiotherapy given routinely is overtreatment in about 80% of the patients in whom local tumor control has already been achieved by sector resection alone. This disadvantage must be weighed against the threat of breast loss, the psychological trauma, and other consequences of local recurrences in a large minority of patients. In the future, postoperative radiotherapy ideally should be used only in the subset of women who remain at high risk of local recurrence even after a meticulous and microscopically radical sector resection. The increasing trend over time (Table 2) suggests that careful patient selection and surgical treatment can further decrease the local recurrence rate. We need to know more about how mammographic and histopathologic selection criteria can predict the risk of local recurrence. Surgically, sector resection results in a good cosmetic result, can be standardized through dissection within defined anatomical structures (3), and provides a greater chance than most other breast-conserving surgical procedures to accomplish local control.

In our practice, sector resection is now used without radiotherapy only in randomized trials and in women who refuse radiation therapy. More knowledge about risk factors for local tumor recurrence—the prerequisite for using radiotherapy selectively—will emerge from a detailed investigation of individual records and histopathologic slides in this study. Longer term follow-up must be done to estimate the risk of cancer recurrence in these women 10 and 15 years later, and methods must be developed to identify those women who have a higher risk of recurrence. New studies are also needed to quantify in detail the morbidity caused by local recurrence and radiotherapy, to analyze cost-effectiveness of different treatment combinations, and to study the efficacy of radiotherapy as well as other adjuvant treatments in improving local tumor control.

### Table 2. Cox multivariate proportional hazards analysis of local recurrence 5 years after surgery

<table>
<thead>
<tr>
<th>Relative hazard</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-XRT</td>
<td>7.2</td>
<td>3.0-17.3</td>
</tr>
<tr>
<td>Tumor size, mm</td>
<td>1.1</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.97</td>
<td>0.9-1.0</td>
</tr>
</tbody>
</table>

*Seven patients were excluded because of incomplete information. Results of full model are given.
†Mammographic size.
‡A = Central Hospital, Falun; B = University Hospital, Uppsala; C = Central Hospital, Västerås; D = Central Hospital, Eskilstuna; E = Örebro Medical Center Hospital; F = Central Hospital, Karlstad.

### References

Notes

1Editor's note: This paper cites one or more National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials, to which some falsified data were submitted. Insofar as we are able to determine, impeached data do not alter the conclusions of any of the studies. Reanalyses of data from several of the trials are available through the National Cancer Institute's CancerFax and CancerNet.

To access CancerFax, call 301-402-5874 from the telephone on your fax machine, and when prompted for the six-digit code, enter 400027 (for trial B-06) or 400028 (for trials B-13/B-14). Follow the voice prompts to receive the information. To access CancerNet, send an electronic mail message to canceret@icicb.nci.nih.gov with cn-400027 (for trial B-06) and/or cn-400028 (for trials B-13/B-14) in the body of the message (if requesting both, enter the codes on separate lines). The items will be returned to you via electronic mail, usually within 10 minutes.


2Note that these figures differ slightly from our first report (4). For the present analysis, several manual checks revealed miscodings with regard to the randomization arm. The miscoded patients, however, contributed only less than a total of three woman-years and no events to the previous reports. A reanalysis of our earlier data with correct codings did not change the results in that analysis.

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EXCHANGE

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