Prognostic Factors in Elderly Women with Metastatic Breast Cancer Treated with Tamoxifen

An Analysis of Patients Entered on Four Prospective Clinical Trials

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BACKGROUND. Information regarding prognostic factors and survival in elderly women with metastatic breast cancer treated with tamoxifen is limited.

METHODS. The data from 4 prospective clinical trials were analyzed, including information on 396 postmenopausal women with advanced breast cancer who received tamoxifen as initial therapy for metastatic disease. Emphasis was placed on 184 elderly patients (age greater than 65 years) to characterize the response to therapy, time to progression (TTP), overall survival (OS), prognostic factors, and treatment-related toxicity.

RESULTS. Among 363 patients with measurable or evaluable disease, the objective response rates were higher in the elderly patients (46% versus 33%, $P = 0.06$); but age did not achieve significance in a logistic regression analysis ($P = 0.1$). The median TTP (10.5 months versus 6.2 months, log rank $P = 0.002$) and OS (35.7 months versus 28.8 months, log rank $P = 0.02$) were superior in the elderly cohort. In multivariate analysis, age at diagnosis approached statistical significance ($P = 0.055$) for TTP but was not significant for OS ($P = 0.17$). Among elderly patients, disease free interval (DFI) (greater than 5 years), dominant disease site (soft tissue), prior adjuvant chemotherapy, positive estrogen/progesterone receptor (ER/PgR) and performance status (PS) were independent prognostic factors. Hot flashes were common in both younger and older cohorts (25% versus 33%, $P = 0.14$), while anorexia (14% versus 22%, $P = 0.04$) and mood changes (2% versus 6%, $P = 0.03$) were more common in the elderly patients.

CONCLUSIONS. There was no indication that elderly women with metastatic breast cancer treated with tamoxifen have a poorer outcome with regard to response rate, TTP or OS; in fact, they appeared to have a slightly better prognosis although this was not significant after adjustment for other prognostic factors. In elderly patients, DFI, PS, positive ER or PGR, and dominant disease site are independent prognostic factors. ***Cancer* 1996; 77:683–90.** © *1996 American Cancer Society.*

KEYWORDS: prognosis, elderly, metastatic, breast cancer, tamoxifen.

The number of elderly breast cancer patients has increased significantly in the last few decades.[1,2] Data from the Surveillance, Epidemiology, and End Results (SEER) program suggests that older women present more frequently with advanced disease and that more than 40% of newly-diagnosed breast cancer in the United States occurs in women age older than 65 years.[3] However, patients age older than 65 years have frequently been excluded from clinical trials and, therefore, information on this group is limited. Knowledge gained from studies involving a majority of younger women may not be completely relevant to older women due to complicating effects of factors such as comorbidity, functional impairment, differences in host physiology, competing causes of mortality, and pos-

sible differences in the biology of breast cancer in the elderly.[1,4]

While numerous studies have attempted to identify prognostic features at the time of recurrence in patients with breast cancer,[5-14] only some of these reports have focused on elderly women.[11-14] The effect of age on the prognosis of women with advanced breast cancer is controversial. Some reports indicate no effect of age on prognosis,[5] others report a worse prognosis,[9-10] and still others report a better prognosis with increasing age.[11,12] However, most series are limited by heterogeneity of therapies including chemotherapy,[11-14] lack of multivariate analysis, or small numbers of elderly patients.[11] Elderly women with metastatic disease are generally treated with hormonal therapy and tamoxifen remain the preferred agent.[15] None of the previous studies, to our knowledge, have specifically analyzed prognostic features or clinical course of elderly breast cancer patients who were initially treated uniformly with tamoxifen in prospective clinical trials. Throughout the last two decades, the Mayo Clinic alone,[16,17] or in conjunction with the North Central Cancer Treatment Group (NCCTG),[18,19] has conducted four randomized trials of hormonal therapy of postmenopausal women with advanced breast cancer in which a substantial number of elderly patients (age older than 65 years) were treated. We analyzed the data on those elderly women who received tamoxifen as initial therapy for metastatic disease to characterize the response to therapy, clinical course, prognostic features, and toxicity in this important and enlarging segment of patients with breast cancer.

MATERIALS AND METHODS

Patient Population

The data set for this report comes from 4 clinical trials[16-19] in which 801 postmenopausal patients with histologically-confirmed, advanced breast cancer were randomized to receive either tamoxifen alone or with placebo (n = 396), or with another additive hormonal therapy (n = 405). To maintain uniformity of treatment, this analysis was restricted to patients treated with tamoxifen alone or with placebo. Eligibility criteria for these studies were very similar and have been previously noted. Menopause was defined as more than 12 months following last menstrual period for natural menopause, surgical castration, or at least age 50 years in case of women with prior hysterectomy without an oophorectomy in three of four studies. In the fourth study, the definition required at least five years since last menstrual period.[16] Prior additive hormonal therapy was not permitted except in one study where prior adjuvant hormonal therapy was allowed.[19] No specific exclusions were made based on presence of comorbid conditions, however, patients who were bedridden, Eastern Cooperative Oncology Group (ECOG) performance score 4, were excluded. Estrogen receptor (ER) analysis was not mandatory, but when performed was required to be positive in three studies,[16-18] and could only be negative if associated with a positive progesterone receptor (PgR) in the fourth study.[19] Response criteria were standard as previously reported. Dose and schedule of tamoxifen was identical in all four studies (10 mg orally, twice a day).

Of 396 patients randomized to receive tamoxifen alone or with placebo, 184 patients were age older than 65 years, and 212 patients were age 65 years or younger. A detailed exploratory analysis was carried out on these patients to analyze potential prognostic factors and treatment-related toxicity. The variables specifically analyzed were: age, performance status (PS), prior adjuvant therapy, disease free interval (DFI), dominant disease site, indicator lesion status, hormone receptor status (ER, PgR), response, time to disease progression (TTP), overall survival (OS), toxicity, and cause of death. In analysis of TTP, patients in whom treatment failed due to toxicity or refusal, or who died without disease progression were censored at the time of failure. Overall survival was measured from the date of randomization to death, and death was considered an event regardless of the cause.

Statistical Analysis

All statistical analyses were performed with SAS software (SAS Institute Inc., Cary, NC). Correlation between age, indicator lesion, dominant disease, DFI, PS, ER/PgR, prior chemotherapy, and prior hormonal therapy was assessed with the chi-square test (FREQ program) with two-sided P values. TTP and OS curves were generated using the Kaplan–Meier method[20] and univariate comparisons were performed with the LIFETEST program. The P values were two-sided, associated with the log rank statistic.[21] Multivariate analyses for TTP and OS were performed with the PHREG program to fit a Cox proportional hazards model.[22] A backward regression technique was used to identify the most significant prognostic factors, with variables being eliminated according to the maximum likelihood estimate. Significance was set at the 0.05 level. For assessment of variables in the Cox model, two-sided P values based on the chi-square statistic were used. For response, the backward regression technique was also employed, this time using a logistic regression model.

RESULTS

Three hundred and ninety-six patients were treated with tamoxifen in these trials. Patient characteristics, according to age categories, are shown in Table 1. The most common site of dominant disease in elderly patients (age older than 65 years) was visceral, while osseous metastases were more common in the younger cohort. The subset of very elderly patients (age 76 years and older) had a

TABLE 1
Patient Characteristics

	Age			
	≤65 % of 212	66–75 % of 120	≥76 % of 64	*P* value
Disease-free interval				
<1 year	26	32	38	
1–5 year	51	46	39	
>5 year	23	22	23	0.35
Performance score				
0–1	89	86	77	
2–3	11	14	23	0.05
Dominant disease status				
Soft tissue	14	18	28	
Osseous	46	30	30	
Visceral	41	52	42	0.006
Indicator lesion				
Measurable	60	62	72	
Evaluable	31	30	22	
Not evaluable	9	8	6	0.52
Hormone receptor (ER or PgR)				
Positive	63	62	69	
Not done	37	38	31	0.67
ER (>100)				
≤100 fmol	23	31	39	
>100 fmol	32	24	30	
Not done	45	45	31	0.05
Previous adjuvant chemotherapy	32	19	6	<0.001
Adjuvant hormonal therapy	8	2	0	0.02

ER: estrogen receptor; PgR: progesterone receptor.

TABLE 2
Response to Therapy

	Age		
Response	≤65 (%)	66–75 (%)	≥76 (%)
Measurable			
Total no. of pts.	127	75	46
CR	10 (8)	9 (12)	10 (22)
PR	40 (31)	24 (32)	14 (30)
CR + PR	50 (39)	33 (44)	24 (52)
Evaluable			
Total no. of pts.	65	36	14
CR	1 (2)	3 (8)	0 (0)
REG	13 (20)	15 (42)	3 (21)
CR + REG	14 (22)	18 (50)	3 (21)
Total CR + PR + REG*	64/192 = 33%	51/111 = 46%	27/60 = 45%

CR: complete remission; PR: partial remission; *REG: regression.

higher proportion of predominant soft tissue disease (28%). Disease free intervals and indicator lesion status (measurable versus evaluable) were similar in all three cohorts. More than 80% of the patients had a good ECOG performance score (0 or 1). Quantitative ER values were available in 55% of the younger cohort and 60% of the older cohort. A higher proportion of patients age 65 years and younger had received prior adjuvant chemotherapy (32% versus 14%). Although a distinct minority of patients had received prior adjuvant hormonal therapy, prior hormonal therapy for metastatic disease was not allowed in any of these trials.

Table 2 shows the cohorts' response to initial therapy with tamoxifen. Considering all patients with measurable and evaluable disease, the response rates were higher in the two oldest cohorts. Considering patients age older than 65 years and age 65 years and younger, the overall objective response rate was higher in the older patients, approaching statistical significance (Fisher's exact test $P = 0.06$). However, these differences were not significant when patients with measurable disease alone were considered ($P = 0.22$). A logistic regression analysis was performed to identify factors associated with objective response using age (65 years or younger versus older than 65 years), dominant disease status (soft tissue versus other), performance status (0,1 versus 2,3), disease free interval (5 years or less versus more than 5 years), prior adjuvant chemotherapy, and ER status as variables. Age was not a significant factor ($P = 0.1$).

The TTP and OS in all three cohorts are shown in Figure 1. Because of similarities between the elderly patients (age 66 to 75 years) and the very elderly patients (age older than 75 years) with respect to OS, TTP, and sample size limitations, these 2 groups were combined for further analysis. The median TTP for elderly patients (age older than 65 years) was superior to the cohort of younger patients (10.5 versus 6.2 months, log rank $P = 0.002$). Similarly, the overall median survival in elderly patients was higher than in younger patients (35.7 versus 28.8 months, log rank $P = 0.02$).

Potential prognostic factors were analyzed in the cohort of elderly patients (age older than 65 years) to determine their prognostic significance (Table 3). In the univariate analysis, dominant disease site, disease free interval, prior adjuvant chemotherapy, and performance score were significant prognostic factors both for OS and TTP. With reference to dominant disease site, patients with soft tissue disease did extremely well with a median overall survival of 59 months. Survival of patients with visceral dominant disease was not inferior to that of the cohort with osseous dominant disease (Fig. 2). A longer disease free interval was associated with a more favorable prognosis (Fig. 3). Poor performance status was associated with an adverse prognosis with a median overall survival of only 12 months in that cohort (Fig. 4). Quantitative ER value, when available, utilizing a cut point of more than 100 fmol was a significant prognostic factor for TTP ($P = 0.02$) and for OS ($P = 0.05$) in the univariate model, as

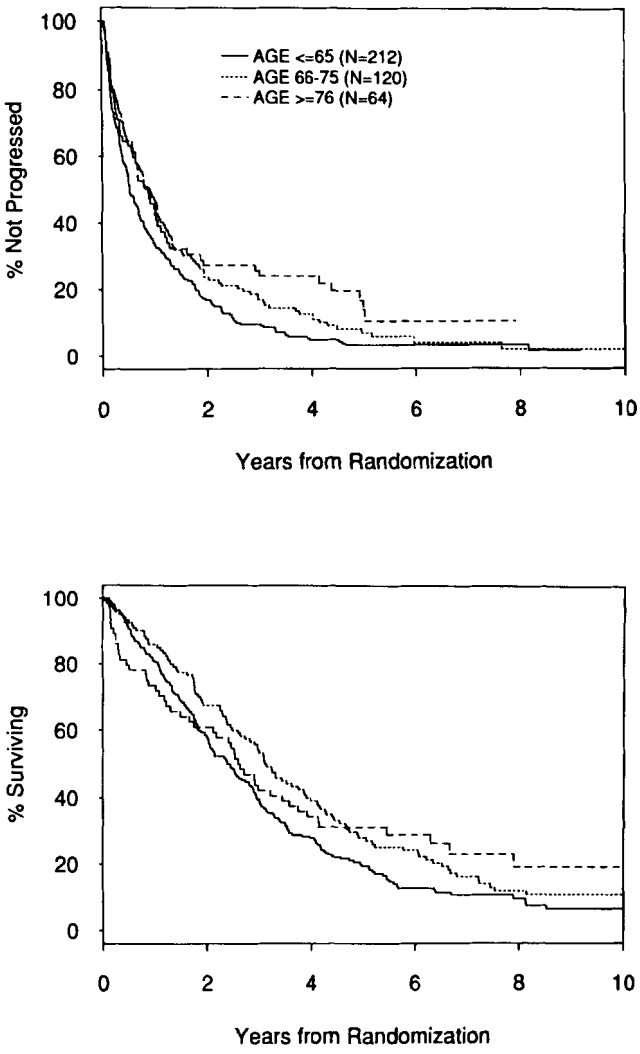


FIGURE 1. Time to progression and overall survival by age group for postmenopausal women treated with tamoxifen.

TABLE 3
Prognostic Factors: Univariate Analysis in Women (More Than Age 65 Years) Treated with Tamoxifen

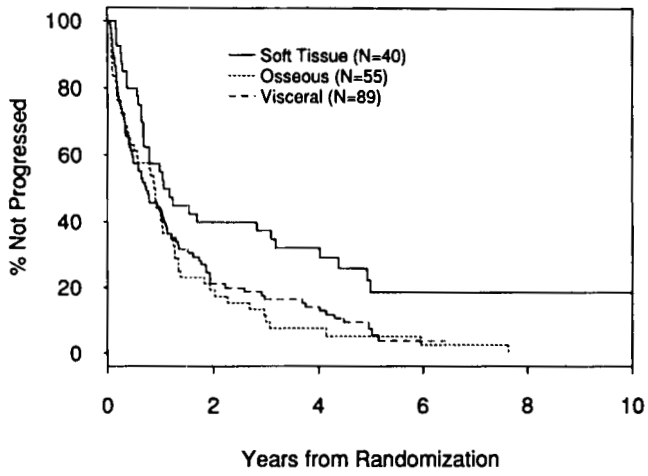
	Time to progression		Overall survival	
	Median (mos)	Log rank *P* value	Median (mos)	Log rank *P* value
Dominant disease				
Soft tissue	13		59	
Osseous	11		31	
Visceral	9	0.008	31	0.0008
Dominant disease				
Osseous	11		31	
Visceral	9	0.57	31	0.61
Dominant disease				
Soft tissue	13		59	
Other	9	0.003	31	0.0002
Disease free interval				
<1 year	8		28	
1-5 year	9		38	
>5 year	14	0.03	41	0.01
Performance score				
0-1	12		42	
2-3	3	0.001	12	<0.0001
Disease status				
Measurable	8		31	
Evaluable	13		38	
Non-evaluable	36	0.07	73	0.30
Hormone receptor				
Positive	12		35	
Not done	8	0.18	39	0.50
Estrogen receptor status				
≤100 fm	11		29	
>100 fm	14		44	
Not done	8	0.02	38	0.05
Previous adjuvant chemotherapy				
Yes	5		38	
No	11	0.30	36	0.84
Adjuvant hormonal				
Yes	15		31	
No	10	0.71	36	0.24

was the case for a cut point of 50 fmol (TTP, $P = 0.0005$; OS, $P = 0.004$), although the optimal cut off was not determined.

Results of multivariate analysis are shown in Table 4. In the initial multivariate model, including all patients treated with tamoxifen, dominant disease site (soft tissue versus other), performance status (0,1 versus 2,3), DFI (5 years or less versus more than 5 years), and prior adjuvant chemotherapy were independent variables for both TTP and OS. ER/PgR receptor status was significant for TTP ($P = 0.003$) and approached statistical significance for OS ($P = 0.08$). Age (65 years and younger versus older than 65 years) approached statistical significance for TTP ($P = 0.055$), but not for OS ($P = 0.17$). Since the patients in this analysis were derived from four sequential studies conducted over a decade, the analysis was repeated with additional stratification by study and the results did not change (data not shown).

When the analysis was restricted to elderly patients, dominant disease status (soft tissue versus others), DFI (5 years or less versus more than 5 years), and PS (0,1 versus 2,3) emerged as independent prognostic factors for both TTP and OS. ER/PgR status (positive versus unknown) was a significant variable for TTP ($P = 0.01$) but was not significant for OS ($P = 0.41$). When the analysis was repeated with stratification by study, the results were similar (data not shown).

The toxicity associated with tamoxifen therapy is shown in Table 5. As expected, tamoxifen was well tolerated with rare Grade 2 or greater toxicity. Hot flashes were somewhat more common in the younger postmenopausal



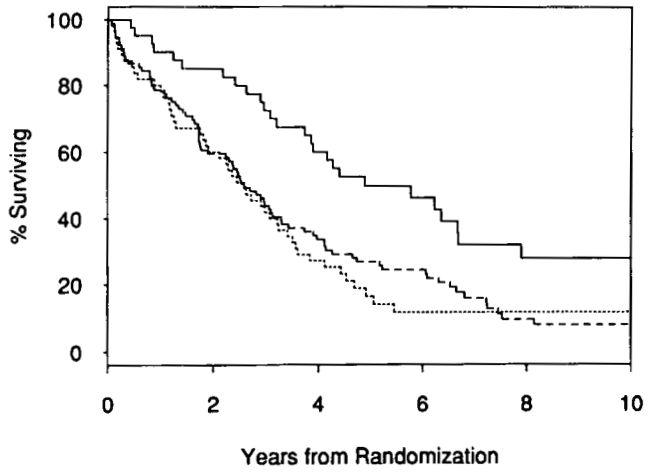
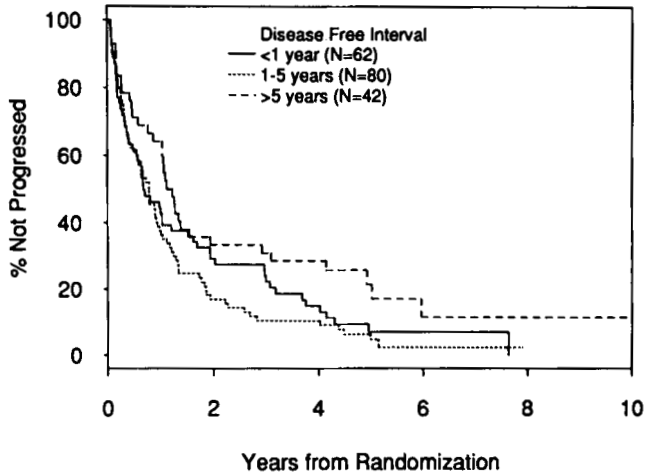


FIGURE 2. Time to progression and overall survival according to dominant disease site in the elderly cohort (age older than 65 years).



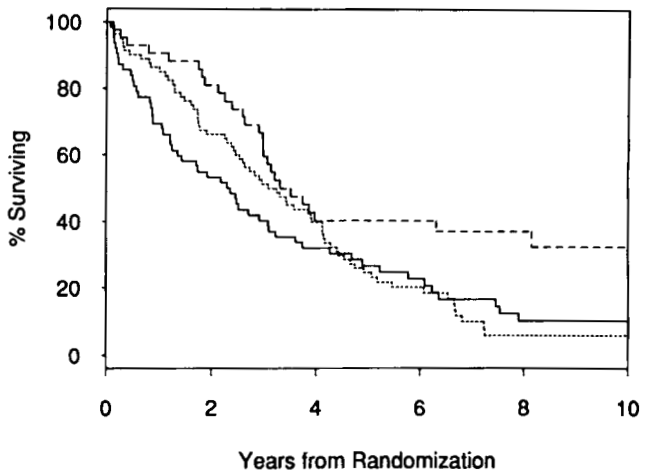


FIGURE 3. Time to progression and overall survival according to disease free interval in the elderly cohort (age older than 65 years).

women, although the difference was not significant (33% versus 25%, $P = 0.14$). In contrast, the older postmenopausal women had a higher frequency of anorexia (22% versus 14%, $P = 0.04$) and mood changes (6% versus 2%, $P = 0.03$), which may be related toxicities. Other notable toxicities included nausea, emesis, lethargy, and edema, which were equally common in both younger and older cohorts. Phlebitis was seen in only one patient. None of the patients developed endometrial cancer.

Of this cohort of 396 patients, 54 patients were still alive at last follow up. The cause of death in 335 patients (84%) was metastatic breast cancer. The cause of death in the remaining 7 patients (1.8%) was sepsis/infection (3 patients), cardiac (3 patients), and pulmonary embolus (1 patient). It is not known whether the one case of pulmonary embolus was related to tamoxifen, fortunately the occurrence of this event was rare in this series.

DISCUSSION

A review of our experience with postmenopausal women with metastatic breast cancer treated with tamoxifen in 4 prospective trials reveals that elderly patients (age older than 65 years) had a significantly superior time to progression and overall survival, and a higher response rate, which approached significance ($P = 0.06$), than younger women. This superiority, however, did not retain statistical significance when examined in multivariate analysis involving commonly employed clinical prognostic factors. Information was not available on subsequent systemic therapies after failure with tamoxifen. The impact of such therapies on survival cannot be evaluated from this study.

A limited number of studies have specifically analyzed elderly patients and included multivariate analysis

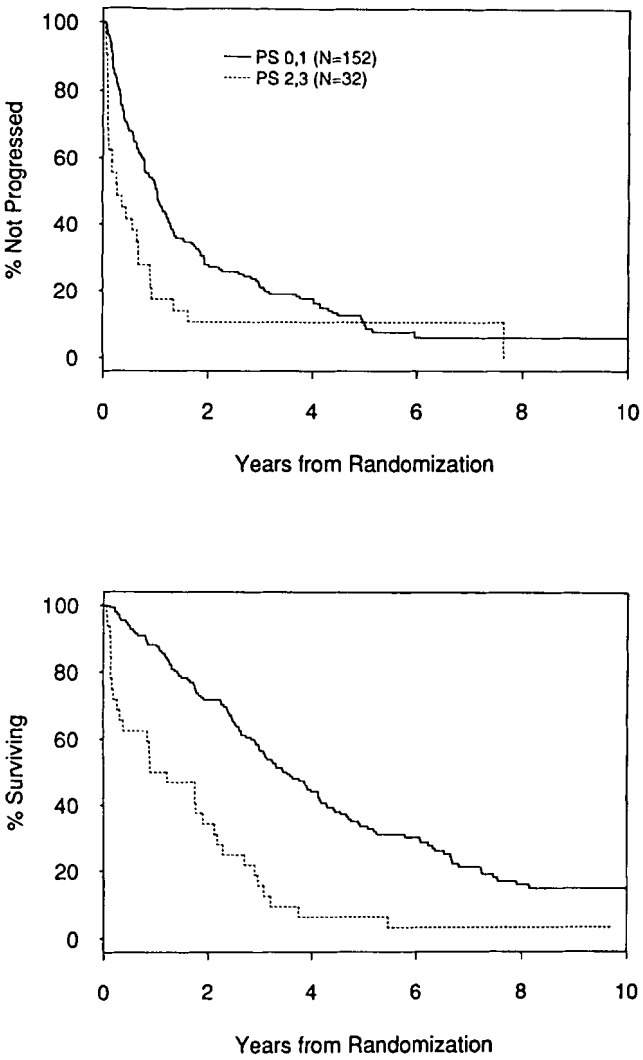


FIGURE 4. Time to progression and overall survival according to performance score in the elderly cohort (age older than 65 years).

for prognostic factors in metastatic disease. Taylor et al.[13] reported on 181 elderly patients (age older than 65 years) randomized to tamoxifen or cyclophosphamide, methotrexate, and fluorouracil (CMF) in a crossover study. No significant differences in response or survival were seen although a trend favoring tamoxifen was noted. Features associated with favorable prognosis included age 70 to 79 years, PS 0 or 1, osseous dominant disease, and DFI more than 5 years. Alberts et al.[12] evaluated 216 elderly women (age 65 years or older) and 209 postmenopausal women (age younger than 65 years) from a single institution treated with a number of regimens. Considering 114 elderly and 34 younger postmenopausal women treated with hormonal therapy only, the median survivals were 31.0 months and 16.6 months, respectively.

Considering the elderly cohort, dominant disease status, disease free interval, and performance score were independent prognostic factors. Elderly women with soft tissue dominant disease had a relatively good prognosis with a median TTP and OS of 13 months and 59 months, respectively. The outcome for patients with osseous and visceral dominant disease were similar in this study. The apparent lack of adverse prognosis with visceral disease in the elderly is interesting and unexplained, whether this was due to differences in the biology of the cancer in the elderly or sample size is unknown. Performance score was a particularly important factor. Elderly patients with a poor performance score (2 or 3) had a median survival of only 12 months.

While prospectively collected data and uniform therapy and follow-up eliminates a number of potential biases, one still exists and that is the requirement for ER positive tumors when the receptor status was known. However since more than 80% of the tumors in elderly patients are receptor positive,[4] these findings should still apply for the great majority of elderly women. Another factor potentially influencing survival in this group of patients is the extent and frequency of comorbidity. Detailed information regarding comorbidity and quality of life was not available from these trials. Since comorbidity was not an exclusion criteria in these trials, it is unlikely that the participating clinicians excluded patients with comorbid conditions. However, since only 1.8% of the deaths in this study were not directly related to breast cancer, comorbidity is unlikely to play a major role in overall survival of these patients.

Since metastatic breast cancer is incurable with current therapeutic armamentarium, potential benefit with any therapy must be weighed against associated toxicity. The toxicity analysis from this study confirms the fact that tamoxifen is well tolerated in all groups of postmenopausal women, including elderly patients. The most frequent and bothersome side effect of tamoxifen therapy, hot flashes, were somewhat less common in the elderly cohort, although the differences were not statistically significant. In contrast, anorexia and mood changes were more common in the elderly patients. The reasons for these age-related differences in toxicity are not clear and some may be related to comorbid conditions. It is not known whether the one case of fatal pulmonary embolus was related to tamoxifen, fortunately the occurrence of this event was rare in this series.

In conclusion, there was no indication that elderly women with metastatic breast cancer treated with tamoxifen have a poorer outcome with regard to response rate, TTP, or OS, rather, they appear to have a slightly better prognosis, although this is not significant after adjustment for other prognostic factors. For elderly patients, age older than 65 years, performance score, disease free interval, positive ER or PgR status, and dominant disease

TABLE 4
Multivariate Analysis

	Time to progression			Overall survival		
	Hazard ratio	95% Confidence interval	*P* value	Hazard ratio	95% Confidence interval	*P* value
All patients (n = 396)						
Age ≥66 yrs vs. ≤65	0.812	(0.614, 1.074)	0.0550	0.859	(0.645, 1.144)	0.1719
Soft tissue vs. others	0.645	(0.444, 0.938)	0.0025	0.520	(0.347, 0.779)	0.0001
DFI > 5 years	0.579	(0.413, 0.813)	0.0001	0.508	(0.352, 0.733)	0.0001
PS 2-3	1.441	(0.973, 2.113)	0.0166	1.917	(1.296, 2.837)	0.0001
ER or PgR positive	0.714	(0.536, 0.952)	0.0026	0.816	(0.606, 1.099)	0.0785
Prior adj. Chemotherapy	1.524	(1.100, 2.112)	0.0009	1.564	(1.123, 2.179)	0.0005
Age >65 Patients (n = 184)						
Soft tissue vs. others	0.542	(0.322, 0.910)	0.0023	0.453	(0.258, 0.795)	0.0003
DFI > 5 yrs	0.539	(0.314, 0.924)	0.0032	0.552	(0.312, 0.978)	0.0075
PS 2-3	2.131	(1.211, 3.753)	0.0006	2.860	(1.650, 4.958)	0.0001
ER or PgR positive	0.649	(0.419, 1.006)	0.0110	0.864	(0.548, 1.363)	0.4093
Prior adj. chemotherapy	1.546	(0.840, 2.845)	0.0658	1.309	(0.714, 2.399)	0.2522

DFI: disease free interval; PS: performance score; ER: estrogen receptor; PgR: progesterone receptor; ADJ: adjuvant.

TABLE 5
Toxicity Related to Tamoxifen

		CTC toxicity grade			
Type	Age	I	II	III	*P* value
Hot flashes	≤65	23%	10%		
	>65	16%	9%		$P = 0.14$
Anorexia	≤65	10%	4%		
	>65	11%	8%	3%	$P = 0.04$
Nausea	≤65	11%	4%	1%	
	>65	10%	5%	1%	
Vomiting	≤65	7%	2%	1%	
	>65	5%	1%		
Edema	≤65	9%	3%		
	>65	8%	6%		
Diarrhea	≤65	5%	1%		
	>65	5%	2%	1%	
Lethargy	≤65	7%	2%		
	>65	7%	1%	1%	
Neuro-mood	≤65	1%	1%		
	>65	4%		2%	$P = 0.03$

CTC: Common toxicity criteria.

status had an important effect on TTP, and all but ER/PgR effected OS. Tamoxifen is well tolerated in most elderly patients, although there may be some age-related differences in toxicity profile.

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