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Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy

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Abstract

For treatment of early breast cancer in older women, little evidence is available from randomised trials. We conducted a randomised trial comparing modified radical mastectomy (MRM) with tamoxifen (TAM) as the sole initial therapy in 164 patients aged $\geqslant 70$ years with operable breast cancer. 82 were treated by MRM and 82 with TAM. Survival curves were estimated using the Kaplan–Meier method: multivariate analyses were performed using the Cox's proportional hazards model. Endpoints included survival, time to first relapse or progression, loco-regional progression, time to distant progression and progression-free survival. After a median follow-up of approximately 10 years, there was a significantly decreased time to progression in the TAM only group (logrank $P<0.0001$) and significantly shorter time to local progression within the TAM group (logrank $P<0.0001$). Overall survival of the two groups was similar. The results indicate that tamoxifen alone leads to an unacceptably high rate of local progression or relapse.

Keywords: Breast cancer; Randomised trial; Elderly; Mastectomy; Tamoxifen

1. Introduction

Management of breast cancer is becoming an increasing problem since age is the major risk factor for breast cancer [1]. For the guidance of the oncologist, there is little evidence from randomised trials and many patients do not see an oncologist because of misconceptions that breast cancer in older women is a more indolent disease compared with younger patients, despite evidence to the contrary [2,3]. Many older women suffer under-treatment and the reasons for this are often arbitrary and bear little or no relation to the presence of co-morbidity [4,5].

As a result of concerns about competing deaths from co-morbidity in older patients, women aged $\geqslant 70$ years were excluded from all the trials of breast conservation therapy so that there are no trial-based results comparing mastectomy with standard breast conservation therapy in older women. In an effort to reduce the extent of surgery in older women with breast cancer, several clinicians treated patients with tamoxifen alone in non-randomised studies [6–8].

In 1984, the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Co-operative Group designed two prospective randomised trials, designated 10850 and 10851, for older women

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with operable breast cancer. At that time, there were no reported results from randomised trials. It was agreed that a modified radical mastectomy had to be regarded as standard treatment and also was decided that adjuvant tamoxifen should not be given since the only results which were available on tamoxifen in older patients were derived from the Danish Breast Cancer Cooperative Group which had not found any benefit by that time [9]. In terms of the experimental treatment, some surgeons wished to excise the cancer and then give tamoxifen in a pseudo-adjuvant role. Others were hoping to avoid hospitalisation in older patients and wanted to use tamoxifen to control or destroy the tumour. Because of the incompatibility of these aims, it was decided to run two trials in parallel, with contributing centres entering patients into only one of the studies. In EORTC 10851, patients were randomised to either modified radical mastectomy (MRM) or tamoxifen (TAM) 20 mg daily. The first analysis of this trial is reported in this paper.

2. Patients and methods

Eligible patients were women aged $\geqslant 70$ years with operable breast cancer (T1 T2 T3a, N0 N1a N1b, M0), who were suitable for either form of treatment. There had to be only one primary tumour and no evidence of Paget's disease of the nipple. Staging investigations including full blood count, biochemical screen, chest X-ray, bilateral mammograms and bone scan were performed to confirm that there was no evidence of tumour spread. None had had prior breast cancer treatment nor previous or concomitant other malignancy, except curatively treated basal cell carcinoma of the skin or cone-biopsied *in situ* carcinoma of cervix. Informed consent to participate was obtained according to regulations in individual participating centres. Randomisation with stratification was performed centrally by the EORTC Data Centre. After positive cytology (C5) or core biopsy confirming the malignant nature of the breast tumour, patients were stratified by TNM stage, without knowledge of the oestrogen receptor (ER) status, and randomised to either modified radical mastectomy (MRM) or tamoxifen 20 mg daily (TAM).

Patients randomised to modified radical mastectomy were treated by Patey or Madden operation according to the standard procedure used by the participating surgeon. No adjuvant radiotherapy, chemotherapy or endocrine therapy was given. Patients who relapsed after mastectomy were treated with tamoxifen as first-line treatment. For those randomised to tamoxifen, this was commenced within 48 h at a dosage of 20 mg once daily and continued until death or evidence of progressive or recurrent disease.

Follow-up was at 1 month, 2 months, 3 months and then three-monthly until 3 years, six monthly until 5 years and thereafter annually. The main endpoint was survival and secondary endpoints were: time to first relapse or progression, time to loco-regional progression, time to distant progression and progression-free survival. In the mastectomy group, loco-regional progression was defined as local skin, axillary recurrence or regional node involvement. Distant relapse was supraclavicular node involvement or evidence of distant metastases or occurrence of pleural effusions or ascites. In the TAM group, local-regional recurrence was progression of the primary tumour and/or increase in size by $>25\%$ of axillary nodes, occurrence of new axillary nodes or regional node invasion.

2.1. Statistical methods

The aim of this trial was to show that tamoxifen alone was equivalent to mastectomy in terms of overall survival. The null hypothesis that the difference in median survival between the two treatment groups was above a pre-specified difference was re-formulated in terms of hazard ratio and the modified logrank test described by Com-Nouge and colleagues was used [10]. At the time of design of this trial the sample size was calculated to be 100 patients on each treatment arm. This was based on the required power of 0.8 ($\beta = 0.2$), the required significance of 0.1 ($\alpha = 0.1$), the assumption of a 5-year survival rate of 50% in the mastectomy group and a pre-specified difference of 15% (corresponding to a hazard ration of 1.51). The modified logrank test was therefore used to test whether the true value r of the ratio of hazard rates between the two treatment groups is at least equal to a value of 1.51. Treatment effects for other endpoints as well as comparisons of time to event according to prognostic variables was tested using the logrank test with the common formulation of the null hypothesis.

Survival curves were estimated using the Kaplan–Meier product limit method and multivariate analyses were performed using Cox's proportional hazards model. All possible prognostic factors were included within the model and using a backward elimination procedure, unimportant variables were excluded.

3. Results

The study started in October 1985 and closed in November 1991, during which time 177 patients were entered from 14 institutions. The major contributors were University Hospital Gasthuisberg, K.U. Leuven (72), Daniel Den Hoed RRTI, Rotterdam (30), Antoni van Leeuwenhoekhuis/The Netherlands Cancer Institute Amsterdam (23), Medical Academy Lodz (19), Sophia Ziekenhuis, Zwolle (10, Institute of Oncology, Warsaw (9) and Twee Steden Ziekenhuis, Tilburg (6).

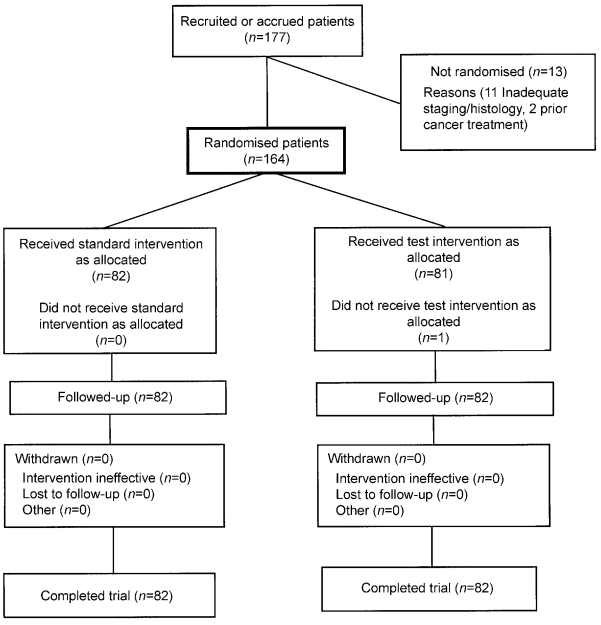

Fig. 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.)

There were 88 (49.7%) patients randomised to mastectomy (MRM group) and 89 (50.3%) to tamoxifen (TAM group) (Fig. 1). Thirteen patients (6 MRM, 7 TAM) were ineligible and these were excluded from the analysis. One patient was randomised to TAM, but was treated by mastectomy, but this case was included in the analysis as randomised (intent-to-treat). Hence, the trial comprised 164 eligible patients; 82 in the MRM group and 82 in the TAM group. The median follow-up was 11.7 years (95% CI: 11.2–12.8; range: 0–14.3) for the mastectomy arm and 10.2 years (95% CI: 10.3–11.2; range: 0–14.9) for the tamoxifen only arm.

Table 1 shows the comparative features of the patients in the two arms of the trial, including age at entry, T and N stage, tumour type, and ER status, when known. Patient characteristics were well balanced and there was a similar distribution of stages in the two groups. Two patients with T4 tumours were entered, one in each arm and these have been included within the analysis. The time to progression of the two treatment arms is shown in Fig. 2 which indicates a significantly increased risk in the TAM only group (logrank $P<0.0001$). In terms of progression-free survival and time to loco-regional progression, there was also a significantly increased risk within the TAM group as shown in Fig. 3, (logrank $P=0.0006$ and $P<0.0001$ respectively). In contrast, as indicated in Fig. 4, there was no difference in time to distant progression ($P=0.654$). For overall survival, the modified logrank test led to a significant P value (modified $P=0.001$) rejecting the null hypothesis of non-equivalence and therefore indicating that the two treatment groups are not significantly different in terms of overall survival (Fig. 5).

Table 1
Comparative features of patients in the two arms of 10851 trial

Feature	Mastectomy ($n=82$)	Tamoxifen ($n=82$)
Age at entry		
⩾70, °5	8 (10%)	10 (12%)
⩾75, <80	45 (55%)	36 (44%)
⩾80, <85	20 (24%)	26 (32%)
⩾85	9 (11%)	10 (12%)
Performance status		
0	37 (45%)	29 (35%)
1	36 (44%)	43 (52%)
2	7 (9%)	8 (10%)
Unknown	2 (2%)	2 (2%)
Clinical tumour size		
T1	14 (17%)	12 (15%)
T2	57 (70%)	56 (68%)
T3	9 (11%)	12 (15%)
T4	1 (1%)	1 (1%)
Unknown	1 (1%)	1 (1%)
Clinical axillary node status		
N0	59 (72%)	57 (70%)
N1A	8 (10%)	11 (13%)
N1B	14 (17%)	14 (17%)
Unknown	1 (1%)	0
Tumour type		
Ductal grade I	8 (10%)	0
Ductal grade II	25 (30%)	1
Ductal grade III	8 (10%)	1
Ductal unknown grade	15 (17%)	6 (7%)
Lobular	13 (16%)	4 (5%)
Mucoid	3 (4%)	0
Other	3 (4%)	7 (9%)
Unknown	7 (9%)	63 (77%)
ER status		
Negative <10	8 (10%)	1 (1%)
Positive ⩾10	30 (37%)	7 (9%)
Unknown	44 (54%)	74 (90%)

ER, oestrogen receptor.

The types of first relapse and causes of death of the two groups are given in Table 2. Only 7 (9%) of the MRM group had a loco-regional relapse as a first recurrence compared with 47 (57%) of the TAM group. There were more distant recurrences in the MRM group (13 vs. 3). In the TAM group, 4 had both local and distant relapse, as did 2 of the MRM group. A comparison of the results of treatment according to the endpoints of time to progression, time to loco-regional progression, time to distant progression, progression-free and overall survival is given in Table 3. In the TAM group, progression occurred in 68% compared with only 29% of the MRM cases. Loco-regional control of disease failed in 9 (11%) of the MRM group and 51 (62%) of the women treated with tamoxifen alone.

In a univariate prognostic factor analysis, thirteen variables were considered: age (70–74 years vs. 75–79 years vs. 80–84 years vs. ⩾85 years), performance status (0 vs. ⩾1), tumour laterality (right vs. left), tumour site (upper outer vs. upper inner vs. lower outer vs. lower inner vs. central), clinical tumour size (TNM: T1 or T2 vs. T3 or T4) and axillary node status (TNM: N0 vs. N1a, N1b, N2 or N3), concomitant disease (no vs. yes), tumour type (infiltrating ductal vs. infiltrating lobular, mucoid, tubular or other), tumour grade (grade 1 vs.

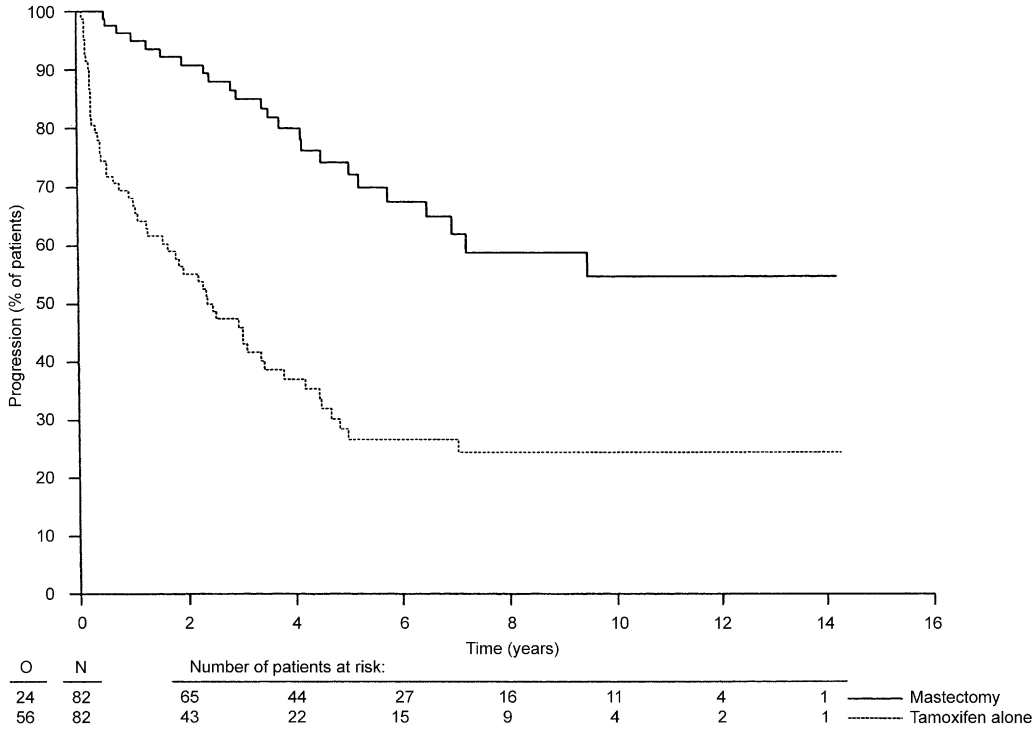

Fig. 2. Time to progression (TTP) of mastectomy (MRM) or tamoxifen (TAM) cases. *O*, observed; *N*, number.

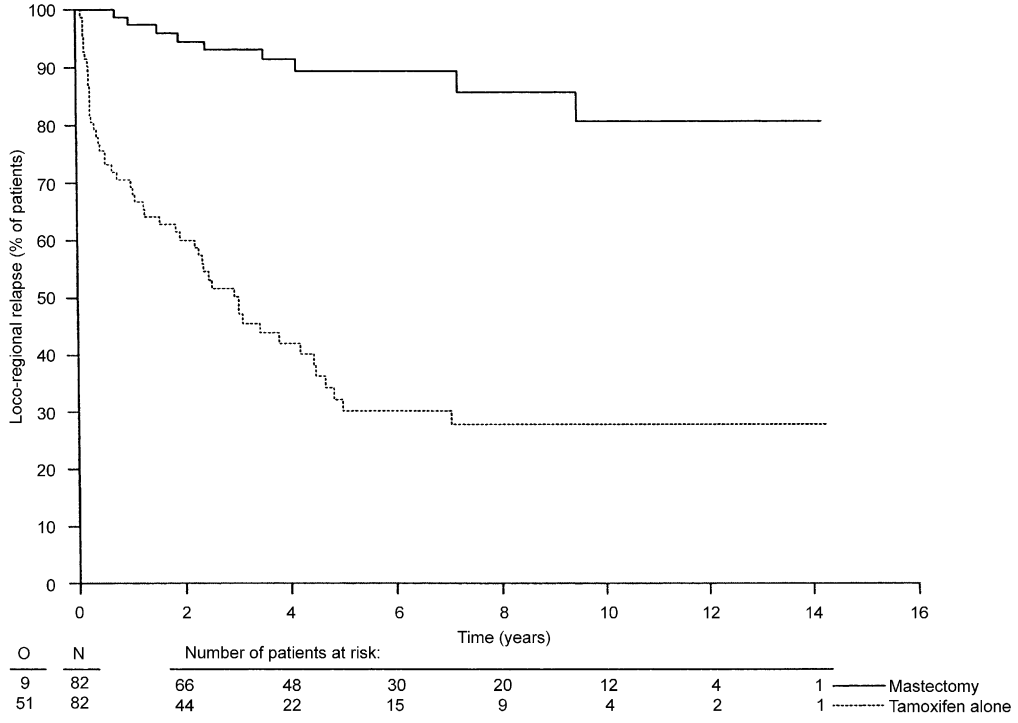

Fig. 3. Time to loco-regional relapse of MRM or TAM cases.

grade 2 vs. grade 3), number of positive nodes (0 positive nodes vs. $\geqslant 1$), ER status ($\leqslant 10$ vs. >10), progesterone receptor status (PgR) ($\leqslant 10$ vs. >10) and number of days from first symptom to randomisation (<61 vs. $\geqslant 61$). Only two variables were significant for overall survival: performance status ($P=0.022$) and presence or absence of concomitant disease ($P=0.014$). Risk of death was higher for patients with PS of 1 or above and for patients suffering from other concomitant diseases. For time to progression, the significant variables were

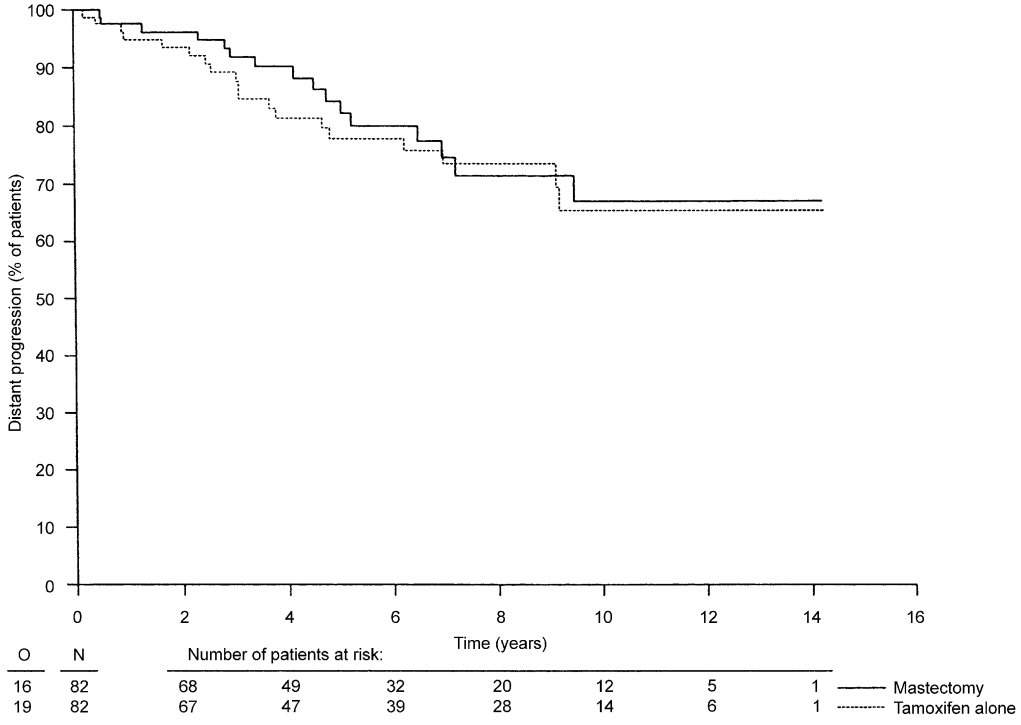

Fig. 4. Time to distant progression of MRM or TAM cases.

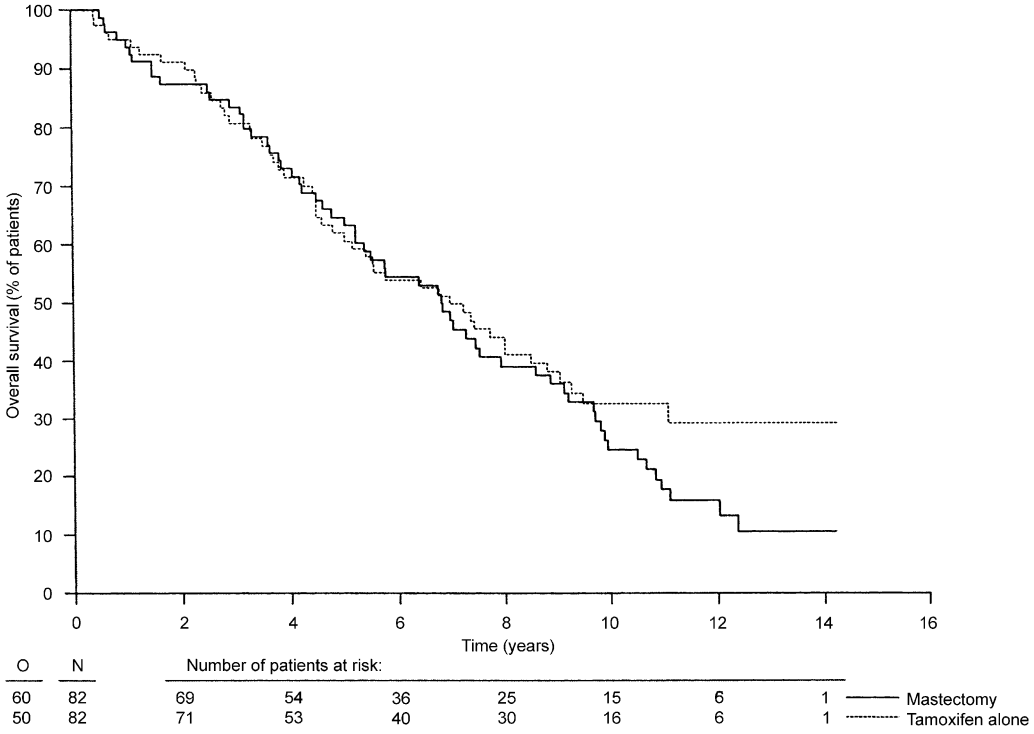

Fig. 5. Overall survival of MRM or TAM cases.

Table 2
Type of first relapse and causes of death in 10851

Type of first relapse	Mastectomy ($n=82$)	Tamoxifen ($n=82$)
No progression	58 (71%)	26 (32%)
Loco-regional	7 (9%)	47 (57%)
Distant	13 (16%)	3 (4%)
Local and distant	2 (2%)	4 (5%)
Unknown	2 (2%)	2 (2%)
Total relapsed	24 (29%)	56 (68%)
Cause of death		
Malignant disease	19 (32%)	23 (46%)
Cardiovascular disease	13 (22%)	12 (24%)
Infection	6 (10%)	0
Other chronic disease	1 (2%)	2 (4%)
Other	8 (13%)	9 (18%)
Unknown	13 (22%)	4 (8%)
Total deceased	60	50

tumour grade ($P=0.022$) and the presence or absence of concomitant disease ($P=0.018$), the former reducing the risk of relapse as a result of a reduced-life expectancy (median survival shorter by 2 years for patients with concomitant disease).

Variables were considered for possible inclusion into the multivariate Cox's proportional hazards model if they were significant in the univariate analysis with an α-level of 20% or if the variable was medically important or if no less than 10% of the data were missing. This meant that ER and PgR status was not included because these were unavailable in 64 and 60%, respectively. In addition, tumour grade and nodal status were not considered as this information was only available for patients with infiltrating ductal tumour and patients treated by mastectomy, respectively.

In terms of overall survival, all explanatory variables including randomised treatment were removed from the model with the exception of age and performance status. To decrease the bias in estimation and the number of missing variables, the model was fitted again with the variables age and performance status only and without a backward elimination procedure. The hazard ratio for age was 1.331 ($P=0.024$) and for performance status 1.55 ($P=0.029$), indicating that older age and performance status above 0 are predictors of a higher risk of death. After stratification for age and performance status, the modified logrank test still rejected the null hypothesis of non-equivalence, confirming that survival is similar between both treatment groups.

Similar prognostic variables were fitted in the model for time to progression. After backward elimination only treatment and other concomitant disease remained in the model. For treatment the hazard ratio was 3.676, ($P<0.0001$; 95% CI: 1.331 (1.036–1.660)), that is a 3.7-fold higher risk of local progression in those who were randomised to tamoxifen only. The hazard ratio was 0.454 ($\chi^2=7.5$, $P=0.0062$; 95% CI: 1.553 (1.045–2.308)) in favour of those with concomitant disease. This seems to confirm that such individuals were more likely to die of other causes before showing progression of breast cancer.

3.1. Salvage treatment

The frequency of usage of salvage surgery, radiotherapy and systemic therapy after first progression which was loco-regional is shown in Table 4. Local

Table 3
Comparison of endpoints in 10851[a]

Endpoints	No of events	Median time to event (years)	Range	Hazard ratio estimates (95% CI)[b]	P value
Time to progression					
Mastectomy	24 (29%)	–	0–14.2	–	<0.0001
Tamoxifen	56 (68%)	2.49	0.1–14.3	1.56–3.43	
Progression-free survival					
Mastectomy	63 (77%)	5.22	0–14.2	3.86–6.75	0.0006
Tamoxifen	69 (77%)	2.31	0.1–14.3	1.25–3.04	
Time to loco-regional progression					
Mastectomy	9 (11%)	–	0–14.2	–	<0.001
Tamoxifen	51 (62%)	3.03	0.2–14.3	–	
Time to distant progression					
Mastectomy	16 (20%)	–	0–14.2	–	0.654
Tamoxifen	19 (23%)	–	0.2–14.3	–	
Duration of survival					
Mastectomy	60 (73%)	6.81	0–14.2	5.23–8.59	0.001
Tamoxifen	50 (61%)	6.97	0.2–14.3	5.02–8.82	

P value for the common logrank test for overall survival: 0.301. 95% CI, 95% Confidence Interval.
[a] Modified logrank test H_0: $r<1.51$ (1-sided 95% CI: 0–1.125).
[b] Mastectomy is the reference group.

Table 4
Salvage treatment after a first loco-regional progression

	Mastectomy	Tamoxifen
Loco-regional relapse patients	7	47
Salvage surgery		
Yes	5 (71%)	34 (72%)
No	–	3 (6%)
Unknown	2 (29%)	7 (15%)
Other	–	3 (6%)
Radiotherapy		
Yes	3 (43%)	10 (21%)
No	1 (14%)	14 (30%)
Unknown	3 (43%)	23 (49%)
Endocrine therapy		
Yes	2 (29%)	11 (23%)
No	1 (14%)	8 (17%)
Unknown	4 (57%)	28 (60%)
Chemotherapy		
Yes	–	–
No	2 (39%)	18 (38%)
Unknown	5 (71%)	29 (62%)

relapse as first evidence of progression occurred in 7 (9%) of the MRM group compared with 47 (57%) in the TAM group. In the MRM group, salvage surgery comprised wide excision of recurrence and this was used in 5 (71%). For those treated with tamoxifen alone, salvage surgery was mastectomy for 29 (62%) and wide excision in 5 (11%). Radiotherapy was given to 3/7 (43%) of those that relapsed in the MRM group, but to 10 (21%) of the TAM group.

4. Discussion

This was the first prospective randomised trial of treatment for operable breast cancer in which tamoxifen alone was compared with modified radical mastectomy. The statistical consideration and the design of this study both suffer from the lack of precision that would be required nowadays and the results of the study have to be regarded within this limitation. Thus far, with a median follow-up of 11.2 years, overall survival is similar for the two forms of treatment and we found no significant difference in terms of distant relapse-free survival. Despite this, there was a very high rate of loco-regional progression in the tamoxifen only group (62%) compared with loco-regional relapse in only 11% of the MRM group. ER-positive status was not used as an entry criterion for this study, but it has since become apparent that this is the major determinant of patients deriving benefit from tamoxifen [11].

Since this study was designed, four randomised trials have been reported, each of which compared tamoxifen alone with some form of surgery [12–15]. The St George's Hospital trial compared wide excision or total mastectomy with tamoxifen alone [12]. After a median follow-up of 6 years, the trial had accrued 200 patients, with 100 treated by tamoxifen and 100 by surgery [16]. Local relapse or progression occurred in 56% of the tamoxifen group and 44% of the surgery group. Mortality rates were similar in both arms.

In the Nottingham trial, patients were treated by either tamoxifen (40 mg daily) or by wedge mastectomy [13]. After a median follow-up of 145 months, there was no difference in overall survival, but significantly better local control in the surgery group. Loco-regional relapse occurred in 38% of the wedge mastectomy group, but in the tamoxifen group 81% had relapsed or progressed [17].

In the Cancer Research Campaign (CRC) trial, patients received either tamoxifen alone or optimal surgery plus tamoxifen. After a median follow-up of 5 years, there were 446 participants and significantly more of the tamoxifen group needed a change of treatment (46 vs. 21%) [18]. Furthermore, 28% of the tamoxifen group had died compared with 21% of the surgery and tamoxifen group and this difference just reached statistical significance ($P = 0.048$).

In the GRETA trial, 473 patients aged >70 years were randomised to either a loading dose of tamoxifen followed by 20 mg daily (236) or to surgery plus tamoxifen (237) [15]. After a median follow-up of 3 years, local progression occurred in 6% of the surgery group compared with 25% of the tamoxifen alone arm.

In EORTC 10851, no mortality difference was found, although there was a significantly worse progression-free survival in the TAM group. Taken together, these studies indicate that tamoxifen alone is an inadequate single treatment for unselected older women with breast cancer because of the unacceptably high rate of local progression or relapse. Selection on grounds of ER/PR-positive tumours may reduce the treatment failure rate. At present, the optimum treatment comprises surgery with or without radiotherapy plus tamoxifen for women with ER+ tumours. It is in the best interests of both the patient and society if the primary treatment offers the maximum chance of local control with minimal toxicity. Subsequent progression of disease may be more difficult to treat because of the chance of an increase in co-morbidity.

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Appendix

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Poland	J. Berner	Inst Oncology Lodz
	M. Nagadowska	Inst Oncol Warsaw

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