

# RADIOTHERAPY AFTER BREAST-PRESERVING SURGERY IN WOMEN WITH LOCALIZED CANCER OF THE BREAST

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**Abstract Background and Methods.** Conservative surgery and radiotherapy have become well-established treatments for breast cancer, and many trials in progress are attempting to define the most acceptable type of procedure. Between 1987 and 1989 we randomly assigned 567 women with small breast cancers (<2.5 cm in diameter) to quadrantectomy followed by radiotherapy or to quadrantectomy without radiotherapy. All patients underwent total axillary dissection. The median follow-up period was 39 months (range, 28 to 54).

**Results.** The incidence of local recurrence was 8.8 percent among the patients treated with quadrantectomy

without radiotherapy, as compared with 0.3 percent among those treated with postsurgical radiotherapy ( $P = 0.001$ ). However, there was a substantial effect of age: patients more than 55 years old who did not receive radiotherapy had a low rate of local recurrence (3.8 percent). The four-year overall survival was similar in the two treatment groups.

**Conclusions.** Administering radiotherapy after quadrantectomy reduces the risk of local recurrence in women with small cancers of the breast, but radiotherapy may not be necessary in elderly women. (N Engl J Med 1993;328:1587-91.)

TWELVE years ago we observed in a randomized trial that the results of Halsted radical mastectomy might be equaled by those of more conservative treatment, such as quadrantectomy with axillary dissection and radiotherapy.<sup>1</sup> These results were subsequently confirmed by other investigators.<sup>2-4</sup> In recent years, additional clinical trials have been undertaken to identify treatment programs that would allow maximal local control of the disease and the best cosmetic results.<sup>5-8</sup>

At the Milan Cancer Institute we tried two different approaches: one procedure reduced the extent of the surgical resection while optimizing the effect of radiotherapy, and the other maintained the extent of resection while reducing the intensity of radiotherapy. The first procedure was tested in a randomized trial in which classic quadrantectomy combined with radiotherapy was compared with a simple "tumorectomy" followed by intensive, partly interstitial radiotherapy.<sup>5</sup> Survival was similar in the two groups of patients, but there were significantly more local recurrences among those treated with tumorectomy and radiotherapy.

The second trial, reported here, was a controlled study in which quadrantectomy combined with radiotherapy was compared with quadrantectomy alone. Patients treated with quadrantectomy alone underwent radiotherapy only if they had a recurrence; therefore, the ultimate comparison was between the results of immediate (prophylactic) radiotherapy after quadrantectomy and the results of delayed (therapeutic) radiotherapy after quadrantectomy.

## METHODS

### Treatment Groups

Between 1987 and 1989, 579 women with carcinomas of the breast less than 2.5 cm in maximal diameter at pathological examination were randomly assigned to one of two treatments: 299 patients were assigned to quadrantectomy combined with axillary dissection and radiotherapy, and 280 to quadrantectomy combined

with axillary dissection without immediate radiotherapy. Randomization to prophylactic radiotherapy or to therapeutic radiotherapy only in case of recurrence was performed immediately after surgery (quadrantectomy and axillary dissection). In 12 patients the margins of the resection were found to contain tumorous tissue (5 patients assigned to quadrantectomy with radiotherapy and 7 assigned to quadrantectomy alone); consequently, these patients were excluded, since they were candidates for a second operation or radiotherapy.

There was no significant difference between the two treatment groups in age, site and size of the primary carcinoma, histologic characteristics, and prevalence of axillary invasion (Table 1). Similarly, there was no significant difference between the groups in the distribution of patients with nodal involvement according to the adjuvant treatments administered for this condition (Table 2). The two groups of patients were therefore comparable.

### Surgical Technique

Quadrantectomy consisted of extensive breast resection, including a portion of the skin overlying the tumor and the underlying fascia, generally performed with a radial incision. Axillary dissection always included total removal of all lymph nodes of the three levels up to the apex of the axilla. When the tumor was located in the upper outer quadrant, the nodes were removed en bloc with the primary carcinoma. In other locations, the dissection was performed through a separate incision.

### Pathological Examination

The specimen of breast tissue was examined, and the whole surface of the resected area was stained. The primary carcinoma and the extent of the normal tissue removed around the tumor were measured on the cut surface. The minimal distance of the tumor (whether the carcinoma was infiltrating, intraductal, or both) from the inked margin was measured with the aid of a micrometric ocular after at least five histologic sections 5  $\mu$ m thick were examined.

### Radiotherapy

Patients treated with both quadrantectomy and radiotherapy received radiation therapy from a cobalt unit or a 6-MeV linear accelerator, starting four to six weeks after surgery. The breast was treated with two opposing tangential fields (a total of 50 Gy given over a five-week period, with a daily target dose of 2 Gy) and then with a boost dose to the tumor bed with an orthovoltage unit (10 Gy in five fractions).

### Follow-up

Follow-up was strict and included routine clinical examination every four months and mammography, chest radiography, bone scanning, and ultrasonography of the liver every year. If a local

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Table 1. Characteristics of the Treatment Groups.

CHARACTERISTIC	QUADRANCTECTOMY WITH RADIOOTHERAPY (N = 294)	QUADRANT- ECTOMY (N = 273)
	% of group	
Age (yr)		
≤45	26	23
46-55	37	38
>55	37	39
Tumor site		
Upper outer quadrant	51	49
Other quadrants	49	51
Tumor diameter (cm)		
≤1	25	27
1.1-2	57	57
>2	16	15.5
Not determinable	2	0.5
Histologic features		
Invasive ductal tumor	62	58
Invasive lobular tumor	17	20
Invasive ductal tumor with extensive intra- ductal component	14	15
Other histotypes	7	7
Axillary-node involvement		
Negative nodes	72	67
1-3 positive nodes	20	25
4-9 positive nodes	6	5
≥10 positive nodes	2	3

recurrence was suspected, mammography and a fine-needle biopsy were performed. The median length of follow-up was 39 months (range, 28 to 54).

#### Adjuvant Treatment

Patients with positive axillary nodes (nodal involvement) were treated with adjuvant medical therapy: premenopausal patients and postmenopausal patients negative for estrogen receptors received chemotherapy (a regimen of cyclophosphamide, methotrexate, and fluorouracil), and postmenopausal patients positive for estrogen receptors received tamoxifen. Nine patients with positive nodes declined adjuvant treatment (six patients in the group treated with quadrantectomy and radiotherapy and three in the group treated with quadrantectomy).

#### Statistical Analysis

Life tables were constructed by the Kaplan-Meier method, and P values calculated with the log-rank test, on the basis of overall follow-up.<sup>9,10</sup>

### RESULTS

As in our previous trials, we defined a local recurrence as the appearance of any new tumor in the breast within 2 cm of the surgical scar, and a second primary carcinoma as the appearance of any new tumor in other quadrants of the breast more than 2 cm from the scar.

We observed a considerable difference in the rate of local recurrence between the two treatment groups

Table 2. Adjuvant Treatment Administered to Patients with Nodal Involvement.

ADJUVANT TREATMENT	QUADRANCTECTOMY (N = 90)	QUADRANCTECTOMY WITH RADIOOTHERAPY (N = 83)
	no. of patients (% of group)	
Chemotherapy	47 (52)	49 (59)
Tamoxifen	40 (44.5)	28 (34)
No treatment	3 (3.5)	6 (7)

(Table 3). Only 1 of the 294 patients treated with quadrantectomy and radiotherapy (0.3 percent) had a local recurrence, as compared with 24 of 273 patients treated with quadrantectomy (8.8 percent) (Fig. 1).

Although the analysis of risk factors for local recurrence was not the primary objective of the study, we found that among the many variables evaluated (Table 4 and Fig. 2), age was the most important. In the quadrantectomy group, the recurrence rate was 17.5 percent among patients 45 years of age or younger and 3.8 percent among those over 55. Since a difference between subgroups in the rate of distant recurrence might obscure the risk of local recurrence, we analyzed the rate of occurrence of distant metastases. There were no differences among the various age groups. We also found no differences in recurrence rates among subgroups defined according to tumor size or the status of the axillary nodes (positive or negative) (Fig. 3). Patients with an extensive intra-ductal component had a much higher rate of local

Table 3. Local Recurrences and First Adverse Events in the Treatment Groups.

EVENT	QUADRANCTECTOMY WITH RADIOOTHERAPY (N = 294)	QUADRANCTECTOMY (N = 273)
	no. of patients	
Local recurrence	1	24
New, ipsilateral primary tumor	0	4
Contralateral carcinoma	2	5
Distant metastases	21	16
Other cancer	4	3

recurrence (7 of 42, or 16.7 percent) than patients without this histologic feature (17 of 231, or 7.4 percent) (Fig. 4). There was no difference between the rate of local recurrence among 184 estrogen-receptor-positive patients (16 recurrences, or 8.6 percent) and the rate among 48 estrogen-receptor-negative patients (5 recurrences, or 10.4 percent).

Second primary carcinomas of the ipsilateral breast developed in four of the patients treated with quadrantectomy, but in none of those treated with quadrantectomy and radiotherapy.

According to the protocol, patients in the quadrantectomy group who had a local recurrence were to be treated with radiotherapy after reexcision. However, of the 24 patients with recurrences, only 15 received this treatment. The other nine patients underwent total mastectomy, performed either because the recurring carcinoma was too large and the breast too small (four patients) or because the patient asked that the breast be removed (five patients). Of the 15 patients treated with reexcision and radiotherapy, 1 patient had a second local recurrence and 1 had a new carcinoma in another quadrant. Of four patients with second primary carcinomas, three underwent a second excision and radiotherapy and one underwent a mastectomy.

There was no difference between the two treatment groups in survival four years after the beginning of the trial (actuarial survival curves were calculated according to the product-limit method of Kaplan and Meier<sup>10</sup>; data not shown).

**DISCUSSION**

The results of this trial show clearly that postoperative radiotherapy administered directly after quadrantectomy has a protective action against local recurrences and new primary carcinomas. This was not unexpected, but the difference between the outcomes was marked (24 local recurrences and 4 new carcinomas after quadrantectomy alone, as compared with 1 recurrence and no new tumors after quadrantectomy combined with radiotherapy). In the quadrantectomy group, local recurrences occurred mainly in patients under 55 years of age and rarely in patients beyond

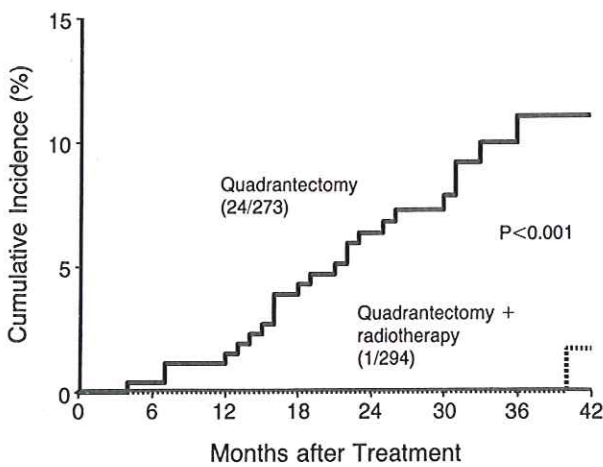


Figure 1. Cumulative Incidence of Local Recurrences among 567 Women with Breast Cancer, According to Treatment Group. The values in parentheses are the number of recurrences, followed by the number of patients in the treatment group.

this age. The presence of an extensive intraductal component was confirmed as an important predictor of the risk of a local recurrence.<sup>11</sup>

In the quadrantectomy group, the patients who had positive nodes treated with adjuvant therapy and those who had negative nodes did not differ in the incidence of local recurrence. This finding contradicts our previous data, which showed a low rate of recurrence among patients with positive nodes that was ascribed to the protective effect of adjuvant therapy.<sup>12</sup> The results of the present study suggest an alternative explanation: patients with positive axillary nodes may be a selected subgroup with tumors that are more radiosensitive than those of patients with negative nodes. This might explain the absence of a difference in the rate of local recurrence in the present trial between node-positive and node-negative patients in the quadrantectomy group, since the node-positive patients received adjuvant therapy but no radiotherapy to the breast.

Table 4. Local Recurrences among 273 Patients Treated with Quadrantectomy Alone, According to Tumor Diameter, Age, Nodal Status, and Presence or Absence of Extensive Intraductal Component.

VARIABLE	NO. OF PATIENTS	NO. OF RECURRENCES	RECURRENCE RATE (%)
Tumor diameter (cm)			
≤1.5	165	11	6.7
>1.6	107	13	12.1
Not determinable	1	—	—
Age (yr)			
≤45	63	11	17.5
46-55	104	9	8.7
>55	106	4	3.8
Axillary nodes			
Negative	182	13	7.1
Positive	91	11	12.1
Extensive intraductal component			
Present	42	7	16.7
Absent	231	17	7.4

In fact, the degree of influence of nodal status on the risk of local relapse is uncertain. The many reports in the literature that consider the problem of local recurrence after conservative treatments do not include nodal involvement in their lists of risk factors.<sup>13-17</sup> In contrast, according to Rose et al.<sup>18</sup> the use of adjuvant chemotherapy lowered the incidence rate from 15 percent to 4 percent for relapses during the five years after treatment of the primary tumor.

The limited number of local recurrences among postmenopausal women treated with quadrantectomy without radiotherapy may reflect the difference between the structure of the mammary glands in women in this age group and that in young women. After menopause, the complex structure of the mammary gland disappears and the breast is reduced to a fatty organ with scattered islands of fibroepithelial tissue, without connections between them.

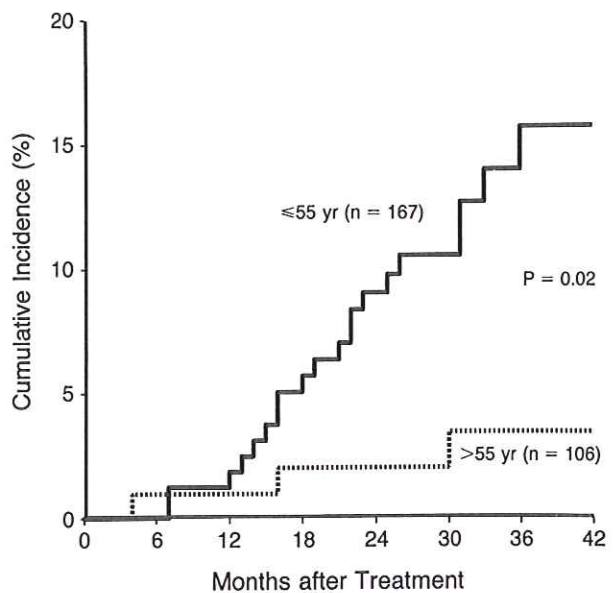


Figure 2. Cumulative Incidence of Local Recurrences among 273 Patients Treated with Quadrantectomy Alone, According to Age.

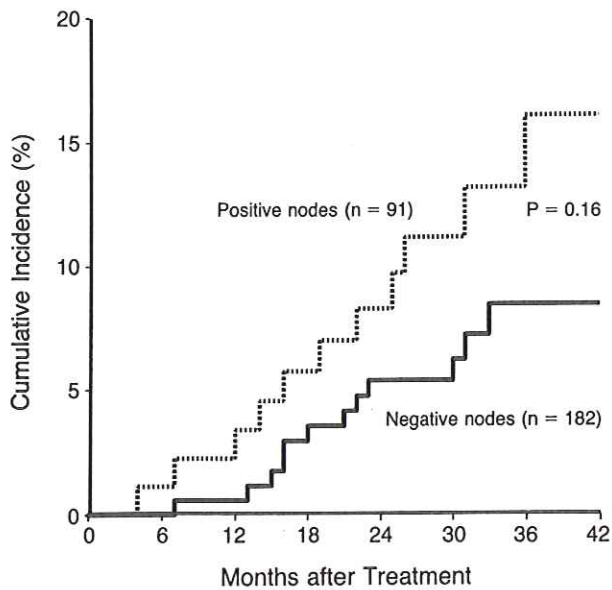


Figure 3. Cumulative Incidence of Local Recurrences among 273 Patients Treated with Quadrantectomy Alone, According to Nodal Status.

This trial confirms that quadrantectomy combined with axillary dissection and radiotherapy is an effective treatment that does not appear to expose patients to a significant risk of local recurrence. An important issue in weighing our findings is the difference between our results and the long-term results of the National Surgical Adjuvant Breast and Bowel Project previously reported by Fisher et al. (trial B-06).<sup>19</sup> In the latter trial, among patients treated with lumpectomy without radiotherapy there was little difference between age groups in the incidence of local recurrence: there

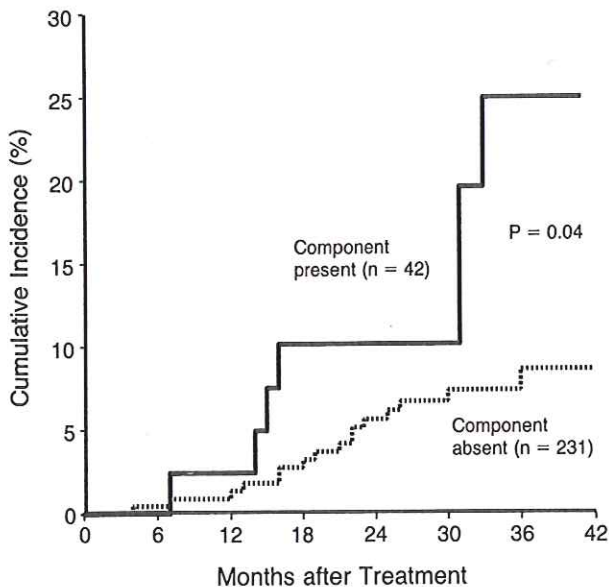


Figure 4. Cumulative Incidence of Local Recurrences among 273 Patients Treated with Quadrantectomy Alone, According to the Presence or Absence of an Extensive Intraductal Component.

were 89 recurrences among the 236 patients 49 years of age or younger (37.7 percent), but 104 recurrences among the 336 patients 50 years of age or older (30.9 percent).<sup>19</sup>

The difference between the data of Fisher et al.<sup>19</sup> and our results may be explained by the difference in surgical procedures. In their study, the operation consisted of a simple excision of the primary carcinoma (lumpectomy) without removal of the skin and the pectoral fascia. In our study, the operation was much more extensive, removing 2 to 3 cm of normal breast tissue around the tumor, the corresponding portion of overlying skin, and the underlying muscular fascia.

Regardless of such differences, the results of both these studies lead us to conclude that in young women, even an extensive surgical resection offers only incomplete protection against local recurrence and that postsurgical radiotherapy is essential. In contrast, in older women a more extensive operation such as quadrantectomy may be sufficient to prevent local recurrence without a need for radiotherapy, whereas this may not be true of a simple operation such as lumpectomy.

#### REFERENCES

- Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981;305:6-11.
- Sarrazin D, Lê MG, Fontaine MF, Arriagada R. Conservative treatment versus mastectomy in T1 or small T2 breast cancer—a randomized clinical trial. In: Harris JR, Hellman S, Silen W, eds. *Conservative management of breast cancer: new surgical and radiotherapeutic techniques*. Philadelphia: J.B. Lippincott, 1983:101-11.
- Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985;312:665-73.
- van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. In: National Institutes of Health Consensus Development Conference on the Treatment of Early-Stage Breast Cancer. NCI monographs. No. 11. Washington, D.C.: Government Printing Office, 1992:15-8. (NIH publication no. 90-3187.)
- Veronesi U, Volterrani F, Luini A, et al. Quadrantectomy versus lumpectomy for small size breast cancer. *Eur J Cancer* 1990;26:671-3.
- Stewart HJ, Prescott RJ, Forrest PA. Conservation therapy of breast cancer. *Lancet* 1989;2:168-9.
- Ribeiro GG, Dunn G, Swindell R, Harris M, Banerjee SS. Conservation of the breast using two different radiotherapy techniques: interim report of a clinical trial. *Clin Oncol (R Coll Radiol)* 1990;2:27-34.
- The Uppsala-Orebro Breast Cancer Study Group. Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Natl Cancer Inst* 1990;82:277-80.
- Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley, 1980.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Harris JR, Connolly JL, Schnitt SJ, et al. The use of pathologic features in selecting the extent of surgical resection necessary for breast cancer patients treated by primary radiation therapy. *Ann Surg* 1985;201:164-9.
- Veronesi U, Salvadori B, Luini A, et al. Conservative treatment of early breast cancer: long-term results of 1232 cases treated with quadrantectomy, axillary dissection, and radiotherapy. *Ann Surg* 1990;211:250-9.
- Schnitt SJ, Connolly JL, Recht A, Silver B, Harris JR. Breast relapse following primary radiation therapy for early breast cancer. II. Detection, pathologic features and prognostic significance. *Int J Radiat Oncol Biol Phys* 1985;11:1277-84.
- Solin LJ, Fowble BL, Schultz DJ, Goodman RL. The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1991;21:279-87.

15. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. *Int J Radiat Oncol Biol Phys* 1989;17:719-25.
16. Chauvet B, Reynaud-Bougnoux A, Calais G, et al. Prognostic significance of breast relapse after conservative treatment in node-negative early breast cancer. *Int J Radiat Oncol Biol Phys* 1990;19:1125-30.
17. Chu AM, Cope O, Russo R, Lew R. Patterns of local-regional recurrence and results in stages I and II breast cancer treated by irradiation following limited surgery. *Am J Clin Oncol* 1984;7:221-9.
18. Rose MA, Henderson IC, Gelman R, et al. Premenopausal breast cancer patients treated with conservative surgery, radiotherapy and adjuvant chemotherapy have a low risk of local failure. *Int J Radiat Oncol Biol Phys* 1989;17:711-7.
19. Fisher B, Redmond C. Lumpectomy for breast cancer: an update of the NSABP experience. In: National Institutes of Health Consensus Development Conference on the Treatment of Early-Stage Breast Cancer. NCI monographs. No. 11. Washington, D.C.: Government Printing Office, 1991:7-13. (NIH publication no. 90-3187.)

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