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Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen

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Abstract

We have examined the outcome of older patients with operable breast cancer treated in a randomised trial by either standard surgery or less extensive surgery and tamoxifen. There were 236 participants aged $\geqslant 70$ years, randomised to either modified radical mastectomy MRM ($n=120$) or wide local excision (WLE) and tamoxifen (T) 20 mg daily ($n=116$). Survival curves were estimated using the Kaplan–Meier method and multivariate analyses were performed using Cox's proportional hazards model. Endpoints were survival and time to first relapse or progression, loco-regional progression, time to distant progression and progression-free survival. No significant difference was seen in terms of progression-free survival, but there were significantly more loco-regional relapses in the WLE + T group. In contrast, there were more distant metastases in the MRM group, but with a similar overall survival in both groups. The results of this trial give cautious support for the use of WLE + T for selected older women.

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

1. Introduction

Increasing age is the major risk factor for breast cancer with more than 50% of cases being aged over 70 years in both the US and Europe [1]. As life expectancy improves, so this proportion will increase, imposing a major burden on oncologists with little evidence from randomised trials. There has also been a misconception that breast cancer in older women is a more indolent disease although comparative histological studies have not shown any significant increase in well-differentiated tumours in elderly women [2,3]. In a series from Guy's Hospital, 27% of the cancers in the over 70 year old age group were infiltrating ductal carcinoma grade III, a tumour type not necessarily associated with a good prognosis [3].

At present, there is abundant evidence of undertreatment in the elderly which has resulted in those aged over 50 years comprising 60% of the deaths from breast cancer [1]. Reasons for undertreatment are often arbitrary, bearing little or no relationship to the presence of co-morbidity [4,5]. Improvements in breast cancer treatment have come about largely as a result of clinical trials, and there is consistent evidence that selected patients can be as safely treated by breast conservation therapy as by mastectomy.

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. This means that there are no trial results comparing mastectomy with standard breast conservation

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therapy in older women. In an attempt to avoid surgery in older women with breast cancer, several non-randomised studies used tamoxifen alone as treatment [6–8]. In 1984, the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Co-operative Group designed two prospective randomised trials, 10 850 and 10 851, for older women with operable breast cancer.

At that time, there were no reported results from randomised trials. Participating surgeons were agreed that a modified radical mastectomy had to be regarded as standard treatment. It was decided that adjuvant tamoxifen should not be given since the only available results on tamoxifen in older patients from the Danish Breast Cancer Cooperative Group had found no benefit [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 shrink or destroy the tumour. Because of the incompatibility of these aims, it was decided to run two trials in parallel, with contributing centres entering cases into only one of the studies. In EORTC 10850, patients were randomised to either modified radical mastectomy or complete local excision and tamoxifen 20 mg daily. The first analysis of this trial is reported in this paper.

2. Patients and methods

Eligible patients were aged $\geqslant 70$ years with operable breast cancer (T1 T2 T3a, N0 N1a N1b, M0), suitable for either form of treatment. There had to be a single primary 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 exclude metastatic spread. None had had any prior or concomitant malignancy except 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, patients were stratified by TNM stage, without knowledge of the oestrogen receptor (ER) status and randomised to either modified radical mastectomy (MRM) or wide local excision plus tamoxifen 20 mg daily (WLE + T). Tamoxifen was to be given for life and stopped only if the patient suffered undue side-effects or relapsed.

In core needle negative cases, the lump was excised with an attempted 1 cm of surrounding tissue and if confirmed as malignant the patient was then randomised. Patients randomised to modified radical mastectomy were treated by a Patey or Madden operation according to the standard procedure of 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 of surgery at a dosage of 20 mg once daily and continued until death or evidence of recurrent disease.

Follow-up was at one month, two months, three months and then three-monthly until 3 years, six monthly until 5 years and annually thereafter. 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 excision plus tamoxifen group, local-regional recurrence was recurrence of the primary tumour and/or an 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 wide local excision plus tamoxifen was as effective as mastectomy in terms of overall survival. The null hypothesis was that the difference in median survival between the two treatment groups was above a pre-specified difference and this was re-formulated in terms of a hazard ratio using the modified log-rank test described by Com-Nouge and colleagues [10]. At the time of instigation of this trial, and with respect to this formulation i.e. a required power of 0.8 ($\beta = 0.2$), a required significance of 0.1 ($\alpha = 0.1$), the assumption that the overall 5 year survival rate was 50% in the mastectomy group and a pre-specified difference of 15% (corresponding to a hazard ration of 1.51), the sample size was calculated to be 100 patients on each treatment arm. 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.

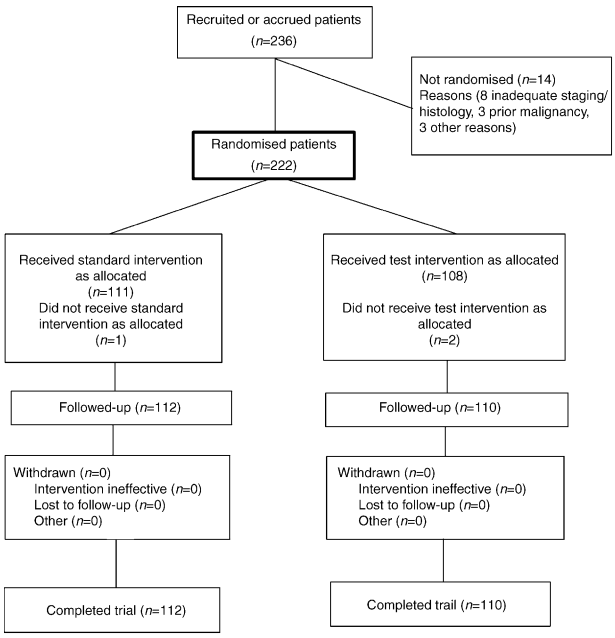

Fig. 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.

3. Results

Trial 10850 started in September 1985 and was closed in October 1991 and during this period 236 patients were entered from 11 institutions. There were 120 (51%) randomised to treatment by modified radical mastectomy (MRM) and 116 (49%) to wide local excision plus tamoxifen (WLE + T). Two patients were treated by mastectomy although randomised to WLE + T and one patient randomised to MRM was treated by WLE + T, but these cases were included in the analysis as randomised (Fig. 1). There were 14 ineligible cases: 8 randomised to mastectomy (3 because of inadequate staging or histology, 3 having had a prior malignancy and 2 for other reasons): 6 cases in the WLE + T group, (5 because of inadequate staging or histology and 1 for other reasons). These ineligible patients were excluded from all of the analyses. These results are given after a median follow-up of 10.9 years (0.3–15 years range) for the mastectomy arm and 10.4 (0–14.9 range) for the WLE + T arm. The comparative features of the two groups are given in Table 1 which indicates that there were no major imbalances in terms of age, performance status, tumour stage, clinical nodal involvement, tumour type or ER/progesterone receptor (PR) status.

Fig. 2 shows the time to progression of the two treatment arms with no significant difference between the two groups (logrank $P = 0.548$). In terms of time to loco-regional progression, however, there seems to be an increased risk within the WLE + T group as shown in Fig. 3 (logrank $P = 0.068$). In contrast, as indicated in Fig. 4, there was a significantly higher risk of distant metastases in the MRM group (logrank $P = 0.006$). 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 similar in terms of overall survival (Fig. 5). The type of first recurrence and causes of death are summarised in Table 2. Loco regional relapse was the first event in 14 of the MRM group and 26 of the WLE + T group. Distant metastases were the first event in 24 of the MRM group and 5 of the WLE + T cases. Two patients in the MRM group and 3

Table 1
Comparative features of cases in the two arms of 10850 trial

Feature	Mastectomy ($n = 112$)	WLE + Tamoxifen ($n = 110$)
Age at entry (years)		
< 75	27 (24%)	18 (16%)
75– < 80	53 (47%)	55 (50%)
80– < 85	23 (21%)	29 (26%)
⩾ 85	9 (8%)	7 (6%)
Unknown	0	1 (1%)
Performance status		
0	96 (86%)	95 (86%)
1	15 (13%)	12 (11%)
2	0	3 (3%)
3	1 (1%)	0
Tumour size		
T1	21 (19%)	19 (17%)
T2	84 (75%)	79 (72%)
T3	6 (5%)	12 (11%)
T4	1 (1%)	0
Unknown	1 (1%)	0
N0	70 (63%)	77 (70%)
N1a	15 (13%)	14 (13%)
N1b	26 (23%)	18 (16%)
N2	0	1 (1%)
Ductal ungraded	17(15%)	13 (12%)
Ductal grade I	8 (7%)	15 (14%)
Ductal grade II	40 (36%)	33 (30%)
Ductal grade III	18 (16%)	15 (14%)
Lobular	16 (14%)	15 (14%)
Mucoid	3 (3%)	4 (4%)
Tubular	2 (2%)	0
Other	5 (4%)	14 (13%)
Unknown	3 (3%)	1 (1%)
ER status		
< 10	17 (15%)	21 (19%)
⩾ 10	55 (49%)	55 (50%)
Unknown	40 (36%)	34 (31%)
PR status		
< 10	17 (15%)	30 (27%)
⩾ 10	52 (46%)	41 (37%)
Unknown	43 (38%)	39 (35%)

ER, oestrogen receptor; PR, progesterone receptor; WLE, wide local excision.

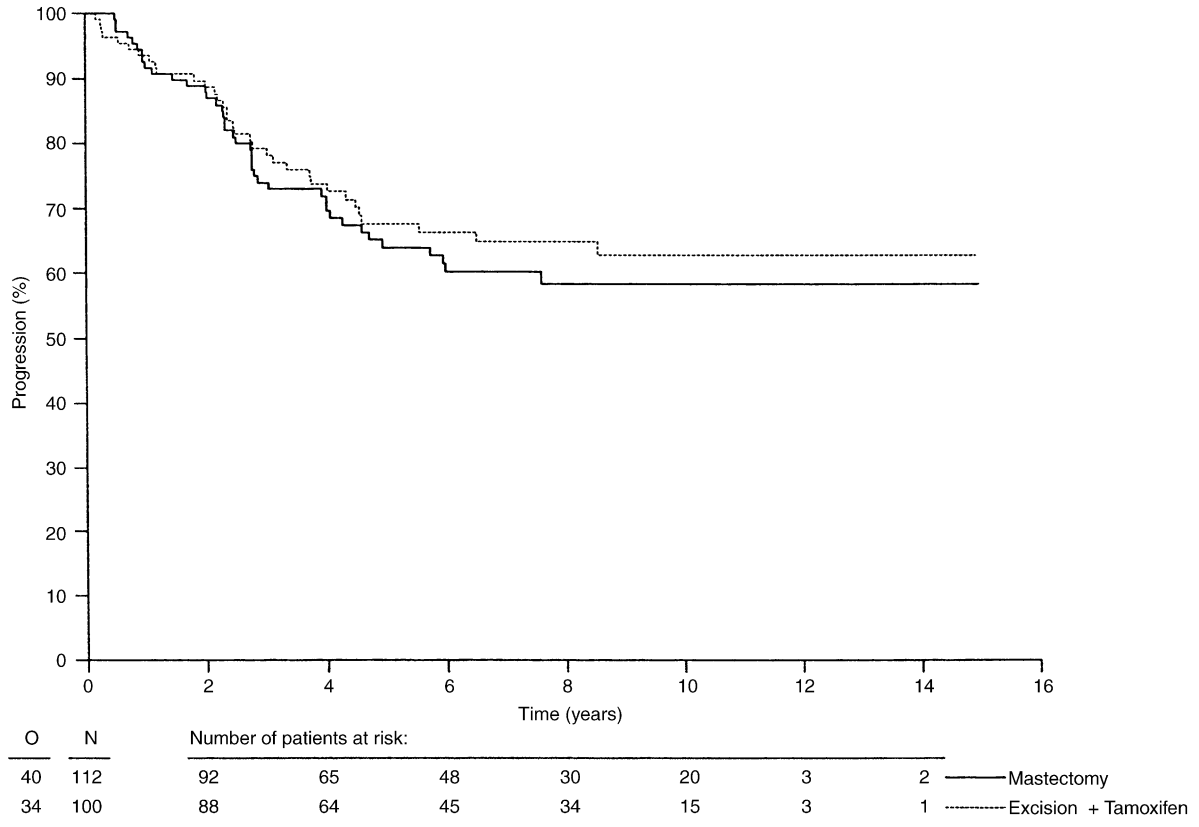

Fig. 2. Time to progression of mastectomy and wide local excision + Tamoxifan (WLE + T) cases. *O*, observed; *N*, number.

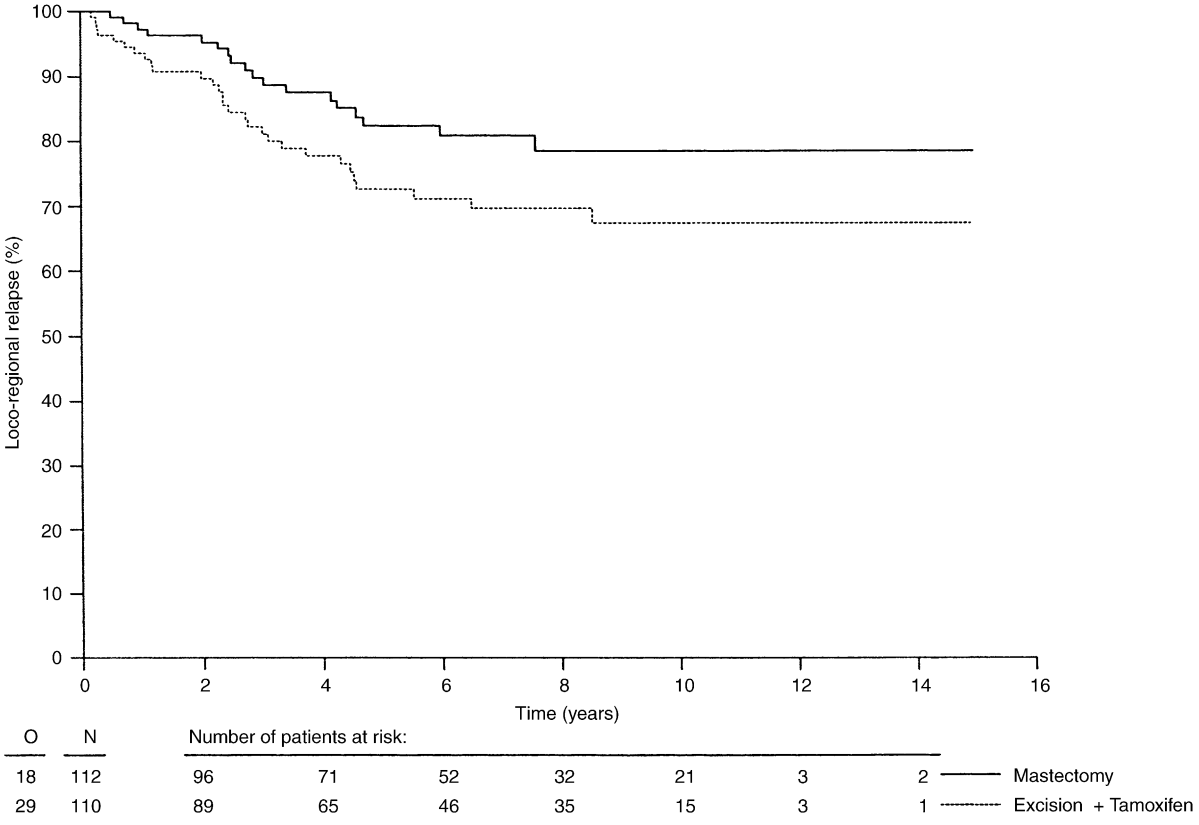

Fig. 3. Time to loco-regional relapse of mastectomy and WLE + T cases.

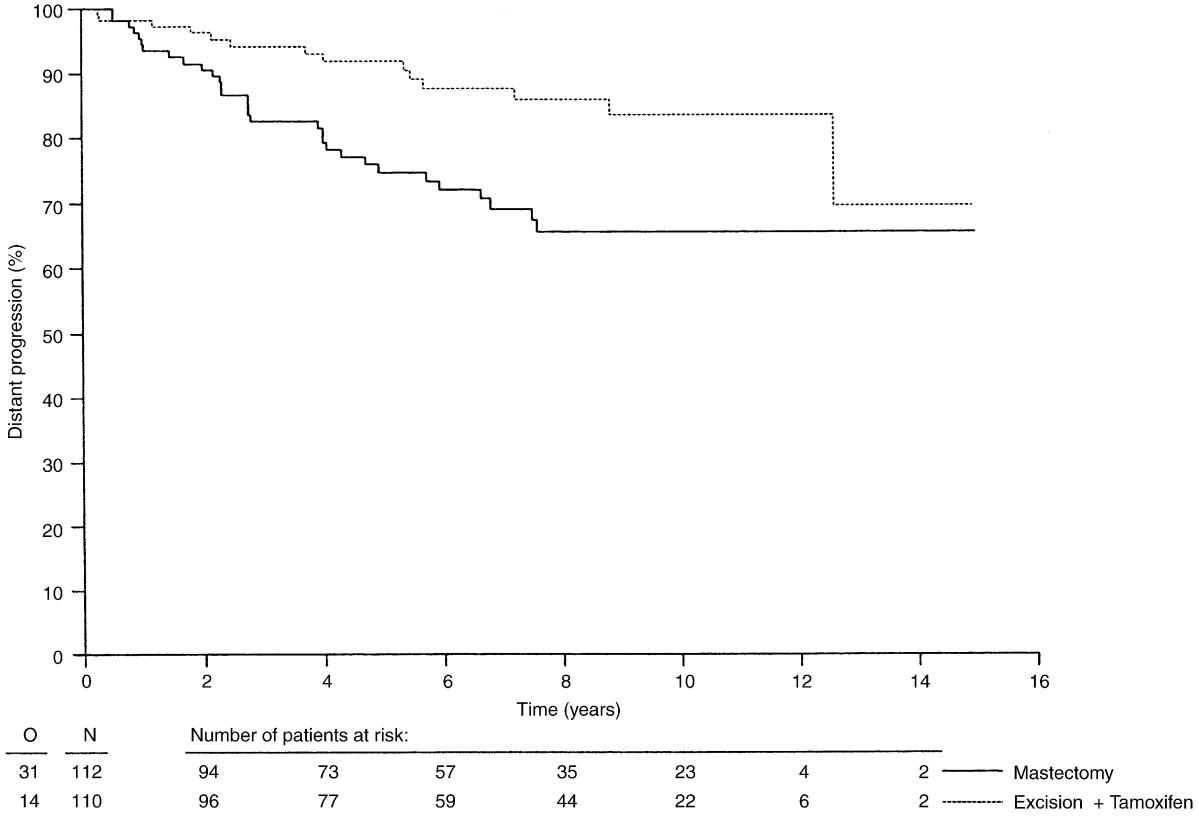

Fig. 4. Time to distant progression of mastectomy and WLE + T cases.

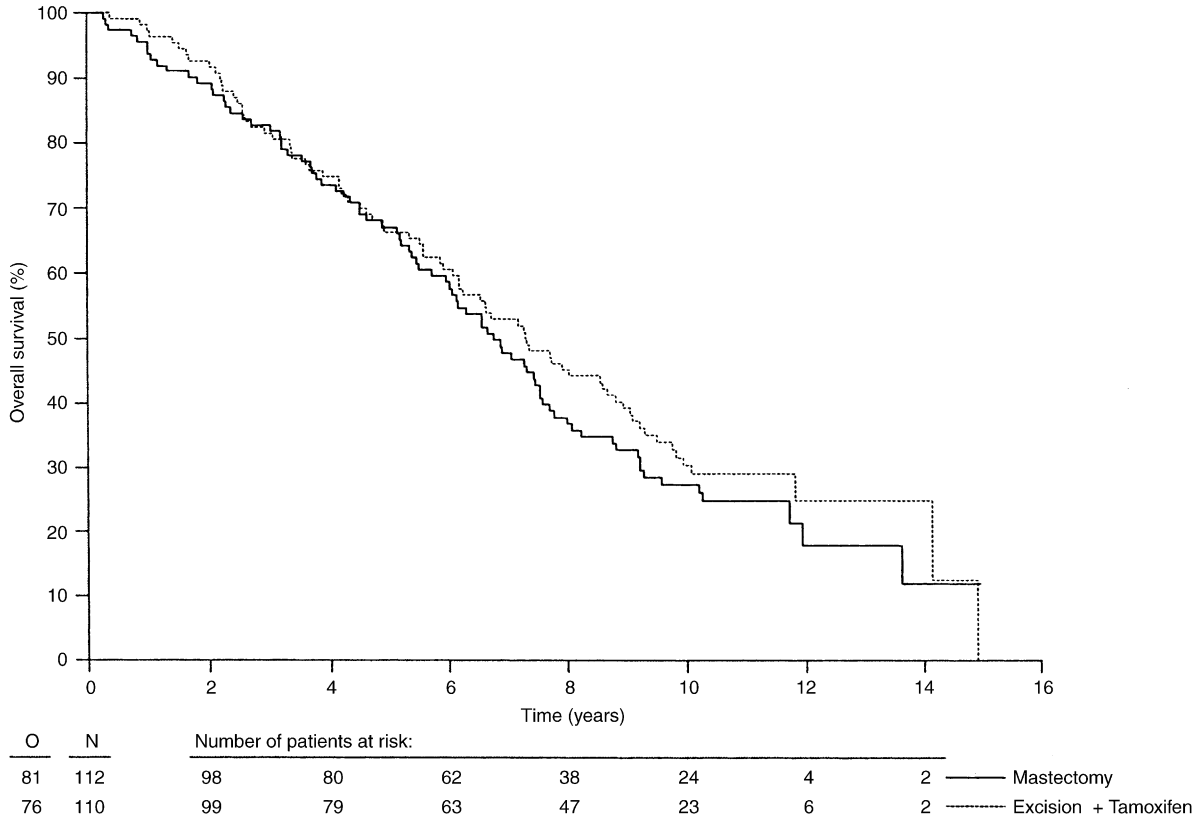

Fig. 5. Overall survival of mastectomy and WLE + T cases.

Table 2
Type of first relapse and causes of death in 10850

Type of first relapse	Mastectomy	WLE + T
No relapse	72 (64%)	76 (69%)
Relapse	40 (36%)	34 (31%)
Loco-regional (1st)	14 (13%)	26 (24%)
Distant	24 (21%)	5 (5%)
Local and distant	2 (2%)	3 (3%)
Cause of death		
Malignant disease	33 (41%)	19 (25%)
Cardiovascular	31 (38%)	30 (39%)
Infection	4 (5%)	6 (8%)
Other chronic disease	1 (1%)	3 (4%)
Other	10 (12%)	13 (17%)
Unknown	2 (2%)	5 (7%)
Total	81	76

in the WLE + T had both local and distant progression at the same time.

A summary of outcomes is given in Table 3 which shows no significant difference between the MRM and WLE + T groups in terms of time to progression and progression-free survival (0.548 and 0.982, respectively). In the WLE + T group, there was a borderline non-significant elevated risk of loco-regional relapse (hazard rate 1.717, $P = 0.068$). Risk of distant relapse was significantly diminished in the WLE + T group (hazard rate 0.426, $P = 0.006$).

3.1. Univariate analysis

Thirteen possible prognostic variables were considered: age (70–74, 75–79, 80–84, $\geqslant 85$ years), World Health Organization (WHO) performance status (0 vs. $\geqslant 1$), tumour laterality (right vs. left), tumour site (upper outer vs. upper inner vs. lower outer vs. lower inner vs. central), T stage (T1 or T2 vs. T3 or T4), N stage (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. grade 2 vs. grade 3), nodal status (0 positive nodes vs. $\geqslant 1$), ER status ($\leqslant 10$ vs. > 10), PR status ($\leqslant 10$ vs. > 10) and number of days from first symptom to randomisation (< 61 vs. $\geqslant 61$). Only three were significant for overall survival, namely age ($P < 0.001$), PR level ($P = 0.002$) and ER level ($P = 0.019$). Risk of death increased with age, although in the oldest group there was a fall in the hazard ratio that might be due to the small number of patients in this category. Oestrogen and progesterone levels of 10 or more were associated with a lower risk of death. Performance status was of borderline significance ($P = 0.057$), with an increased risk of death in those with PS > 1. For time to progression, the significant variables were nodal status ($P < 0.001$), N stage ($P = 0.038$) and tumour grade ($P = 0.042$), with a higher risk of progression for patients with one or more positive nodes, N stage different from N0 or increasing grade.

3.2. Multivariate analysis

Variables were considered for possible inclusion in the Cox's model if they were significant on univariate analysis, with an α-level of 20%, had importance from a medical viewpoint and if no more than 10% of values were missing. This excluded ER/PR because of missing values, and tumour grade as this information was only

Table 3
Comparison of endpoints in 10850

Endpoints	No of patients	No of events	Median time to event (years)	Hazard ratio estimates	95% CI	*P* value
Time to progression						
Mastectomy	112	40 (36%)	–	1	0.551–1.374	0.584
WLE + tamoxifen	110	34 (31%)	–	0.870		
Progression-free survival						
Mastectomy	112	86 (77%)	5.4	1	0.743–1.356	0.982
WLE + tamoxifen	110	84 (76%)	4.9	1.004		
Time to loco-regional progression						
Mastectomy	112	18 (16%)	–	1	0.954–3.092	0.068
WLE + tamoxifen	110	29 (26%)	–	1.717		
Time to distant progression						
Mastectomy	112	31 (28%)	–	1	0.227–0.801	0.006
WLE + tamoxifen	110	14 (13%)	–	0.426		
Duration of survival						
Mastectomy	112	71 (72%)	6.7	1	0.646–1.209	0.001[a]
WLE + tamoxifen	110	76 (69%)	7.3	0.884		

P value for the common logrank test for overall survival: 0.440.
[a] Modified logrank test H0: $r < 1.51$ (1-sided 95% confidence interval (CI): 0–1.150).

Table 4
Salvage treatment after relapse

	Mastectomy	WLE + tamoxifen
Relapse	40	34
Loco-regional relapse cases	14	26
Distant relapse	26	8
Salvage surgery		
Yes	9 (23%)	16 (47%)
No	24 (60%)	15 (44%)
Unknown	7 (18%)	3 (9%)
Hormone therapy		
Yes	24 (60%)	13 (38%)
No	8 (20%)	17 (50%)
Unknown	8 (20%)	4 (12%)
Chemotherapy		
Yes	1 (3%)	1 (3%)
No	27 (68%)	28 (82%)
Unknown	12 (30%)	5 (15%)
Radiotherapy		
Yes	6 (15%)	7 (21%)
No	24 (60%)	22 (65%)
Unknown	10 (25%)	5 (15%)

Table 5
Randomised trials of treatment for breast cancer in older women

Trial	Follow-up	Surgery arm	Tamoxifen arm
St George's Hospital	6 years	$n=100$	$n=100$
Local relapse/progression		44%	56%
Breast cancer deaths		15	17
Other deaths		13	16
Nottingham City Hospital	12 years	$n=65$	$n=66$
Local relapse/progression		38%	81%
Breast cancer deaths		22	20
Other deaths		24	25
CRC Elderly Trial	12.3 years	$n=223$	$n=223$
Local relapse/progression		21%	46%
Breast cancer deaths		21%	28%
Other deaths			
GRETA Trial	3 years	237	236
Local progression		6%	25%
Deaths		48	41
EORTC 10850	11 years	$n=112$	$n=110$
Relapse/progression		40 (36%)	34 (31%)
Breast cancer deaths		33 (29%)	19 (17%)
Other deaths		48 (43%)	57 (52%)
EORTC 10851	11 years	$n=82$	$n=82$
Relapse/progression		24 (29%)	56 (68%)
Breast cancer deaths		19 (23%)	23 (28%)
Other deaths		41 (50%)	27 (33%)

The figures given for trial 10850 and 10851 correspond to the number of overall relapses/progression (and not to the number of local relapses/progression). CRC, Cancer Research Campaign; EORTC, European Organization for Research and Treatment of Cancer. GRETA, Group for Research on Endocrine Treatment in the Elderly.

available for patients with infiltrating ductal tumour, and nodal status as this information was available only for those treated by mastectomy. The possible prognostic factors included in the model were age, performance status, axillary nodes other concomitant disease and randomised treatment. For time to progression, the only variable remaining in the model after backward elimination was the axillary nodal status, patients with a classification other than N0 having a hazard ratio of 1.624 ($P=0.040$). To analyse the effect of treatment, a stratified model was fitted with axillary nodes as a stratification variable. This stratified model shows no treatment effect according to time to progression (Hazard Ratio: 0.896, $P=0.0639$, 95% CI = 1.624 (1.023–2.577); 0.896 (0.566–1.417)).

In terms of overall survival, after backward elimination all explanatory variables were removed from the model except for age. A model fitted with age as the only variable shows that patients in the most elderly group had the highest mortality hazard ($P<0.001$). After stratification for age, the modified logrank test still rejected the null hypothesis of non-equivalence, confirming that survival was similar between the treatment groups.

3.3. Management after progression

In the trial protocol, it was suggested that patients who developed loco-regional relapse after mastectomy should be treated by either surgery or radiotherapy and should they develop distant relapse the first-line treatment should be tamoxifen. For those in the WLE + T group, locoregional relapse was to be treated by mastectomy, whenever possible and distant relapse according to local protocols. Local treatments given after first progression are indicated in Table 4. Within the MRM group, 9 (23%) of the relapsed cases had surgical treatment, but only 6 (15%) were treated with radiotherapy. Of the WLE + T cases that relapsed, 16 (47%) underwent surgery and 7 (21%) received radiation. After relapse, endocrine therapy was used in 24 (60%) of the mastectomy group and 13 (38%) of the WLE + T group.

4. Discussion

This was the first prospective randomised trial of treatment for operable breast cancer in which tumorectomy and tamoxifen 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 10.5 years (range 0–15.0), the results suggest an equivalence of the two forms of treatment in terms of overall survival. In addition, we were not able to show a difference between the two treatment arms in term of time to progression.

Nevertheless, these results mask the fact that there were more loco-regional relapses in the WLE + T group, but significantly fewer distant relapses. The increased local relapse rate was in part because treatment was not selected on a basis of ER status and it is now clear that this is the major determinant of patients deriving benefit from tamoxifen [11]. Some of the ER- cases will have had residual disease after WLE which will have been non-responsive to the tamoxifen and hence manifested subsequently as a loco-regional or distant relapse.

The increased distant recurrence rate in the mastectomy group was a consequence of these cases receiving no adjuvant therapy since this was the decision at the time of trial design, based on the available data. Since this study commenced, four randomised trials have been reported, all of which compared tamoxifen alone with some form of surgery [12–14] and the results of these are summarised in Table 5. The St George's Hospital trial compared wide excision or total mastectomy with tamoxifen alone and was first published when 116 patients had been entered with a median follow-up of 3 years [12]. At that time, the relapse rate and overall survival in the surgery group was similar to that in the tamoxifen-treated group. The study was criticised because the surgery was not standardised, in that for patients with smaller cancers, total mastectomy was performed in 18% and wide excision in 82%. Among those with larger tumours, total mastectomy was carried out in 67% and wide excision in 33%. Of the patients treated surgically by wide excision, breast relapse occurred in 35%. It was therefore argued that the study had shown tamoxifen was the equal of inadequate surgery [15]. After a median follow-up of 6 years, the trial had accrued 200 patients, of whom 100 were 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.

The second trial was conducted in Nottingham and patients were treated by either tamoxifen (40 mg daily) or by wedge mastectomy [13]. After a median follow-up of 24 months, 47% of the tamoxifen group were alive without recurrence compared with 70% of the wedge mastectomy group. Mortality rates for the 2 groups were similar, 11 versus 15%. At a mean follow-up of 65 months, there was a significantly increased failure rate for local control in the tamoxifen arm, with 59% developing local relapse or progression, compared with 30% of the wedge mastectomy group [17]. Mortality rates for the two groups were similar, 41 versus 42%. The most recent update after a median follow-up of 145 months showed no difference in terms of overall survival, but significantly better local control in the surgery group: 38% of these had developed local relapse whereas 81% of the tamoxifen group had relapsed or progressed [18].

In the Cancer Research Campaign (CRC) Trial, both arms received tamoxifen, and was first reported in 1991 when there were 381 participants with a median follow-up of 34 months [14]. At that time, the overall survival of the tamoxifen only and the surgery plus tamoxifen groups was similar as was quality of life as measured by a socio-demographic questionnaire and the General Health Questionnaire (GHQ). A change of management as a result of recurrence was necessary in 21% of the surgery and tamoxifen group, but by 35% of the tamoxifen alone group.

After a median follow-up of 12.3 years, when there were 446 participants, significantly more of the tamoxifen group needed a change of treatment (46 versus 21%) [19]. Furthermore, 28% of the tamoxifen group had died compared with 21% of the surgery and tamoxifen group and this difference just reached statistical significance ($P = 0.048$). The largest clinical trial had thus shown that tamoxifen led to an increased mortality from breast cancer. This was a strong argument against the use of tamoxifen for older women with breast cancer who were fit enough to have a predicted survival of more than 12 months.

The Group for Research on Endocrine Treatment in the Elderly conducted the GRETA trial in which 473 patients aged >70 years were randomised to either a loading dose of tamoxifen (160 mg) followed by 20 mg daily ($n = 236$) or to surgery plus tamoxifen ($n = 237$) [20]. 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 the present EORTC 10850, no mortality difference was found, although there was a significantly improved time to distant progression in the WLE + T group and normally it would be expected that this would manifest in time as an overall survival advantage. That this was not seen may be in part because of deaths from other diseases. The study gives cautious support for the use of wide local excision and tamoxifen for older women. Currently the decision to use tamoxifen would be based upon the patient having an ER-positive tumour [21] and provided that this is the case, mastectomy may be avoided in the majority of older women.

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Appendix

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	A. Hennipmah	Academic Ziekenhuis Utrecht
	T.A.W. Splinter	Dijkzigt Rotterdam
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