Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer

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Abstract

Study objective—Comparison of tamoxifen and mastectomy in treatment of breast cancer in elderly patients.

Design—Randomised trial of treatment of operable breast cancer by wedge mastectomy or tamoxifen, with median follow up 24 and 25 months respectively (range 1-63).

Setting—University hospital; most patients from primary catchment area.

Patients—135 consecutive patients with breast cancer aged over 70 with operable tumours (<5 cm maximum diameter); 68 were allocated to tamoxifen group and 67 to mastectomy group. Histological diagnosis by biopsy. Two incorrect randomisations in each group. Patient characteristics similar in the two groups and all under care of one surgical team.

Interventions—Mastectomy group received wedge mastectomy plus excision of symptomatic axillary lymph nodes. Tamoxifen group received continuous treatment with tamoxifen 20 mg twice daily. Patients in tamoxifen group received wedge mastectomy if there was sign of local progression. Those in mastectomy group received further excision or radiotherapy for locoregional recurrence and when local treatments had been exhausted or metastatic disease diagnosed they received tamoxifen.

End point—Treatment efficacy was assessed by local control of disease and by survival.

Main results—Mortality from metastatic cancer in tamoxifen group was 7 (10·6%) and in mastectomy group 10 (15·3%) (NS). There was no difference in survival between the two groups. In mastectomy group 70% remained alive and free of local recurrence at 24 months; in tamoxifen group only 47% remained alive and free of local progression. In mastectomy group locoregional recurrence occurred in 16 patients and metastatic disease in 13; in tamoxifen group locoregional progression occurred in 29 patients and metastatic disease in seven.

Conclusions—As a high proportion of patients treated with tamoxifen eventually required surgery treatment of elderly patients with breast cancer should include mastectomy. Optimum treatment may include both mastectomy and tamoxifen.

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Introduction

The standard treatment for operable breast cancer in elderly patients is surgery. The efficacy of tamoxifen as primary treatment was first reported by Preece *et al*[1] and this has been confirmed by further studies.[2,3] Direct comparison between treatment with tamoxifen and by surgery is difficult, as treatment groups have been non-randomised and often non-comparable—for example, tamoxifen has been used for patients who are unfit for surgery. Since the report by Preece *et al*[1] the need for a prospective randomised study has been acknowledged. We report a prospective study in which patients were randomised to receive either surgery or tamoxifen as initial treatment.

Patients and methods

During 1982-7 elderly patients who had operable breast cancer were entered into a prospective randomised study that compared wedge mastectomy with tamoxifen as a primary treatment. Breast cancer was diagnosed histologically from trucut biopsy samples. The criteria for entering patients into this study were that they had operable breast cancer (maximum diameter of tumour <5 cm); that they were aged >70 years; and that they were assessed as being fit for either treatment at the time of entry into the study.

Patients who were judged to fulfil these criteria were randomised to receive either tamoxifen 20 mg twice daily or a wedge mastectomy. Randomisation was performed using cards with the treatment (25 wedge mastectomy and 25 tamoxifen) hidden behind tabs. A tab was removed, and the patient received the treatment thus chosen. Wedge mastectomy entails holding up the breast and cutting around the base, with primary skin closure but without undercutting the flaps, and removing all breast tissue up to the clavicle as in a simple mastectomy (fig 1). A very small amount of breast tissue is therefore left. The operation is, however, essentially the same as a mastectomy, leaving a flat chest wall. Wedge mastectomy was carried out in preference to simple mastectomy in these elderly patients because it is quicker to perform and associated with less morbidity. Axillary lymph nodes, when present, were excised only if patients were symptomatic.

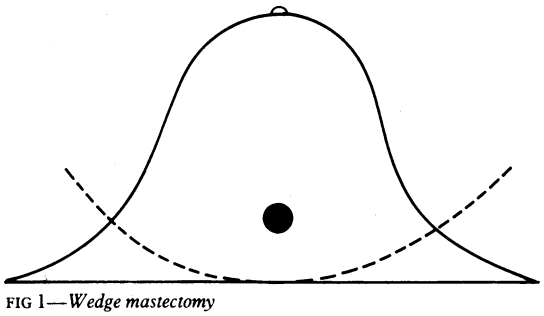

FIG 1—*Wedge mastectomy*

Of the 135 consecutive patients who were entered into the study, 68 were randomised to receive tamoxifen as initial treatment and 67 to receive wedge mastectomy. There were two incorrect randomisations for similar reasons in each group; one patient was aged

TABLE I—*Comparison of patients treated by mastectomy and with tamoxifen*

	Treatment	
	Mastectomy	Tamoxifen
Age (years):		
Mean	76	75
Median	76	75
Range	70-88	70-87
Side:		
Left	39	38
Right	26	28
Volume (cm^2):		
<4	18	13
2-9	24	35
-16	21	16
-25	2	2
Follow up (months):		
Mean	25	26
Median	24	25
Range	1-57	2-63

<70 years, and another had a tumour >5 cm in diameter. Sixty six patients who received tamoxifen and 65 who received wedge mastectomy were therefore assessable. The two groups were similar for age, volume or site of the primary tumour on entry into the study, and duration of follow up (table I). All patients were under the care of one surgeon (RWB) and were followed up in one of two clinics both run by the same surgical team. Patients who had a wedge mastectomy were routinely followed up in the postmastectomy clinic every three months for 18 months and then every six months. Patients who were treated with tamoxifen were seen in another primary breast cancer clinic at similar intervals. At each visit the size of the tumour was measured in two perpendicular diameters and the area (cm^2) calculated as the product of these two measurements.

It is our policy to follow up all patients who have breast cancer until death. One hundred and twenty two patients were either still currently attending the clinic or had been followed up regularly until death. Thirteen patients, after a period of follow up at the clinic, had returned to their general practitioner's care because of age or infirmity or because they had moved out of the area to live with relatives. The general practitioners of all 13 patients were contacted, and the current state of disease or state of disease at death was established.

In patients who were initially treated by wedge mastectomy further surgery was the preferred treatment for local or regional recurrence. Radiotherapy was used when surgery failed to control local or regional recurrence. Treatment with tamoxifen was started in patients treated by wedge mastectomy when local treatments had been exhausted or when the patient had developed systemic disease. Patients initially treated with tamoxifen received a wedge mastectomy on local recurrence followed by further surgery or radiotherapy, or both, if either were subsequently required for locoregional disease. Treatment with megestrol acetate 160 mg twice daily was started when local treatments had been exhausted, if the recurrent primary tumour was >5 cm in diameter, or if the patient had developed systemic disease.

The response to tamoxifen was assessed after six months of treatment unless there was evidence of earlier progression. Fifty seven patients were assessable (see table II); nine patients had non-progressive disease but had been taking tamoxifen less than six months. The "best assessment" of response to tamoxifen took account of patients who had static disease at six months going on to show a partial or complete response and those who showed a partial response at six months going on to show a complete response. Patients who responded or were static continued to take tamoxifen until the tumour progressed.

TABLE II—*Response in 57 patients treated initially with tamoxifen (figures are numbers (percentages) of patients)*

	Assessment at six months (n=57)	Best assessment (n=57)
Complete response	22 (39)	25 (44)
Partial response	9 (16)	11 (19)
Static disease	9 (16)	4 (7)
Progression	17 (30)	17 (30)

The histological grade of the primary tumour was assessed by one pathologist (IOE) with Elston's modification of the Bloom and Richardson method. This takes account of three histological features—namely, tubule formation, nuclear pleomorphism, and mitotic frequency.[4] The grade was assessed in 64 of the 65 tumours of patients who were randomised and assessable for wedge mastectomy as initial treatment and in 23 of 26 patients who after local progression while being treated with tamoxifen had a wedge mastectomy.

The log rank test was used to calculate survival from the date of initial treatment. When other statistical tests were used these are clearly indicated.

Results

Table II shows the response rate to tamoxifen as initial treatment. There was no operative mortality in the group who had a wedge mastectomy. There was no difference in survival between patients treated initially with tamoxifen and those treated by wedge mastectomy, though the 95% confidence intervals were wide, especially over the later years in the study (fig 2).

There was no significant difference between the number of deaths in the wedge mastectomy group (17) and that in the tamoxifen group (10) ($\chi^2=2{\cdot}42$, 1 df, $p>0{\cdot}05$). Table III shows the causes of death for each group. To date, 13 patients treated initially by wedge mastectomy and seven treated initially with tamoxifen have developed metastatic disease either as first evidence of recurrence or after local or regional recurrence, or both (see tables IV and V); the time taken for metastases to occur and survival after metastases is unknown in one of the patients treated by wedge mastectomy. There was no difference between the patients who received wedge mastectomy and those who received tamoxifen in the time until systemic

TABLE III—*Cause of death in both groups*

	Treatment	
	Mastectomy	Tamoxifen
Metastatic disease	10	7
Non-malignant:		
Breast cancer present	2	2
Breast cancer absent	5	1

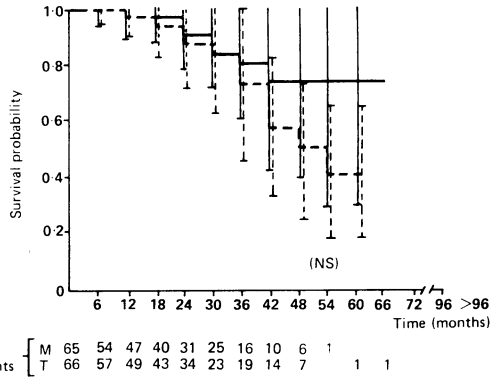

FIG 2—*Survival in both treatment groups. ——=Initially treated with tamoxifen. -----=Initially treated by mastectomy. NS=Not significant*

TABLE IV—*Clinical course and further treatments of patients treated initially by mastectomy (n=65)*

	No (%) of patients	
Clinical course:		
No recurrence	42 (65)	
Local recurrence	3 (4)	8 patients subsequently developed metastatic disease
Regional recurrence	7 (11)	
Locoregional recurrence	6 (9)	
Metastatic disease (no local or regional recurrence)	5 (8)	
Contralateral primary carcinoma	2 (3)	
Total treatments:		
Wedge mastectomy	65	
Further surgery	16	
Radiotherapy	5	
Tamoxifen	15	
>1 hormone treatment	5	

TABLE V—*Clinical course and further treatments of patients treated initially with tamoxifen (n=66)*

	No (%) of patients	
Clinical course:		
Primary tumour controlled	35 (53)	
Local progression	20 (30)	5 patients subsequently developed metastatic disease
Locoregional progression	9 (14)	
Metastatic disease	2 (3)	
Total treatments:		
Tamoxifen	66	
Wedge mastectomy	26	
Further surgery	7	
Radiotherapy	13	
>1 hormone treatment	13	

recurrence ($\chi^2=1{\cdot}29$, 1 df) or in survival from the time that systemic recurrence was diagnosed ($\chi^2=0{\cdot}085$; 1 df).

Tables IV and V show the details of recurrent disease and the number of treatments required in patients treated initially by wedge mastectomy and with tamoxifen respectively. Figure 3 shows the risk of a subsequent wedge mastectomy for local recurrence in patients treated initially with tamoxifen. The comparison is with the risk of local recurrence in the group randomised to receive mastectomy. Twenty six patients had a salvage mastectomy after local progression with tamoxifen; table VI gives the details of further recurrent disease after salvage mastectomy.

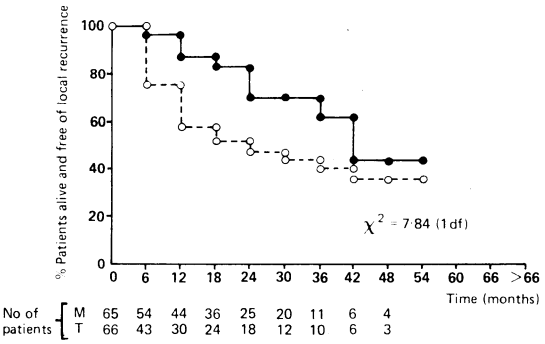

FIG 3—*Percentage of patients alive and free of local recurrence in both treatment groups. ○=Initially treated with tamoxifen. ●=Initially treated by mastectomy*

TABLE VI—*Recurrent disease in 26 patients treated by wedge mastectomy because of local progression after initial treatment with tamoxifen*

	No (%) of patients (n=26)
No recurrence	15 (57)
Regional recurrence	4 (15)
Locoregional recurrence	2 (8)
Metastatic disease:	
No locoregional recurrence	2 (8)
Locoregional recurrence	2 (8)
Regional recurrence	1 (4)

In the group treated by wedge mastectomy 12 patients (19%) had grade 1 tumours, 25 (39%) had grade 2 tumours, and 27 (42%) had grade 3 tumours. Grade of tumour was an important factor in determining the disease free interval and survival in the group who received wedge mastectomy (figs 4 and 5). In the group treated with tamoxifen 15 of 23 patients (65%) who later had a wedge mastectomy for local progression had grade 3 tumours.

The initial area of the primary tumour was important in determining survival in the group treated with tamoxifen: patients who had small tumours (<4 cm^2) at presentation survived significantly longer than patients who had larger tumours (fig 6). The initial area

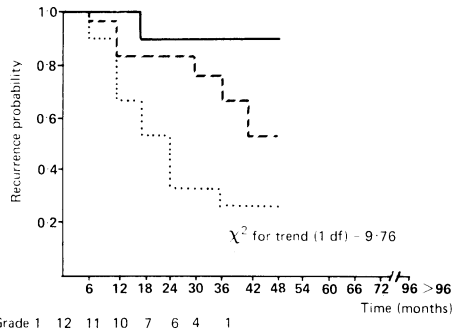

FIG 4—*Disease free interval compared with grade of the primary tumour in group treated initially by mastectomy. ——=Grade 1 tumour. – – – –=Grade 2 tumour. – – – –=Grade 3 tumour*

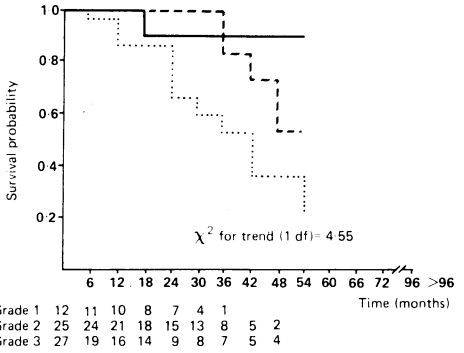

FIG 5—*Survival compared with grade of primary tumour in group treated initially by mastectomy. ——=Grade 1 tumour. – – – –=Grade 2 tumour. – – – –=Grade 3 tumour*

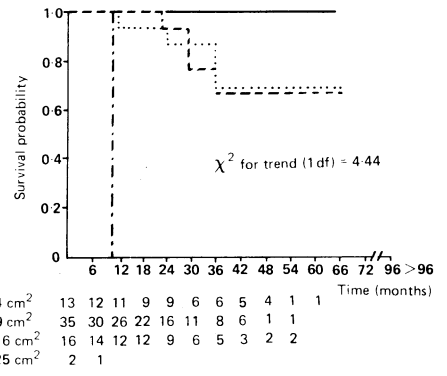

FIG 6—*Initial area of primary tumour compared with survival in group treated initially with tamoxifen. ——≤4 cm^2. – –≤9 cm^2. – – – –≤16 cm^2. —·—·—≤25 cm^2*

of the primary tumour was not important in affecting the survival of patients treated initially by wedge mastectomy.

Discussion

Tamoxifen is reported to be an appropriate primary treatment for elderly women who have operable breast cancer,[2] but it has never been compared with wedge mastectomy in a prospective randomised study. We have shown no difference between the overall survival of patients treated by each method nor in the time until systemic recurrence. Wedge mastectomy gave significantly better control of primary disease than tamoxifen: at 24 months only 47% patients treated with tamoxifen were alive and free from local recurrence that required mastectomy.

There were further disadvantages in using tamoxifen as initial treatment—namely, patients who are receiving tamoxifen and in whom the disease is responding or remaining static require indefinite treatment with regular assessment, and on progression the

patient may not be fit for surgery or the tumour may be inoperable, as in two of our patients. By contrast, no patient who received wedge mastectomy and who had recurrent disease was unfit to receive tamoxifen.

The rate of local or regional recurrence, or both, after wedge mastectomy at a mean follow up of 25 months was 24%, comprising 4% local recurrence only, 11% regional recurrence only, and 9% local and regional recurrence. The Cancer Research Campaign (Kings/Cambridge) trial for early breast cancer reported corresponding recurrence rates after simple mastectomy alone of 16% at 24 months and 26% at 48 months.[5] In patients aged under 70 treated by simple mastectomy in our unit the rate of local or regional recurrence, or both, at 48 months was 24%,[6] comprising 12% local recurrence only, 7% regional recurrence only, and 5% local and regional recurrence. The increased rate of recurrence in our wedge mastectomy group compared with that seen after simple mastectomy is due mainly to more regional recurrence rather than local recurrence. This might have been expected, as lymph nodes were excised at the time of wedge mastectomy only if they were symptomatic. Elderly patients who have palpable glands at the time of wedge mastectomy should perhaps have these excised at that time. Wedge mastectomy does not seem to result in an increased rate of local recurrence yet retains the advantages of rapidity and reduced morbidity compared with simple mastectomy.

The number of deaths and the causes were similar in each treatment group; the number of deaths due to metastatic disease were again similar in both groups. There was no significant difference between the two groups in the time until metastatic disease occurred or in survival once metastatic disease was diagnosed, though the numbers were small and confidence intervals wide.

The grade of the tumour was a significant factor that affected both the disease free interval and survival in the wedge mastectomy group; similar data from a Nottingham study of a much larger group of patients, who were aged less than 70 years and had operable breast cancer, showed similar correlations.[4] In a prospective study multivariate analysis has confirmed grade as being the most important prognostic factor in operable disease in patients aged less than 70 years.[7] Of 23 patients treated initially with tamoxifen and in whom the grade of tumour was assessed from a mastectomy specimen after local progression, 15 (65%) had grade 3 tumours. This compared with 42% of the patients treated initially by mastectomy who had grade 3 tumours. More grade 3 tumours seem to progress during tamoxifen treatment than grade 1 and grade 2 tumours. The results of this study confirm the importance of the grade of the primary tumour, even in elderly patients.

Previous studies have shown a high incidence of tumours rich in oestrogen receptors in elderly patients.[2] In patients who have locally advanced breast cancer tamoxifen has a reported response rate of 44%.[8] The high response rate (>60%) to tamoxifen in elderly patients who have operable disease may be due to the high concentration of oestrogen receptors, though other factors such as the size of the tumour must also be considered: in this series patients who had small tumours treated initially with tamoxifen seem to have fared better than patients who had large tumours. This may support the use of adjuvant hormone treatment.

As yet there is no single factor that can be used to predict accurately which tumours might be well controlled by tamoxifen for long periods, though further investigation of factors such as size, grade, and oestrogen receptor state taken together might identify a subgroup of patients in whom tamoxifen would give good local control.

Tamoxifen seems to be an alternative primary treatment for elderly patients who have breast cancer, in that survival is not significantly different from that of patients treated by wedge mastectomy. Surgery, however, has advantages over tamoxifen as an initial treatment, as wedge mastectomy controls primary disease in more patients, and on recurrence of local disease patients treated by wedge mastectomy are always fit to take tamoxifen, irrespective of the state of the patient or disease. Furthermore, tamoxifen has no advantage over wedge mastectomy in respect of the time until systemic recurrence. We believe that in elderly patients who have operable breast cancer mastectomy is the initial treatment of choice if they are fit for surgery. In elderly patients who are unfit for surgery, however, tamoxifen seems to be the most appropriate first line treatment. Small, well differentiated tumours fared better than larger grade 3 tumours.

This study supports the findings of Herbsmen *et al* that survival in older and younger patients who have breast cancer is comparable[9] and also the conclusions of Donegan that breast cancer in the elderly is no less malignant than in younger women and that optimum treatment is indicated in all patients irrespective of age.[10] Because most of the group treated with tamoxifen ultimately required mastectomy we believe that the treatment of elderly patients who have operable breast cancer should include mastectomy. The optimum treatment may include both mastectomy and tamoxifen.

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(Accepted 25 May 1988)

ONE HUNDRED YEARS AGO

IN a recent address, Dr. T. D. Crothers referred to the various temperance revivals in America and England as physiological cyclones. Enthusiasts believed on each occasion that the power and influence of alcohol were destroyed for ever. Yet as each wave of enthusiasm receded, it was seen that intemperance flourished apace. The same ebb and flow of the tide of temperance is still witnessed. As the whirlwind of revolution clears the air and prepares the way for the advance of truth, all these revivals and missions have directed the attention of the thoughtful to the study of the whole subject. The voice of science is beginning to teach that inebriety is a disease, and must be treated accordingly. Four medical societies and one quarterly journal are devoted exclusively to the study of the laws which govern inebriety. This increasing recognition of the disease aspect of intemperance is only the re-affirmation of a truth urged centuries ago, but the times were not then propitious for its reception and growth.

(*British Medical Journal* 1888;i:655)