Acta Oncologica Vol. 32, No. 6, pp. 641–646, 1993

THE TOTAL INCIDENCE OF LOCO-REGIONAL RECURRENCE IN A RANDOMIZED TRIAL OF BREAST CANCER TNM STAGE II

The South Sweden Breast Cancer Trial

LENA TENNVALL-NITTBY, INGRID TENGRUP and TORSTEN LANDBERG

We studied loco-regional recurrence during follow-up (median observation time 8 years) in 1 153 patients, who underwent modified mastectomy and were randomly assigned to one of the following postoperative treatments; Premenopausal patients: radiotherapy, cyclophosphamide, or both; Postmenopausal patients: radiotherapy, tamoxifen, or both. Recurrence occurred in a total of 419 patients, 123 of whom had loco-regional recurrence with or without distant metastasis. The loco-regional recurrence rate was 7% in the irradiated subgroups and 17% in the non-irradiated subgroups, the corresponding cure rates being 43% and 58%. Complete remission of all local recurrence was obtained after the first treatment in 67% of the cases, and was persistent in 67% of them (44% overall). Complete remission was obtained in all patients with local recurrence who received local treatment only, and was persistent in 65%. Of local recurrences treated with a combination of surgery, radiotherapy and hormone therapy, complete response was obtained in 94% of the patients, and was persistent in 94% of them (88% overall). Complete remission of all regional recurrence was obtained after the first treatment in 58% of the patients and was persistent in 67% of them (39% overall). Postoperative radiotherapy reduced not only the total number of loco-regional recurrences but also the number of uncontrolled loco-regional recurrences. Aggressive local treatment would appear to yield both satisfactory initial control and, when combined with the hormone therapy, a high rate of persistent loco-regional control.

Reported loco-regional recurrence rates after modified radical mastectomy with or without adjuvant therapy vary from less than 5% to more than 30% (1, 2). Patients with more extensive initial loco-regional disease are thought to be at the greatest risk of loco-regional recurrence. Many authors have advocated the use of postmastectomy radiation therapy to decrease loco-regional recurrence (3, 4). There is no consensus on the management of loco-regional recurrence after mastectomy. Treatment recommendations vary widely and frequently include different combinations of local and systemic treatments.

The present analysis was undertaken to study the overall incidence of loco-regional recurrence after modified radical mastectomy and adjuvant therapy in TNM stage II breast cancer, to study its morbidity, and to review the outcome of different treatment modalities.

Received 8 March 1993.
Accepted 22 August 1993.
From the Department of Oncology, Malmö allmänna sjukhus, Malmö, Sweden.
Correspondence to: Dr Lena Tennvall-Nittby, Department of Oncology, Malmö allmänna sjukhus, S-214 01 Malmö, Sweden.

Material and Methods

The prospective randomized study comprised 1 153 breast cancer patients, 434 premenopausal and 719 postmenopausal, from southern Sweden, who fulfilled the inclusion criteria between 1978 and 1985 (5). In most patients the disease was classified as T_pN_pM stage II, but patients with TNM stage I disease with a tumour size 20 mm were also

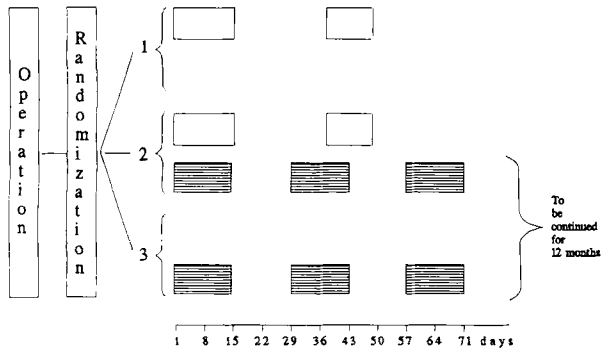

Fig. 1. The different adjuvant treatment regimens for premenopausal patients. □ Radiotherapy, ▤ Cyclophosphamide 130 mg/m² daily.

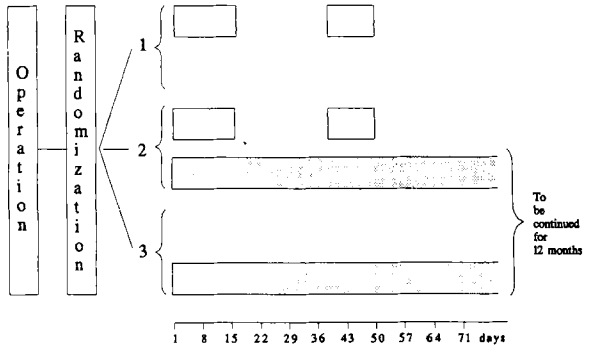

Fig. 2. The different adjuvant treatment regimens for postmenopausal patients. □ Radiotherapy, ▩ Tamoxifen 30 mg daily.

included. Only patients under 71 years of age at the time of the operation were included in the trial. After mastectomy and axillary resection (6), the patients were randomly assigned to different adjuvant treatment groups (Figs. 1 and 2). The patients were considered to be premenopausal up to 5 years after the menopause.

Postoperative radiotherapy was administered according to a standardized schedule, with target doses of 45–48 Gy in the axillary and supraclavicular lymph nodes, 48 Gy in the parasternal lymph nodes, and 38 Gy to the thoracic wall (7).

Cyclophosphamide was given at daily doses of 130 mg/m² on days 1–14 of each treatment cycle. Dosage was reduced according to a standard schedule when white blood cell counts were $<3.9 \times 10^9$/l and/or the platelet count was less than 125×10^9. When haemorrhagic cystitis was diagnosed, all further cyclophosphamide treatment was stopped. Tamoxifen was given at a daily dose of 30 mg. Cyclophosphamide or tamoxifen was given during one year.

Loco-regional recurrence was said to be present either when verified by a biopsy or fine-needle aspiration, or when the clinical findings (9% of the patients) were considered definite enough to necessitate start of new treatment or change of therapy. Recurrence was regarded as local when occurring on the chest wall, and regional when seen in lymph nodes in the axilla and/or in the supra/infraclavicular fossa. Loco-regional cure after treatment was defined as complete remission of the recurrence and no further signs of loco-regional disease for the duration of the follow-up or the remainder of the patient's life. The median observation time after surgery was 8 years (range 4–11 years). The characteristics of the different subgroups were compared with Fisher's exact test or the Mann-Whitney U-test.

Results

Of the 1 153 patients, 419 have so far manifested recurrence, of which 123 were loco-regional (Table 1). The treatment randomly assigned was not adhered to for various reasons in 7 of these 123 patients and 5 patients were incorrectly included. There were significantly more patients with loco-regional recurrences in the two groups without postoperative radiotherapy (treatment groups 3) than in the other four groups. The median time for loco-regional recurrence to develop in these 123 patients was 26 months

Table 1

Distribution of patients with regard to recurrence, loco-regional recurrence, and adjuvant treatment. The figures in parentheses are the loco-regional recurrence rates for the different treatment groups. RT = Radiotherapy. C = Cyclophosphamide. TAM = Tamoxifen

	Treatment group	Number of patients	Number of patients with recurrence	Number of patients with loco-regional recurrence
Premenopausal				
	1 (RT)	147	56	12 (8%)
	2 (RT + C)	148	52	9 (6%)
	3 (C)	139	51	23 (17%)
Postmenopausal				
	1 (RT)	236	93	20 (8%)
	2 (RT + TAM)	239	73	15 (6%)
	3 (TAM)	244	94	44 (18%)

(range 1–109), 25 months for the irradiated groups and 26 months for the non-irradiated groups. Loco-regional recurrence appeared somewhat later among premenopausal patients (32 months) than among postmenopausal patients (23 months). Of the local recurrences, 30% were detected by the attending physician at a routine checkup and 62% by the patient herself. Of the regional recurrences, 50% were observed at a routine checkup, and 42% by the patient herself.

The size of the local recurrence was less than 1 cm in 31% of patients in the series as a whole, in 37% of cases in the irradiated groups, and in 26% of cases in the non-irradiated groups. Local recurrences larger than 3 cm were found in 22% of the series as a whole. Size was not recorded in 15% of the local recurrences. The proportion of single local recurrences was 56% overall (49% in the irradiated groups, and 62% in the non-irradiated groups). Of the local recurrences in the premenopausal patients, 65% were single as compared with 51% in the postmenopausal patients.

Size was not recorded in 45% of the regional recurrences. Of all regional recurrences, 48% were single (38% in the irradiated groups, and 54% in the non-irradiated groups). There was no difference between pre- and postmenopausal patients regarding the frequency of single regional recurrence.

Of the patients with local recurrence, 30% had at least one symptom during the observation time (ulceration, pain, infection, etc.); all of these patients had disseminated disease. Of the patients with regional recurrence, 24% had at least one symptom regardless of whether their disease was only regional or disseminated as well. The irradiated and non-irradiated groups did not differ significantly in this respect.

The numbers of patients cured of loco-regional relapse in the different treatment groups are given in Table 2, which shows that the cure rate was higher in the non-irradiated than in the irradiated groups. Median survival times after operation are given in Table 3. The difference in median survival between irradiated pre- and postmenopausal patients was statistically significant.

Table 2

Loco-regional recurrence cure rates

	Treatment group	Cured
Premenopausal		
	1	4/12 (33%)
	2	4/9 (44%)
	3	11/23 (48%)
Postmenopausal		
	1	11/20 (55%)
	2	5/15 (33%)
	3	28/44 (64%)

Table 3

Median postmastectomy survival in months

	Median survival (months)
Series as a whole	53 (range, 4–123)
Irradiated groups	48
Non-irradiated groups	53
Premenopausal, irradiated	62
Premenopausal, non-irradiated	45
Postmenopausal, irradiated	36
Postmenopausal, non-irradiated	54

The first recurrence was local in 52 patients, 18 of whom had local recurrences only, and all of whom are still alive, whereas the remaining 34 subsequently developed distant recurrences as well (Table 4). The size of the local recurrence was 3 cm or less in more than 80% of these 52 patients. Among patients without progressive disease, 89% of the recurrences were solitary, as compared with only 56% among patients with progressive disease.

The first recurrence was regional in 30 patients, 8 of whom had regional recurrences only, whereas the remaining 22 subsequently developed distant recurrences as well (Table 4). Among patients without progressive disease, 74% of the regional recurrences were solitary, as compared with only 50% of those among patients with progressive disease. The remaining 41 patients had a distant recurrence before or concomitant with the loco-regional recurrence. Median time to the loco-regional recurrence for these patients was 29 months. Ten of the patients were cured loco-regionally, but only one of them is still alive. Of the local recurrences in this group, 45% were 3 cm or less, and 45% were solitary. Of the regional recurrences 35% were solitary.

Treatment of recurrence. Response rates after the first treatment of local recurrence are given in Table 5. Complete remission was obtained in all patients receiving only local treatment (i.e., surgery and/or radiotherapy) but was persistent in only 65% of cases. When surgery and radiotherapy were combined with hormone therapy, the response rate was 94%, and in 94% of these patients complete remission was persistent. The least effective treatment seemed to be systemic treatment only, which did not lead to a complete response in any patient.

Response rates after the first treatment of regional recurrence are given in Table 6. Local treatment resulted in complete response in all patients, but remission was persistent in only 43%. When surgery and radiotherapy were combined with hormone therapy, complete and persistent remission was obtained in 86% of the patients. Systemic treatment alone seemed to be more effective as treatment for regional recurrences (21% complete response) than as treatment for local recurrences (no cases of complete response).

Table 4

Type and distribution of recurrences, together with median observation times, and median intervals between mastectomy and recurrence and between loco-regional recurrence and distant metastasis

Site	No. of patients	Median interval, mastectomy to loco-regional recurrence (months)	No. of patients with persistant loco-regional recurrence	Median observation time (months)	Median interval, loco-regional recurrence to distant metastasis (months)
Local only	18 (4)*	46	2 (2)*	33	
Local and distant later	34 (18)	22	11 (8)		8
Regional only	8 (2)	40	2 (1)	43	
Regional and distant later	22 (8)	17	8 (3)		9

* Figures in parentheses denote numbers of patients given adjuvant radiotherapy (RT)

Table 5

Distribution of local recurrences with regard to treatment modality, with the local complete response (CR) and persistent CR rates after the first treatment for local recurrence

Treatment	% of patients	% CR	% persistent CR
All treatments (n = 91)	100	67	67
Local treatment only	19	100	65
Systemic treatment only	23	0	0
Radiotherapy + systemic treatment	31	89	80
Chemotherapy + other	14	62	38
Hormone therapy + other	51	89	68
Surgery + other	42	89	79
Surgery + radiotherapy + hormone therapy	20	94	94

Table 6

Distribution of regional recurrences with regard to treatment modality, with the regional complete response (CR) and persistent CR rates after the first treatment for regional recurrence

Treatment	% of patients	% CR	% persistent CR
All treatments (n = 52)	100	58	67
Local treatment only	13	100	43
Systemic treatment only	50	31	38
Radiotherapy + systemic treatment	29	80	100
Hormone therapy + other	36	79	93
Surgery + other	21	82	89
Surgery + radiotherapy + hormone therapy	13	86	100

Discussion

In this prospective randomized study, the overall loco-regional recurrence rate was 11%, a figure lower than those reported from other studies (2, 8, 9–11). The low rate in the present study can be explained in part by the fact that only patients with TNM stage II breast cancer were included. Even though we report all loco-regional recurrences during the observation time, which the CRC and NSABP studies do not, our figures are low (10, 11).

Our findings differ from those of others in several respects. For example, unlike Gilliland et al. (12), whose findings suggested the loco-regional recurrence rate to be solely dependent on the initial stage of disease (12), we found it to be related also to treatment: the recurrence rate in our postoperative radiotherapy subgroup was 7%, as compared with 17% in the subgroup without postoperative radiotherapy. This is also in accordance with earlier findings from the Manchester (1), CRC (10), and NSABP (11)

trials although their loco-regional recurrence rates were much higher. In contrast to Baral et al. (13), we did not find the irradiated and non-irradiated subgroups to differ significantly with regard to the interval between mastectomy and the appearance of loco-regional recurrence (25 and 26 months respectively). Unlike Crowe et al. who found almost no loco-regional recurrences among patients whose first recurrence was a distant metastasis (9), a third of our loco-regional recurrences were in this category. One possible explanation for this difference is that even after the occurrence of distant metastasis, our patients were followed up and loco-regional recurrences carefully noted according to a standardized schedule, thus ensuring that no loco-regional recurrences were missed.

Of the patients with loco-regional recurrence, distant metastases were not found in 26 during follow-up. Most of these loco-regional recurrences were late in appearing, and occurred predominantly in non-irradiated patients (20/26 patients). Of the irradiated patients with loco-regional recurrence, 88% subsequently had distant metastasis, as compared with 72% of the non-irradiated patients. The irradiated and non-irradiated subgroups did not differ with regard to the interval between loco-regional recurrence and the appearance of distant metastasis, or with regard to postmastectomy survival time. Somewhat unexpectedly, however, in the irradiated subgroup loco-regional recurrence was later and survival longer among premenopausal patients than among postmenopausal ones.

Although the loco-regional recurrence cure rate was higher in the non-irradiated than the irradiated subgroups (Table 2), persistent loco-regional recurrence (i.e., persistent for the duration of follow-up or the remainder of the patient's life) was more common in the non-irradiated subgroup. The incidence of subsequent distant metastasis was significantly lower among patients whose first local recurrence was solitary than among those whose first local recurrence was multiple.

Of the series as a whole, 30% of the patients had symptoms of loco-regional recurrence during follow-up; about half of them belonged to the subgroup whose first recurrence was a distant metastasis. These figures are somewhat difficult to compare directly with those of Bedwinek et al. (14, 15), but when our figures are re-calculated in the same manner as theirs our series seem to have had fewer patients with uncontrolled loco-regional disease (32% vs 64%) or clinical problems (54% vs 62%).

Our findings indicate that aggressive local treatment, i.e. surgical excision if possible, followed by radiotherapy (when not already given adjuvantly), resulted in complete remission in almost all cases. Unfortunately, however, permanent control of the loco-regional disease was not obtained in 42% of cases, a figure which is somewhat lower than that reported by Probstfeld & O'Connell (16). When the local treatment was combined with hormone therapy, the rate of failure to control loco-regional disease decreased to 12%. The incidence of subsequent distant metastasis also decreased after combination therapy (i.e., surgical excision, radiotherapy and hormone therapy) as compared with surgical excision and/or radiotherapy alone.

To sum up, we found that adjuvant radiotherapy reduced not only the overall loco-regional recurrence rate, but also the incidence of uncontrolled loco-regional recurrence. Adjuvant radiotherapy did not seem to delay the appearance of loco-regional recurrence, and did not affect postmastectomy survival. Most patients whose first recurrence was loco-regional were cured locally and regionally. Aggressive local treatment yields satisfactory local control initially and, when combined with hormone therapy, a high rate of persistent loco-regional control. Further studies are under way to ascertain whether any prognostic marker can be found that might serve as a guide to the choice of adjuvant treatment and the treatment of loco-regional recurrence.

REFERENCES

1. Lythgoe JP, Palmer MK. Manchester regional breast study: 5 and 10 year results. Br J Surg 1982; 69: 693–6.
2. Wallgren A, Arner O, Bergström J, et al. Radiation therapy in operable breast cancer: Results from the Stockholm trial on adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12: 533–7.
3. Overgaard M, Christensen JJ, Nybo-Rasmussen A, et al. Postmastectomy irradiation in high-risk breast cancer patients: Present status of the Danish Breast Cancer Cooperative Group trials. Acta Oncol 1988; 27: 707–14.
4. Fletcher GH, McNeese MD, Oswald MJ. Long-range results for breast cancer patients treated by radical mastectomy and postoperative radiation without adjuvant chemotherapy: an update. Int J Radiat Oncol Biol Phys 1989; 17: 11–4.
5. Rydén S, Fernö M, Möller T, et al. Long-term effects of adjuvant tamoxifen and/or radiotherapy. Acta Oncol 1992; 31: 271–4.
6. Patey DH, Dyson WH. The prognosis of carcinoma of the breast in relation to the type of operation performed. Br J Cancer 1948; 2: 7–13.
7. Arwidi Å, Aspegren K, Augustsson NE, Hafström LO, Norgren A, Svahn-Tapper G. Postoperative radiation therapy in mammary carcinoma stage II. Target volume, organs at risk, absorbed dose, time–dose schedule and dose to organs at risk in a prospective investigation. Acta Radiol Oncol 1979; 18: 273–81.
8. Toonkel LM, Fix I, Jacobson LH, Schneider JJ, Wallach CB. Postoperative radiation therapy for carcinoma of the breast: Improved results with elective irradiation of the chest wall. Int J Radiat Oncol Biol Phys 1982; 8: 977–82.
9. Crowe JP Jr, Gordon NH, Antunez AR, et al. Local-regional breast cancer recurrence following mastectomy. Arch Surg 1991; 126: 429–32.
10. Cancer Research Campaign Working Party. Cancer Research Campaign (King's/Cambridge). Trial for early breast cancer. Lancet 1980; 2: 55–60.
11. Fisher B, Redmond C, Fisher E, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. New Engl J Med 1985; 11: 674–81.

12. Gilliland MD, Barton RM, Copeland EM. The implications of local recurrence of breast cancer as the first site of therapeutic failure. Ann Surg 1983; 197: 284–7.
13. Baral E, Ogenstad S, Wallgren A. The effect of adjuvant radiotherapy on the time of occurrence and prognosis of local recurrence in primary operable breast cancer. Cancer 1985; 56: 2779–82.
14. Bedwinek JM, Fineberg B, Lee J, Ocwieza M. Analysis of failures following local treatment of isolated local-regional recurrence of breast cancer. Int J Radiat Oncol Biol Phys 1981; 7: 581–5.
15. Bedwinek JM, Lee J, Fineberg B, Ocwieza M. Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. Cancer 1981; 47: 2232–5.
16. Probstfeld MR, O'Connell T. Treatment of locally recurrent breast carcinoma. Arch Surg 1989; 124: 1127–30.