Our study showed that neoadjuvant chemotherapy allowed a conservative approach of locoregional treatment in about 85% of the patients, with exclusive radiotherapy or with surgery plus radiotherapy.

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Tamoxifen as Sole Therapy for Primary Breast Cancer in the Elderly Patient

Norbert A. Foudraine, Lia C.G. Verhoef and Jos T.M. Burghouts

In a retrospective study the data concerning 40 patients, with primary operable breast cancer were analysed. The mean follow-up of the patient group was 29 months. All patients received tamoxifen only. 17 (43%) reached remission and there was stable disease in 16 (40%). 7 (18%) showed progression, although they have had stable disease for at least 18 months. There were 1 local, 1 distant and 5 local plus distant progressions. 3 patients required salvage mastectomy. The mean progression-free interval was 33 months. Death was attributable to breast carcinoma in only 6 patients (15%). The 3-year survival was 47.2%. We conclude that primary treatment with tamoxifen as a sole therapy is acceptable in operable breast carcinoma for those patients for whom surgery is contraindicated or who refuse surgery.
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INTRODUCTION

LITTLE IS known about the best treatment of operable breast cancer in the elderly patient. In most clinical trials concerning the primary therapy of breast cancer patients of 70 years or older are excluded. It is not clear whether the results of these trials can be extrapolated to older patients. At present the standard treatment for stage I or stage II breast cancer is mastectomy or lumpectomy followed by irradiation. It has been questioned whether elderly patients should always receive the same standard treatment. Just because of age older patients have been treated differently from younger women [1, 2]. There are several reasons to treat the elderly patient less aggressively. Elderly patients are often unfit for surgery because of concomittant diseases which increase the risk of operation. A non-surgical therapy would avoid this risk. It is expected that the natural course of disease is less aggressive and slower in elderly patients than in younger ones because of greater incidence of oestrogen receptor positivity [3–5]. In view of their short life expectancy it is argued that protracting the course of disease by conservative treatment would be sufficient to avoid unacceptable complications.

Few authors have reported the results of tamoxifen as sole therapy for operable breast cancer in the frail and elderly patient [6–14]. Remission could be achieved in 25% to 68% of patients 70 years or more during a period of 7–55 months [6–14]. In two randomised trials elderly patients were treated with tamoxifen only or surgery. Gazet *et al.* found no difference in survival between patients treated with lumpectomy or with tamoxifen [10]. In a study of Robertson *et al.* survival did also not differ significantly between patients treated with wedge mastectomy or tamoxifen only, but loco-regional control was better in the former group, although the difference was not statistically significant [13].

Actually we do not know which patients can safely be treated with tamoxifen only as primary therapy. Because life expectancy of octogenarians is still around 8 years, there is a high probability that loco regional control can not be maintained during the rest of their life. Delay of surgery will only enlarge the risk of surgery once it will have become unavoidable.

We were interested in the survival and the possible occurrence of locoregional problems in old female patients who were treated with tamoxifen only. We compared our results with surgical treatment published in the literature so far.

PATIENTS AND METHODS

Patients' characteristics

Between March 1983 and August 1990, 58 patients were treated with tamoxifen only for breast cancer. 18 patients were excluded from the analysis because 13 patients had a T_4, 2 had a N_3 tumour and in 3 patients there was evidence for metastasis.

All tumours were clinically classified according to UICC staging. We report the data of the surmained 40 patients. In all patients breast cancer was suspected by a clinically palpable mass and/or mammography. The diagnosis was confirmed histologically by trucut needle biopsies or cytologically by fine needle aspirations. In all patients an X-ray of the thorax and biochemical blood studies were performed to exclude distant metastasis. Clinical measurement of the largest tumour diameter was compared with the largest diameter on mammography. During the follow up tumour diameter was measured by palpation.

Treatment and end points

All patients were treated with tamoxifen only. The doses given varied from 10 mg to 30 mg daily. In the beginning 30 mg was given but after 1985 the standard dose was reduced to 20 mg daily. Dose reduction was tried when side effects were reported. Patients who showed progression were further treated with surgery, chemotherapy or radiation therapy depending on the extensiveness of the disease. All patients were followed at 3–6 month intervals.

Tumour remission was defined as a shrinkage of 50% or more of the largest original diameter. There was stable disease when the largest dimension was between 50% of 125% of the original diameter. There was progression when distant metastasis appeared or the tumour reached 125% of the original largest diameter anytime during the follow up. If possible, tumour specimens were assayed for oestrogen and progesterone receptor levels. Survival and progression free intervals were computed by the actuarial method [15]. Survival was compared with survival of a cohort of women of comparable age who died by all causes in the general Dutch population [16]. When patients died without known metastasis it was supposed that their cause of death was not breast cancer. In all other cases death was attributed to breast cancer.

Table 1. Data of 40 women with breast cancer treated with tamoxifen only

Age (years)	Mean	82.4
	Range	68–93
TNM T_1		5
T_2		30
T_3		7
N_0		28
N_1		10
N_2		2
Histology		
Ductal		18
Lobular		17
Colloid		1
Unclassified		6
Oestrogen receptor content		
Positive (>10 fm/mg protein)		19
Negative		6
Unknown		17
Follow-up (months)	Mean	29
	Median	25
	Range	1–103

Data of 40 women with breast cancer treated by tamoxifen only

RESULTS

The 40 patients studied had a mean age of 82.4 years (range 68–93 years) (Table 1). 2 patients had bilateral tumours, accounting for a total of 42 tumours. During the treatment period, with a mean of 25 months (range 1–103 months) 30 patients received tamoxifen 10 mg twice a day, 9 patients three times daily, and 1 patient because of subjective side effects 10 mg once daily. Mean follow-up was 29 months (range 1–103 months).

Evidence of cardiopulmonary or severe neurological disease was the reason not to perform surgery in 14 patients. 15 patients refused surgery and in 5 there was a combination of both reasons. In 6 patients age was the only reason to treat the patient hormonally. Clinical staging correlated with the radiographically determined tumour stage in 26 of 42 tumours (65%). Palpation of the tumour overestimated the tumour size in 9 of 42 tumours (30%). In 5 patients the mammography was not suspected for malignancy. Palpation of the tumour was underestimated in 2 cases.

5 patients had a T_1 tumour, 30 a T_2 and 7 a T_3 tumour. There was no lymphadenopathy in 28, 10 patients had a N_{1a}, and 2 patients a N_2 stage lymphadopathy. The diagnosis of breast cancer was confirmed by tissue examination in all patients. Histological classification showed ductal carcinoma in 18, lobular carcinoma in 17, a colloid carcinoma in 1 and undetermined malignancy in 6 tumours. If possible oestrogen and progesterone

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Table 2. Results of tamoxifen treatment

Remission	17 (42.5)
Stable	16 (40.0)
Progression	7 (17.5)
Local recurrence only	1 (2.5)
Distant metastasis only	1 (2.5)
Combination	5 (5.0)
Death:	
All causes	18 (45.0)
Breast cancer	6 (15.0)

Results of tamoxifen treatment

receptor content was assessed. In 19 tumours the oestrogen receptor content was positive (>10 fm/mg protein), negative in 6, and unknown in 17. The progesterone receptor content was positive in 18, negative in 4 and unknown in 20 tumours. Results of therapy are presented in Table 2.

During follow-up remission was achieved in 17 (42.5%) patients in a mean period of 8.9 months. Stable disease was observed in 16 patients. 7 patients showed progression after they had been stable for a mean period of 33 months (range 18–66 months). In 1 patient there was local progression only, in 1 patient there was only distant tumour growth. In 5 patients there was a combination of distant and local progression. 3 of them were treated by salvage surgery (mastectomy), 3 have been treated with second line hormonal therapy and 1 patient has been treated with chemotherapy.

There was no difference in tumour behaviour depending on their oestrogen or progesterone receptor content, (data not shown), but statistical analysis was not performed because of the small numbers of patients in each group.

During follow-up 18 (45%) patients had died. In 2 patients death was definitely attributable to mammary carcinoma, and in 4 breast cancer as cause of death could not be excluded because of the presence of distant metastasis. In 9 patients death was certainly not attributable to mammary carcinoma. In 3 patients the cause of death was unknown, but none of them had signs of metastasis.

The overall survival for these 40 patients was 47.4% after 3 years (Fig. 1). When patients dying from non-malignant causes were excluded the disease specific survival after 3 years was 70.1% Progression free survival after 3 years was 24%.

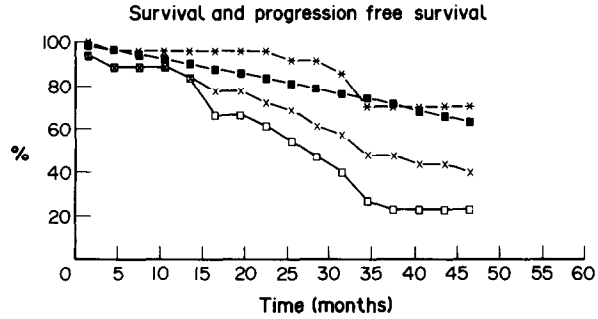

Fig. 1. Overall and disease specific survival and progression free survival by actuarial method. asr = age and sex adjusted survival rate (data by CBS). * = survival, -■- = asr, -□- = progression free, ★ = tumour spec. survival.

DISCUSSION

Nowadays, the standard treatment of operable breast cancer is mastectomy or tumourectomy followed by irradiation. Whether this therapy is also optimal in the elderly patient is not well known. Higher mortality rates after surgery [17], different tumour behaviour, and a shorter life expectancy are factors influencing treatment choice [2, 18]. The percentage of breast tumours that are oestrogen receptor positive increases with the age of the patient. Therefore, it can be expected that elderly patients will have a high response rate to hormonal therapy. Remission rates varying between 25 and 74% have been reported (Table 3).

A few randomised studies comparing surgery and primary tamoxifen treatment have been published. Gazet *et al.* [10] did not find a difference in local recurrence rate or probability of survival between a surgically and a hormonally treated group. However, this study compared simple tumourectomy, which is generally considered an inadequate treatment, with tamoxifen only. Consequently, in this study high local recurrence rates were reported: 25% and 23% after 3 years in the patients treated with, respectively tamoxifen and surgery. From this comparison it cannot be concluded that primary tamoxifen is a safe treatment in all elderly patients.

In the study by Robertson *et al.* the rate of local progression in patients treated by tamoxifen only exceeded the recurrence rate in patients treated by wedge mastectomy [13]. Survival was not impaired by hormonal therapy. The difference in local progression was not statistically significant, but the short follow-up and small patient numbers do not allow firm conclusions.

Bates *et al.* [14] compared various surgical treatments followed by adjuvant tamoxifen with tamoxifen only. A statistically significant higher local recurrence rate after 3 years was reported in the patients treated by tamoxifen only. Again, survival was not impaired in the hormonally treated group.

In our patient group, remission was achieved in 17 (42.5%) of patients in a mean period of 8.9 months. This is lower than the remission rate found by most other investigators (Table 3). Local progression was recorded in 6 (15%) patients and in only 3 (7.5%) salvage surgery was mandatory. This local recurrence rate is lower than generally found in patients who have been treated with tamoxifen only (Table 3). The lower remission rate and local progression rate in our patient group might be explained by the low overall survival time and short mean follow-up.

Life expectancy of women of comparable age in the general population is around 8 years (Fig. 1) [16]. Most patients in our group suffered from concomitant diseases. Their mean survival time was only 35 months, resulting in a 3-year overall survival of 47.2%. In the literature an absolute survival rate of 44% to 85% is found for patients age 60 or older who have been treated with surgery [20, 24, 25]. Since the mean age in our series is 82.4 years, it is not surprising that overall survival was comparable with the lower boundary of this range.

The 3-year disease specific survival, however, was 70.1%. This is comparable with the results achieved by surgery and with normal life expectancy of the normal female population of comparable age. (Fig. 1) [2]. Our lower overall survival rate and progression free survival can be attributed to an increased death rate due to non-malignant disease (Fig. 1).

Comparison of published treatment results of various minimal treatment regimens in elderly patients with breast cancer is cumbersome, because the reasons to opt for a non-standard treatment can vary widely. It is clear, however, that tamoxifen

Table 3. Literature review

Reference		*n*	Mean age (years)	Remission* (%)	Local progression (%)	All progression (%)	T-stage	3-year survival (%)
6		67	78	47	—	13	?	?
7		27	80	74	10	19	T1	?
8		161	77	61	—	14	T3	70†
10	T	60	75	—	25	38	T4	70
	S	56	77	—	38	55	T4	71
13	T	68	75	55	44	47	T2	75
	S	67	76	—	13	35	T2	80
11		52	>70	52	—	35	T4	—
12		30	82	60	30	30	T3	60
14	T	183	76	25	27	31	T3	80
	TS	171	76	—	10	17	T3	80

T, tamoxifen; S, surgery, TS, tamoxifen and surgery; *n*, number of patients; *complete and partial remission; all, loco-regional and distant progression; †5-year survival.

only can never cure the disease. Therefore, it can only be a reasonable option when prevention of tumour progression is the main goal in the light of a limited life-expectancy. Stable disease or remission could be achieved in our patient group in 82.5% of all cases with tamoxifen only. Within a period of 18 months all patients stayed progression free.

High age alone can usually not justify the choice for primary tamoxifen treatment, since life-expectancy is still several years, and there is a high probability that sole tamoxifen will only delay the problem. If major surgery is too risky, lumpectomy under local anaesthesia followed by irradiation should be considered. Gazet reported a high local recurrence rate after simple tumourectomy, but other studies have shown that local recurrence risk can significantly be lowered by post-surgical irradiation [19, 20]. It is surprising that this alternative for elderly patients has not been investigated more extensively, since it can be expected that this treatment option would yield a good local control, while the risks of major surgery can be avoided. However, if life-expectancy is relatively short, tamoxifen as sole therapy might form an acceptable alternative for patients who are suffering from serious illness or who refuse surgery.

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