

Mastectomy or Tamoxifen as Initial Therapy for Operable Breast Cancer in Elderly Patients: 5-Year Follow-up

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135 consecutive patients aged over 70 years with operable primary breast cancer (clinically maximum diameter 5 cm) were randomised to either wedge mastectomy or tamoxifen 20 mg twice daily as initial therapy. The mean time from randomisation is now 65 months. There was no difference between the two groups in terms of overall survival or cause of death. Likewise, the groups were similar for site of initial metastatic disease and the probability of developing metastatic disease. However, failure of locoregional control was significantly greater in the tamoxifen group. The optimum treatment for elderly patients with operable breast cancer includes mastectomy.

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INTRODUCTION

A NUMBER OF studies, the majority non-randomised, have reported on the use of tamoxifen as initial therapy for operable breast cancer in elderly patients [1-10]. The rationale for this approach is that in such patients the oestrogen receptor concentration of the tumour is high [2] and therefore they are likely to respond to endocrine therapy. It is proposed that tamoxifen may keep the tumour under control for prolonged periods. It is hoped that for the majority of patients this delay of surgery will exceed their life expectancy, while for the others salvage surgery will be possible.

We have previously reported the early results of a randomised trial comparing surgery vs. tamoxifen as primary therapy in elderly patients with operable (stage I or II) breast cancer [4]. The present report updates this study in which the mean time from randomisation of patients is now 65 months.

PATIENTS AND METHODS

Description of this study group has been reported in detail [4]. In summary, 135 consecutive patients with operable breast cancer (maximum tumour diameter <5 cm), aged over 70 years and assessed fit for surgery were entered into the study. Patients were randomised to receive either tamoxifen 20 mg twice daily ($n = 68$) or wedge mastectomy ($n = 67$) as initial therapy. Wedge mastectomy was performed as described in our previous report [4]. In each group there were two incorrect randomisations [4]. Analysis of results is based therefore on 66 patients in the tamoxifen group and 65 in the surgery group. The two groups were similar for age of the patients and for volume and site of the primary tumour upon entry into the study [4].

Patients were followed up regularly in our outpatient clinic as previously reported. As noted in our first report, a small number of these elderly patients return to the care of their general

practitioners because of age or infirmity or because they move out of the area to live with relatives. The general practitioners of all such patients were contacted and the current state of disease (or the state of the disease at death) was established.

Assessment of response to tamoxifen was as previously described. At each clinic visit the size of the tumour was measured in two perpendicular diameters. The tumour area was calculated as the product of the largest diameter (cm). In essence, complete response was where the primary tumour disappeared completely, partial response where the surface area (product of maximum tumour diameter in two perpendicular planes) reduced by at least 50% and static disease where the surface area decreased by less than 50% and increased by less than 25% (in all cases with no new lesions appearing). Patients were assessed as showing complete or partial response or static disease only where the minimum duration of response or static disease was 6 months, as recommended by the British Breast Group [11]. All patients are now assessable for response.

As in our initial paper we also report the "best assessment" of response. This takes account of patients with static disease after 6 months who go on to develop a partial response, and patients with a partial response after 6 months who subsequently obtain a complete response. All patients continued on tamoxifen until the tumour showed progression. The protocol for subsequent therapies after failure of either initial therapy has also been described previously [4].

RESULTS

The response of the tumour in patients treated initially with tamoxifen is shown in Table 1. 59% of patients showed a response of a minimum duration of 6 months, with 67% of patients attaining a response as judged by the "best assessment". 26% of patients failed to show any response to tamoxifen.

There was no difference in survival between the two groups (Fig. 1). At 5 years the 95% confidence limits were 12.8% for the tamoxifen group and 13% for the wedge mastectomy group. 28 patients have died in each group. This is over double the number of deaths reported in our earlier publication. For each patient the cause of death was reviewed either by consulting the hospital clinical records or the general practitioner or his notes.

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Table 1. Response in patients treated initially with tamoxifen

	Assessment at 6 months n(%)	Best assessment n(%)
Complete response	28 (42)	33 (50)
Partial response	11 (17)	11 (17)
Static disease	10 (15)	5 (7)
Progression	17 (26)	17 (26)

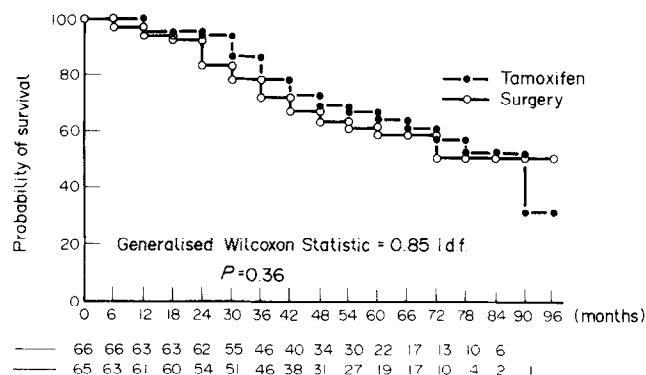


Fig. 1. Survival by primary treatment (Mx/Tam).

The cause of death was allocated to 1 of 3 groups: (1) metastatic breast cancer, (2) not breast cancer but recurrent disease present at death, (3) not breast cancer, no recurrent disease at death. For the tamoxifen group the numbers of patients in each of these three groups were 15, 4 and 9, respectively, while for the surgery group they were 16, 1 and 11, respectively: there was no significant difference between the two groups.

Of the 66 patients who received tamoxifen, 16 (24%) have developed metastases compared with 22 (34%) of the 65 patients who had surgery as initial therapy. There was no difference in the site of initial metastatic disease (Table 2) or in the probability of developing metastasis from the time of commencing initial therapy (Fig. 2).

Loco-regional recurrence in the surgery group was compared with loco-regional progression in the tamoxifen group. There was a highly significant difference in the probability of failure of loco-regional control in favour of the group treated by surgery (Fig. 3). At 5 years the 95% confidence limits were 13.2% for the tamoxifen group and 13% for the wedge mastectomy group. The site of recurrence/progression is shown in Table 3. In 34 out of 40 patients in the tamoxifen group the tumour progressed

Table 2. Metastases by initial therapy

	Tamoxifen	Mastectomy
No metastases	50	43
Bone metastases	4	3
Lung metastases	2	6
Bone and lung metastases	1	0
Visceral metastases	9	13

Tamoxifen vs. mastectomy (metastases or no metastases): $\chi^2 = 1.04$; 1 d.f.: $P = 0.31$.

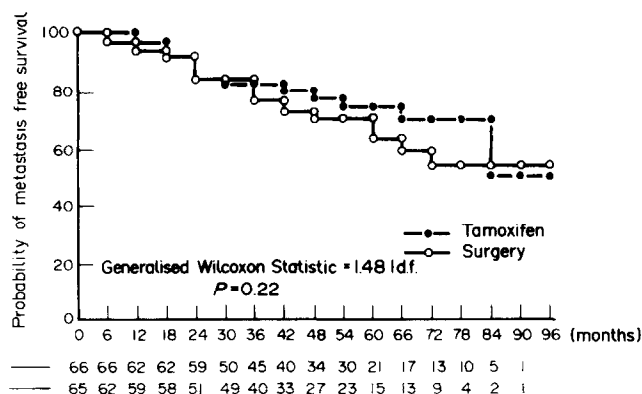


Fig. 2. Metastasis free survival by primary treatment (Mx/Tam).

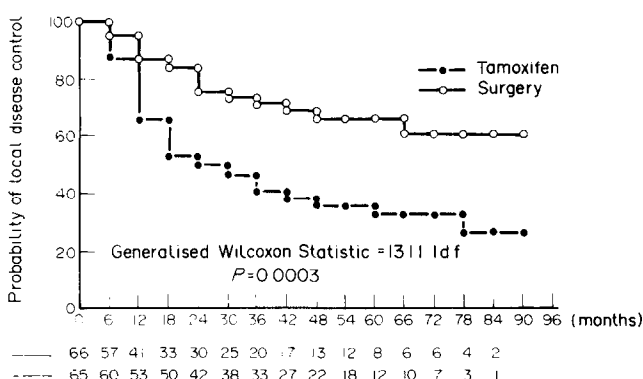


Fig. 3. Local disease control by primary treatment.

locally in the breast. In the surgery group half of the recurrences were in the regional lymph nodes.

We previously reported that histological grade of the primary tumour was a significant factor in determining the survival of patients treated by wedge mastectomy: with further follow up this finding is confirmed (Gehan's generalised Wilcoxon's statistic = 10.23; 2 d.f.: $P = 0.006$). In addition, histological grade predicted both metastatic disease (Gehan's generalised Wilcoxon's statistic = 6.71; 2 d.f.: $P = 0.03$) and loco-regional failure (Fig. 4) (Gehan's generalised Wilcoxon's statistic = 9.44; 2 d.f.: $P = 0.009$).

10 patients in the tamoxifen group did not crossover to have a wedge mastectomy on local progression of disease. In 3 patients the tumour was locally too advanced, 1 patient was medically unfit for surgery and 6 patients who had remained in response to tamoxifen for >12 months received megestrol acetate as second-line therapy. Of the patients treated with megestrol acetate, 1 had a complete response, and 3 had a period of stable

Table 3. Loco-regional recurrence by initial therapy

	Tamoxifen	Mastectomy
Local only	34	8
Regional only	0	9
Loco-regional	6	3

Tamoxifen vs. mastectomy: $P < 0.0001$.

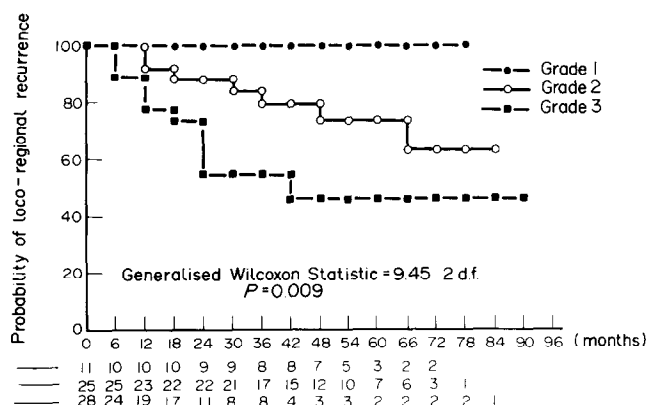


Fig. 4. Loco-regional recurrence by grade of primary tumour.

disease although, all have since progressed and in 2 patients the treatment was discontinued when the patients developed thrombo-embolic disease and diabetes mellitus, respectively. In the mastectomy group no patient was unsuitable for tamoxifen on crossover.

DISCUSSION

Elderly patients are excluded from the UK national breast screening programme on the basis of age. It is therefore to be expected that such patients will continue to present symptomatically with tumours of similar size as reported in this study rather than with smaller screen-detected tumours found in a screened population. The results and conclusions from the study are therefore relevant in the continuing debate regarding the optimal treatment of elderly patients with operable breast cancer.

We have shown no difference in overall survival of elderly patients treated initially by either tamoxifen or surgery. There was no difference in the cause of death between the two groups. Likewise, there was no difference in the probability of developing metastases or in the site of metastatic disease. However, there was a highly significant difference in loco-regional control in favour of the mastectomy group. This was despite a high initial response rate in the primary tumour to tamoxifen and the fact that in the mastectomy group regional lymph nodes were excised only if they were symptomatic at the time of primary surgery. It is worth noting that the majority of recurrences in the tamoxifen group were local in the breast. In the surgery group half the loco-regional recurrences were in the regional lymph nodes. It is therefore possible that with more aggressive surgical treatment this regional recurrence rate could be reduced.

Even with a mean time from randomisation of 65 months the majority of patients treated initially with tamoxifen have required mastectomy. The final rate of local treatment failure is expected to continue to increase with further follow up.

This study was started before routine measurement of oestrogen receptor concentration in the primary tumours by fine-needle aspiration was available as a means of predicting response to endocrine therapy [12]. It may be possible using this method to identify tumours with very high oestrogen receptor concentrations which will be controlled on tamoxifen until the patient dies of another condition. However, we believe that at present, outside of a study context, the initial treatment of elderly patients with operable breast cancer should include mastectomy. While it was not addressed in this study, the authors can see no reason why tamoxifen could not be used as adjuvant therapy to mastectomy. In patients unfit for surgery at presentation tamoxifen seems the most appropriate first-line therapy.

This study now, with a longer follow-up, supports our earlier conclusions [4] that systemic endocrine therapy with tamoxifen holds no advantage over local surgery as initial therapy in terms of patient survival or the development of metastatic disease. Surgery on the other hand gives significantly better loco-regional control and all patients are suitable for tamoxifen as subsequent therapy.

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