

MASTECTOMY ONLY VERSUS RADICAL MASTECTOMY AND POSTOPERATIVE RADIOTHERAPY IN NODE NEGATIVE, RESECTABLE BREAST CANCER

A randomized trial

STIG BORGSTRÖM, FOLKE LINELL, LENA TENNVALL-NITTBY and JONAS RANSTAM

Patients with clinically node negative resectable breast cancer were randomized to either mastectomy only or radical mastectomy and radiotherapy, and followed for 15–20 years. During follow-up axillary metastases occurred with the same frequency after mastectomy as was initially observed in the group that underwent axillary dissection. There was no significant survival difference between the two groups. When adjusting the treatment effect for differences in age, tumour size, lymph node metastases, and histology, the outcome after radical mastectomy plus irradiation was significantly inferior. Comedo carcinoma proved also in this study to carry a poor prognosis.

The role of the regional lymph nodes in the axilla in breast cancer remains unclear. It has been suggested that they might be of importance as a filter, or even exert an immunologic defence role as proposed by Crile (1). If this is the case, it could then be an advantage to leave the nodes, even though this 30 years ago was at variance with the prevalent views in cancer surgery, in which the Halstead operation was usually used. To test that hypothesis, a randomized trial was started in 1969, comparing clinically node negative patients with resectable breast cancer mastectomy only with radical mastectomy, plus postoperative radiotherapy. The group with mastectomy only received no postoperative radiotherapy. Preliminary reports of this investigation have been reported by Borgström et al. (2, 3).

Now the patients have a follow-up of at most 20 years. Furthermore, the initial tumour material has been reclassified using a new nomenclature with prognostic implications according to Linell et al. (4–6). The long-term results are reported in the present communication.

Material and Methods

During the years 1969–1974, 195 women with microscopically verified breast cancer, at most 5 cm in size, and clinically without axillary metastases, were randomized using Pearson's tables of random numbers to either mastectomy only (group A, $n = 98$), or radical mastectomy, including axillary dissection and postoperative radiotherapy (group B, $n = 97$). Eight cases in group A and 6 in group B were not strictly treated according to the protocol. Clinical data on the two patients series are given in Table 1. The two groups seem comparable.

The postoperative radiotherapy given to patients in group B was delivered with conventional x-rays to the axilla (140 kV, HVL 6.6 mm Cu) and chest wall (100 kV, HVL 2.7 mm Cu) with surface doses to the chest wall of 31.5 Gy given with fraction sizes of 3.5 Gy, and to the axilla of 28 Gy, given with fraction sizes of 4 Gy, 5 times

Table 1

Clinical data in the two treatment groups

Group	Number of patients	Mean age, years	Mean tumour diameter (cm)	Number of postmenopausal patients
A	98	57.7 ± 10.0	2 ± 1.0	66
B	97	54.6 ± 10.2	1.9 ± 1.0	61

Received 16 August 1993

Accepted 15 January 1994

From the Departments of Oncology (S. Borgström, L. Tennvall-Nittby), Pathology (F. Linell), Clinical Health Sciences (J. Ranstam), Malmö General Hospital, S-214 01 Malmö, Sweden. Correspondence to: Dr. Lena Tennvall-Nittby, Department of Oncology, Malmö General Hospital, S-214 01 Malmö, Sweden.

per week. The supraclavicular and parasternal nodes were treated either with cobalt-60 or electrons, with peak absorbed doses of 48 Gy given with fraction sizes of 3 Gy, 4 times per week. If axillary metastases were diagnosed in group A later on during follow-up, axillary dissection with postoperative radiotherapy was performed.

The patients were regularly followed after treatment until 1990 or until death. The present analysis includes data up to the end of 1990, thus allowing for a follow-up between 15 and 20 years. Ninety-one patients have died and in 65 of them (71%) autopsy was performed.

For all patients the original surgical biopsies were reviewed, and a histopathological diagnosis was established according to the system described by Linell et al. (4–6). This classification is mainly related to the classification reported by Fisher (7), with the important modification that ductal carcinoma NOS, which constitutes about 70–80% of the material, is divided into two groups. Apparently originating from radial scars, tumours of the tubular type developing into less differentiated tubuloductal types could be identified. This group comprises about half of the tubuloductal carcinomas NOS, and was found to be cancer with a rather favourable prognosis. The remaining half of the tumours have here been labeled comedo cancers. This name has been used previously, but only for in situ cancers, by Foote & Stewart (8). In our previous experience, invasive comedo cancers represent the most malignant form of breast cancer.

Survival and survival without distant metastases were calculated for each group using a Kaplan-Meier analysis, and the difference in survival was tested with a generalized Wilcoxon test as described by Gehan (9). Multivariate analyses using the Cox model were also made.

Results

Chest wall recurrence. In group A, 11 patients had a chest wall recurrence, diagnosed 2–12 years after initial therapy. For group B, the corresponding number was 2. The difference had no obvious bearing upon survival (see below). The chest wall recurrences represented most histopathologic types except the highly differentiated tubular types (Fig. 1).

Axillary lymph node metastases. Histological examination of the axillary contents of patients in group B showed axillary metastases in 28 of the 97 patients, despite negative clinical findings. In group A, three cases of node metastases were diagnosed at the initial surgical exploration and another 11 patients showed axillary lymph node metastases during the first postoperative year. At a follow-up of 5.5 years, all but one of the 26 cases of axillary metastases, diagnosed as first new sign of disease, had been found (Fig. 2). In this respect there was no difference between the two groups.

Survival. The analysis was first made for all patients (Fig. 3a) and secondly for patients who were treated



Fig. 1. Cumulative number of chest wall recurrences in group A (mastectomy only) and group B (radical mastectomy + postop. radiotherapy). 1 = tubular, 2 = tubulo-ductal, 3 = lobular invasive, 4 = comedo, 5 = medullar.

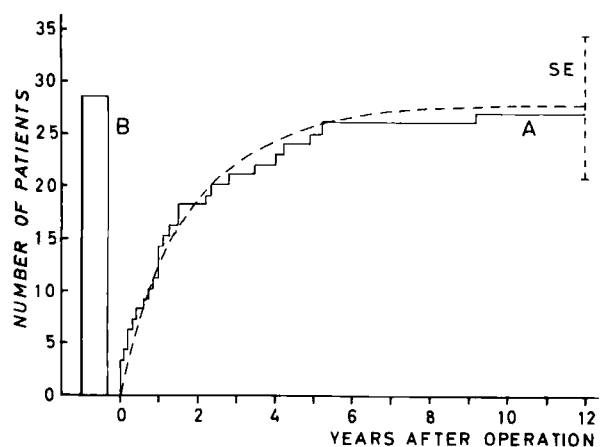


Fig. 2. Cumulative frequency of axillary lymph node metastases in group A (mastectomy only) compared with the initial frequency of such metastases in group B (radical mastectomy, including axillary dissection + postop. radiotherapy).

strictly according to the protocol (Fig. 3b). Since there was no difference in the results, only the latter are reported here. The cumulative survival at 5, 10, 15, and 20 years are given in Table 2. On the whole there was no statistically significant difference ($p = 0.38$), even though the 5-year survival showed a difference of more than two standard deviations (Table 2 and Fig. 3). When only deaths from or with cancer are taken as terminal events, the difference between the two groups were again not significant ($p = 0.18$) (Table 3). The number of patients at the endpoints were, however, small.

Survival without distant metastases. When the first appearance of distant metastases was taken as the final event, the pattern was similar, and there was no significant difference between the two groups ($p = 0.32$) (Fig. 4).

Histopathology. Patients with comedo cancer had a poorer survival than those with other types of tumour and a significantly higher breast cancer death rate, most clearly seen in group B ($p = 0.01$) (Table 4 and Fig. 5). Survival at 10 years for patients in group B with comedo cancer was

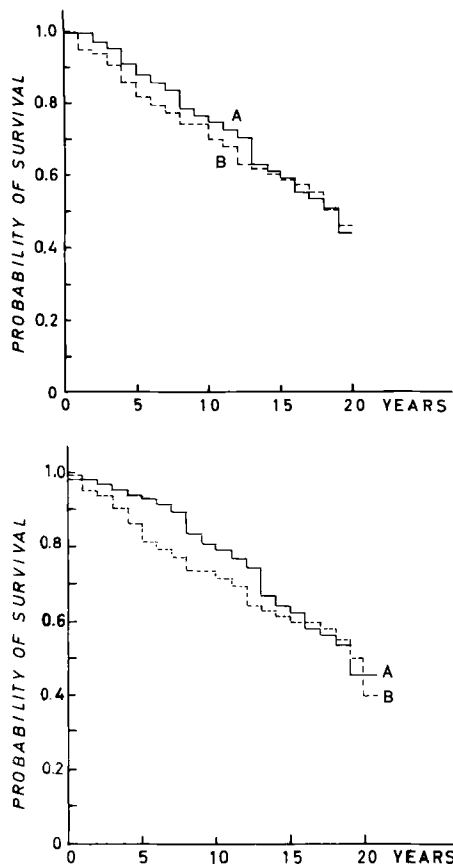


Fig. 3. a) Survival in groups A and B. All patients. b) Survival in groups A and B. Patients not treated strictly according to the protocol are excluded.

Table 2

Patients treated according to protocol. Kaplan-Meier analyses. No significant difference. $p = 0.38$. (see Fig. 3)

Group	n	Survival (years)			
		5	10	15	20
A	90	93 ± 2.6	79 ± 4.3	62 ± 5.2	45.4 ± 7.2
B	91	81 ± 3.7	71 ± 2.5	60 ± 1.3	40 ± 8.3

Table 3

Only cancer deaths used as terminal events. Cases treated according to protocol. Kaplan-Meier analyses

Group	n	Adjusted survival (years)			
		5	10	15	20
A	90	96 ± 2.2	85 ± 3.8	77 ± 4.7	77 ± 4.7
B	91	86 ± 3.7	80 ± 4.3	72 ± 5.0	72 ± 5.0

only 59% compared with 92% for tubuloductal cancers ($p = 0.01$). A simultaneous analysis of different predictive factors was made using Cox's proportional hazard regression model (10). Adjustment for menopausal status was

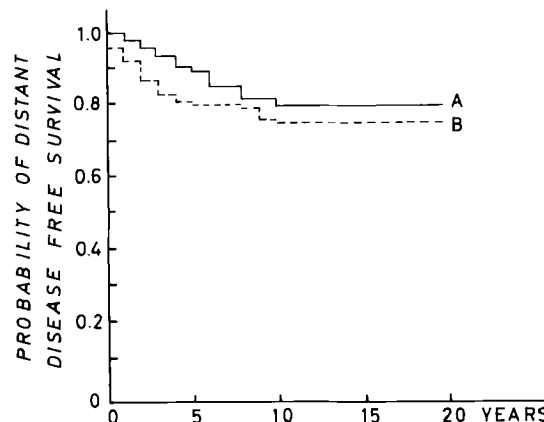


Fig. 4. Survival without distant metastases in groups A and B.

Table 4

Comparison of survival with respect to histologic pattern and treatment groups. Statistic evaluation of the parameters illustrated in Fig. 5

Group	Histology	n	p-value
1A	Tub. duct.	70	0.18
2B	Tub. duct.		
1A	Tub. duct.	61	0.06
3A	Comedo		
2B	Tub. duct.	59	0.01
4B	Comedo		
3A	Comedo	50	0.41
4B	Comedo		

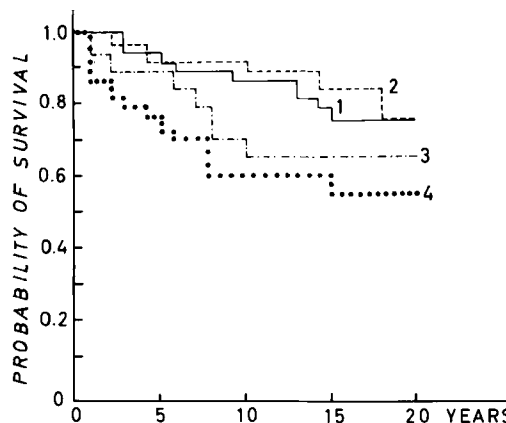


Fig. 5. Survival according to histopathology. 1 = tubuloductal cancer (group A); 2 = tubuloductal cancer (group B); 3 = comedo cancer (group A); 4 = comedo cancer (group B).

made. The results showed for tumour size $RR = 1.5$ ($p = 0.006$), for lymph node metastases $RR = 3.9$ ($p = 0.005$) and for comedo cancer histology $RR = 2.3$ ($p = 0.014$) and these variables were thus significantly correlated with prognosis. Menopausal status gave $RR = 2.0$ ($p = 0.156$), and age $RR = 0.95$ ($p = 0.058$). Tubular and

tubulo-ductal histologies gave $RR = 1.6$ ($p = 0.404$) and treatment regimen $RR = 2.2$ ($p = 0.062$) which also suggested a correlation, although it did not reach statistical significance. When adjusting the treatment effect for differences in age, size, lymph node metastases and comedo histology, the outcome after radical mastectomy plus irradiation was significantly inferior i.e. $RR = 0.43$ ($p = 0.042$).

Discussion

In this prospective, randomized trial, mastectomy only was compared with radical mastectomy followed by radiotherapy, in patients with resectable breast cancer, clinically node negative. Half of the patients thus had their axillary lymph nodes left untreated at the time of initial therapy, even though approximately 1/3 of them probably had subclinical axillary metastases according to experience from the more radically treated group.

There were less loco-regional recurrences in the more radically treated patients than in those who had mastectomy only. However, in the patients with well differentiated tubular cancers, no loco-regional metastases at all were found. Loco-regional metastases did not imply a worse prognosis *quo ad vitam*.

The NSABP study of 1971 (11) compared simple mastectomy with mastectomy combined with radiotherapy and with radical mastectomy. There is a difference in survival rates at 5 and 10 years after mastectomy between the NSABP study and the present investigation. In our groups, the 5-year survival were $96 \pm 2\%$ (simple mastectomy) and $86 \pm 4\%$ (radical mastectomy plus radiotherapy) respectively. In NSABP, the corresponding figures were $60 \pm 3\%$ (radical mastectomy), $65 \pm 3\%$ (mastectomy plus radiotherapy) and $56 \pm 3\%$ (simple mastectomy). At 10 years our results are $81 \pm 4\%$ and $73 \pm 5\%$ and the ones in the NSABP-study $47 \pm 3\%$, $48 \pm 3\%$ and $42 \pm 3\%$ respectively. Part of the explanation might be that the mean tumor diameter in our groups was 2.0 cm and in their groups 3.2 cm.

The life table calculations 6 years after the start of the trial showed a difference in favour of group A (Table 2). This difference has successively diminished and is now (after 15–20 years) not significant. The numbers of patients at the endpoints are, however, small. During the last 10 years there has been no new cases of generalization of the disease and during the last 5 years no new cancer deaths have been observed.

Multivariate analysis suggested that treatment regimen influenced the prognosis. Adjusted for age, size of tumour,

lymph node metastases and comedo histology, the outcome after radical mastectomy plus irradiation was significantly inferior. A possible explanation is reduced host defence against tumour cells in group B. Surgical trauma and radiation therapy may be two causes leading to immunosuppression (12–14).

REFERENCES

1. Crile Jr. G. A biological consideration of treatment of breast cancer. Springfield, Illinois: Charles C. Thomas Publisher, 1960.
2. Borgström S, Wenckert A, Linell F, Gynning I, Langeland P. Simple mastectomy or radical mastectomy and radiotherapy in a randomized trial of breast cancer, stage I. *Svensk Kirurgi* 1975; 32: 113–4 (In Swedish).
3. Borgström S, Langeland P, Lindahl S. The significance of preserving regional lymph nodes during the treatment of mammary carcinoma. Proceedings of the UICC Conference on Clinical Oncology, Lausanne, 1981.
4. Linell F, Ljungberg O, Andersson I. Breast carcinoma. Aspects of early stages, progression and related problems. *Acta Pathol Microbiol Scand (Sect A)*. Copenhagen: Munksgaard, 1980; (Suppl. 272).
5. Linell F, Ljungberg O, Andersson I. Brustkarzinoma. Frühstadien, Progression und verwandte Probleme. *Pathologie* 1981; 2: 150–5.
6. Linell F, Ljungberg O. Atlas of breast pathology. Copenhagen: Munksgaard, 1984.
7. Fisher ER. The pathology of invasive breast cancer. *Cancer* 1975; 36: 1–85.
8. Foote FW, Stewart FW. A histological classification of carcinoma of the breast. *Surgery* 1946; 19: 74–99.
9. Gehan EA. A generalized Wilcoxon test for comparing arbitrarily single-censored samples. *Biometrika* 1965; 52: 203–23.
10. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley and Sons, 1980: 70–117.
11. Fischer B, Redmond C, Risher E, et al. Ten-year result of a randomized clinical trial comparing radical mastectomy and mastectomy with or without radiation. *N Engl J Med* 1985; 312: 674–81.
12. Hammer JH, Moesgaard F, Kehlet H. The immunological consequences of surgery, anesthesia and blood transfusion. *Ugeskr Laeger* 1989; 151: 2348–52.
13. Newman GH, Rees GJ, Jones RS, Grove EA, Preece AW. Changes in helper and suppressor T-lymphocytes following radiotherapy for breast cancer. *Clin Radiol* 1987; 38: 191–3.
14. Rothstein S, Blomgren H, Petrini B, Wasserman J, Baral E. Long-term effects on the immune system following local radiation therapy for breast cancer. Proliferative responses and induction of suppressor activity of the blood lymphocyte population. *Radiother Oncol* 1986; 6: 223–30.
15. Ederer F. A simple method for determining standard errors of survival rates, with tables. *J Chron Dis* 1960; 1: 632–45.