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LONG-TERM EFFECTS OF ADJUVANT TAMOXIFEN AND/OR RADIOTHERAPY

The South Sweden Breast Cancer Trial

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In a multicenter trial of adjuvant therapy in stage II breast cancer, 719 postmenopausal patients were randomized to one of three treatment regimens: radiotherapy only or in combination with adjuvant tamoxifen for one year, or adjuvant tamoxifen without radiotherapy. At twelve years of follow-up (median 9 years), no statistically significant differences in survival or recurrence-free survival were observed. However, the rate of loco-regional recurrency was lower among patients treated with both radiotherapy and tamoxifen. The rate of bilateral breast cancer was reduced in tamoxifen-treated patients whereas the rate of new primary malignancies other than breast cancer was somewhat higher in tamoxifen-treated patients. Adjuvant therapy in breast cancer may influence not only breast cancer recurrences and mortality but also later disease patterns and cause-specific mortality.

Key words: Breast cancer, adjuvant therapy, radiotherapy, tamoxifen.

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Postoperative radiotherapy following mastectomy can reduce the number of loco-regional recurrences but seems to have only limited if any effects on survival (1). A meta-analysis of radiotherapy trials with long-term follow-up has shown an increased mortality rate for patients given radiotherapy (2). The reasons for this are not yet elucidated but an increased morbidity in cardio-vascular diseases after radiotherapy has been postulated as one possible cause.

Several clinical trials on adjuvant tamoxifen have been performed during the last 15 years. Some have shown a positive effect on breast cancer mortality, some have not. A meta-analysis of all randomized trials on adjuvant tamoxifen has, however, shown that two years of adjuvant tamoxifen to women over 50 years of age results in an about 20% reduction in mortality at 5 years (3). This effect was persistent even at 10 years (Peto R 1990, personal communication). Adjuvant tamoxifen is now a well-established standard adjuvant therapy for postmenopausal patients with breast cancer. The possibility that tamoxifen treatment may alter later disease patterns have been suggested by some investigators. Fornander et al. (4) have shown an increased risk of endometrial carcinoma in tamoxifen-treated women. The organization and compliance in the present study and the earlier results regarding recurrences and mortality of the adjuvant therapy have been presented elsewhere (5–7). The purpose of the present study was to obtain further insight into possible effects on disease patterns and cause specific mortality after a longer follow-up.

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Material and Methods

Postmenopausal (>5 years after menopause) patients under 71 years of age, with stage II breast cancer were included in the trial. After modified radical mastectomy, the

patients were randomized to one of three alternatives for adjuvant therapy: radiotherapy (RT), radiotherapy and tamoxifen (RTAM) or tamoxifen without radiotherapy (TAM). Patients were stratified according to hospital, size of tumor and number of positive axillary nodes. Randomization was centralized with closed envelopes and permuted blocks of six for each stratum. The trial was open from 1978 to 1985, during which time more than 80% of all eligible patients in southern Sweden were included in the trial. Staging was based on the histopathological examination of breast and axilla; 40% of the patients were node negative.

Radiotherapy was administered to the chest wall and regional lymph nodes in accordance with a standardized protocol (8). Tamoxifen was given in a daily dose of 30 mg for one year. Follow-up was standardized. Physical examinations were performed threemonthly for 2 years, sixmonthly up to 5 years, and once a year thereafter. Chest x-rays and bone scan were performed once a year up to 5 years, mammography of the contralateral breast was performed once a year up to 10 years.

Patient data were reported on forms to a secretariat at the regional tumor registry. The database was tailor-made in DSM on a VAX 11/780 computer. Record linking by means of the civic registration number was performed with the population-based regional tumor register and the national cause of death register (9). These registers were used for comparing reported data in the follow-up forms with the data collected in the regional tumor and mortality registers. Regarding malignancies other than breast cancer, only those diagnosed after the diagnosis of breast cancer were taken into account. For patients, deceased without a report of recurrent disease, patients charts and death certificates were retrieved to evaluate the cause of death. Breast cancer mortality thus refers to mortality in patients with a verified recurrence of breast cancer.

For comparison of differences in disease-free survival and survival, life table analysis with the generalized Wilcoxon's test was applied. Comparison of characteristics between different subgroups was performed with the χ^2-test for contingency tables.

Results

Seven hundred and nineteen patients were randomized. The characteristics of the patients are given in Table 1.

The present analysis was performed after a median observation time of 9 years (range 5–12 years). Events regarding recurrences, contralateral breast cancer or a new primary malignancy other than breast cancer in the three different treatment groups are given in Table 2.

A reduction in the number of loco-regional recurrences as first evidence of recurring breast cancer was seen in the two radiotherapy groups: RT (7.6%), RTAM (4.2%) and TAM (17.3%). While there was no statistically significant difference between RT and RTAM, the differences between RT and TAM ($p < 0.0005$) and between RTAM and TAM ($p < 0.005$) were highly significant.

Table 1

Patient characteristics

	RT	RTAM	TAM
Total number	236	239	244
Age (years)			
<50	2	1	0
50–59	62	61	75
60–69	158	162	157
>70	14	15	12
Tumor size (mm)			
<20	88	112	86
20–50	148	127	158
Positive nodes (No.)			
0	97	96	102
1–3	96	90	97
>3	43	53	45

Table 2

Recurrences, contralateral breast cancer and other malignancies during the observation period

	RT (n = 236)		RTAM (n = 239)		TAM (n = 244)		Total (n = 719)	
	n	%	n	%	n	%	n	%
Recurrences	98	41.5	78	32.6	98	40.2	274	38.1
Contralateral breast cancer	15	6.4	11	4.6	9	3.7	35	4.9
New primary cancer	15	6.4	26	10.9	30	12.3	71	9.9

Regarding both loco-regional and distant recurrence, the reduction in the combined treatment group, RTAM, was statistically significant both in comparison with RT ($p < 0.05$) and with TAM ($p < 0.05$).

During the period of observation, 33 (4.6%) of the patients developed breast cancer in the contralateral breast. Small differences were observed between the treatment groups but the differences did not reach statistical significance (Table 2).

Seventy-one patients (9.9%) were registered with a new primary malignancy other than breast cancer. The rate was higher among tamoxifen-treated patients: RTAM (10.9%) and TAM (12.3%) compared with radiotherapy-treated ones (6.4%). The difference between RT and TAM was statistically significant ($p < 0.05$). The difference between all tamoxifen-treated patients (RTAM + TAM) and patients not treated with tamoxifen (RT) was also statistically significant ($p < 0.05$). The type of malignancies are presented in Table 3.

Overall mortality, breast cancer mortality and mortality not related to breast cancer are presented in Table 4.

Table 3

Number of new primary cancers, number of deceased within brackets

	RT	RTAM	TAM
Head-neck	0	0	3
Stomach	0	2 (1)	5 (5)
Colo-rectal	3 (1)	7 (4)	2 (1)
Pancreas	1	0	1 (1)
Liver-bile duct	0	0	2 (2)
Lung	1	1	1
Melanoma	0	1	1
Skin (non melanoma)	2	4	0
Uterus			
cervix	1	1	0
corpus	2 (1)	4	5
Ovaries, adnex	0	2	2 (1)
Kidney, urinary tract	1	1 (1)	2
Brain	1	0	1 (1)
Thyroid	1	0	1
Other endocrine	0	1	0
Lymphoma	2	1	2
Leukemia	0	1	2 (1)
Subtotal	15 (2)	26 (6)	30 (12)
Breast	15	11	9
Total	30	37	39

Although there was a trend towards a reduction in breast cancer mortality in the combined treatment group RTAM (27.6%) in comparison with the RT group (33.5%), this difference did not reach statistical significance.

Of the 54 patients (7.5%) who died without clinical evidence of recurrent breast cancer, the major causes of death were cardiovascular in 22/54 (40.7%) or another malignancy in 20/54 (37.0%). The number of intercurrent deaths in relation to the treatment groups are presented in Table 5. Events were few and the observed tendencies towards somewhat more deaths caused by another malignancy among tamoxifen-treated patients and towards somewhat more cardiovascular deaths among patients given radiotherapy did not reach statistical significance.

When all events, such as breast cancer recurrence, contralateral breast cancer and overall mortality, were taken into account, the recurrence-free survival rates were: RT (45.3%), RTAM (52.7%) and TAM (49.2%). The differences between the groups were not statistically significant.

Table 5

Mortality from other causes than breast cancer

	RT (n = 236)		RTAM (n = 239)		TAM (n = 244)		Total (n = 719)	
	n	%	n	%	n	%	n	%
Malignancy	2	0.5	6	2.5	12	4.9	20	2.8
Cardio-vascular	6	2.5	12	5.0	4	1.6	22	3.1
Other causes	5	2.1	5	2.1	2	0.2	12	1.7

Discussion

In the present study of postoperative therapy a loco-regional treatment modality was compared with a general treatment modality. The two modalities were then combined in a third alternative for postoperative treatment. Obviously short- and long-term effects of a local and of a general treatment may appear to be quite different. The adjunct of postoperative radiotherapy after primary surgery for breast cancer reduces the rate of loco-regional recurrences, a finding which has been repeatedly reported and which was confirmed in the present study.

Our findings suggest an additive effect of tamoxifen to that of radiotherapy regarding loco-regional tumor control. There was, however, no evidence that tamoxifen treatment could substitute for radiotherapy regarding this effect.

The addition of tamoxifen to radiotherapy reduced the overall recurrence rate by 22% but did not significantly influence overall mortality. However, breast cancer mortality was reduced by 16%, which indicates that tamoxifen can influence the course of events. In the overview of the studies of adjuvant tamoxifen in early breast cancer, presented by Peto et al. (3), two years of adjuvant tamoxifen reduced recurrence rate and mortality. One year of tamoxifen treatment seemed less effective. In our study, 40% of the patients were node negative, a probable reason for the rather limited number of events. These facts may well explain why the differences between the groups in the present study did not reach statistical significance, although they point in the same direction as many other trials of adjuvant tamoxifen (10–13). Since estrogen, endogenous or exogenous, may stimulate breast tumor growth the antiestrogenic effect of tamoxifen could be

Table 4

Mortality

	RT (n = 236)		RTAM (n = 239)		TAM (n = 244)		Total (n = 719)	
	n	%	n	%	n	%	n	%
Overall	92	39.0	89	37.2	91	37.3	272	37.8
Breast cancer	79	33.5	66	27.6	73	29.9	218	30.3
Intercurrent deaths	13	5.5	23	9.6	18	7.4	54	7.5

expected to have a preventive effect against cancer development in the contralateral breast (14–15). In some clinical trials of adjuvant tamoxifen decreased incidences of contralateral breast cancers were found (4, 16). Although the number of contralateral breast cancers in our trial was rather small, a tendency towards a reduction among tamoxifen-treated patients was observed. This finding must await further confirmation after longer follow-up in many of the large tamoxifen trials.

From another Swedish trial of adjuvant tamoxifen, Fornander et al. (4) have reported an increased incidence of endometrial carcinoma among tamoxifen-treated patients when compared with non-tamoxifen-treated controls. There was, however, no significant difference in the total number of secondary cancers, nor in mortality from these secondary cancers (4). In our study, an increased incidence of other malignancies was observed among tamoxifen-treated patients. Although a tendency towards somewhat more cases of GI-cancers and endometrial cancers among tamoxifen-treated patients was observed, the differences were not statistically significant. The overall number of events were too few to allow any firm conclusions but the observation warrants a close, long-term follow-up. Only one of ten patients with endometrial carcinoma died during the observation period which was in accordance with previous reports that endometrial cancer patients with prior estrogen use have a good prognosis (14).

Tamoxifen has been shown to increase high density lipoprotein cholesterol (HDL-C) resulting in an increased ratio of HDL-C to total cholesterol which might be protective against atherosclerosis (17). Although the events were few, there was no evidence in the present study of a reduction in cardiovascular mortality among patients treated with tamoxifen. The number of deaths from myocardial infarction were too few to allow any speculations on the role of postoperative radiotherapy in this respect. However, a tendency towards more cardiovascular deaths among patients treated with a combination of radiotherapy and tamoxifen was observed in the present study. This finding warrants a continuous follow-up of these patients.

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Appendix

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