Original article

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Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial

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On behalf of the Italian Cooperative Group GRETA†

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Background: To evaluate the efficacy of tamoxifen as primary treatment in women aged over 70 years with operable breast cancer versus surgery followed by adjuvant tamoxifen.

Patients and methods: Patients randomly received tamoxifen alone (160 mg day 1, then 20 mg/day) for 5 years or surgery followed by tamoxifen (20 mg/day) for 5 years. Overall survival was the main study end point; secondary objectives included breast cancer survival and local control of the disease.

Results: Between 1987 and 1992, 239 patients were assigned to surgery plus tamoxifen and 235 to tamoxifen alone. Treatment arms were comparable for tumor size, clinical nodal status and performance status. At a median follow-up of 80 months 274 patients had died. No difference between groups had emerged in overall and breast cancer survival. There were 27 local progressions in the surgery plus tamoxifen group and 106 in the tamoxifen-alone group ($P = 0.0001$). In the surgery plus tamoxifen group, no difference in overall survival had emerged according to the extension of operation.

Conclusions: The long-term results of the study confirm the 3-year interim analysis already reported. Surgery (radical or minimal) followed by adjuvant tamoxifen does not modify overall and breast cancer survival as compared with tamoxifen alone in early breast cancer of older women. Because of the high rate of local progressions with tamoxifen alone, minimal surgery followed by tamoxifen appears to be the appropriate treatment in such patients. More extensive surgery is not useful. Tamoxifen alone is an adequate alternative treatment in very old or frail patients.

Key words: breast cancer, elderly, tamoxifen

Introduction

Breast cancer is the most common malignancy in women in western countries. A correlation between breast cancer incidence and age has been demonstrated, with 15–20% of new malignancies occurring in elderly women aged over 70 years [1–5].

A number of studies have evaluated the use of tamoxifen as sole treatment for operable breast cancer in elderly patients. Results were generally encouraging; hovewer, due to the small number of patients, short follow-up or lack of randomization, conclusions are difficult to draw in the older studies [6–12].

Two randomized trials showed no difference in survival between elderly patients treated with tamoxifen alone or surgery alone [9, 11]. Robertson et al. [11] found that locoreginal control was better in the surgery group, but the difference was not statistically significant; Gazet et al. [9] reported a very high rate of local relapses after surgery.

Preliminary results from the Cancer Research Campaign UK randomized trial, started in 1984, comparing tamoxifen alone versus surgery followed by tamoxifen in women aged over 70 years with operable breast cancer, showed similar conclusions [13]. In 1987 we started a new comparative trial to confirm the role of surgery followed by tamoxifen versus tamoxifen alone in a similar group of patients. A preliminary analysis at 3 years of follow-up showed similar survival, a high rate of local relapses, but a significantly lower incidence of distant metastases with tamoxifen alone [14]. Lower incidence of distant metastases was attributed to the loading dose of tamoxifen (160 mg) given on the first day of treatment in the tamoxifen-alone group with the aim of rapidly reaching the optimal plasma drug level [15].

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The results on overall survival were also confirmed by a meta-analysis of the preliminary data of our trial and that of the UK study [16, 17].

We now present the long-term results of the Italian Trial, GRETA, after a complete revision on the full set of data of local responses, distant metastases incidence and dates and causes of death.

Patients and methods

Study design

This was a randomized, multicenter phase III study that compared the efficacy of tamoxifen alone versus surgery followed by adjuvant tamoxifen in women aged over 70 years with operable breast cancer. The primary objective of this study was to compare the overall survival in the two treatment arms. Secondary objectives were to compare the event-free survival, breast cancer survival and local control of the disease. Nineteen Italian centers participated in the trial.

Eligibility

Eligibility required histological or cytological evidence of invasive breast cancer at age over 70 years. In consideration of the high probability of estrogen receptor-positive tumors in this age group, a preliminary receptor content assessment was not required. Operable disease was defined as T1, T2, T3a; N0 or N1 and absence of distant metastases as assessed by clinical examination, chest X-ray, bone scan and liver ultrasound. Patients were required to be fit for surgery and available for follow-up, and to have no history of previous or concomitant malignancy (except treated skin cancer or *in situ* carcinoma of the cervix), no prior chemotherapy and/or hormone therapy. Informed consent was required.

Treatment program

Women aged 70 years and over with operable breast cancer were randomized to receive either tamoxifen alone (160 mg loading dose day 1, followed by 20 mg daily) for 5 years or surgery followed by tamoxifen 20 mg/day for 5 years. The extent of surgery was not prescribed. Written informed consent was required.

Method of randomization

Randomization was made immediately prior to surgery centrally by phone, after confirmation of elegibility. Patients were stratified according to participant center. Allocation (ratio 1:1) was based on random number tables. Treatment was assigned by a method of permuted blocks within strata with a block size of 10. All patients assigned to the treatment groups were included in the analysis according to the intention to treat.

Efficacy assessments

Performance status was assessed referring to the Eastern Cooperative Oncology Group (ECOG) criteria [18]. Toxicity was evaluated according to National Cancer Institute (NCI) criteria [19]. All patients were followed with chest X-ray, bone scan and liver ultrasound yearly. In the tamoxifen-alone group mammography and clinical examination were performed every 3 months for 2 years, every 6 months for 3 more years and yearly thereafter. Local tumor response was assessed by mammography, referring to ECOG criteria [18]. In the surgical group clinical examination was made every 6 months and mammography yearly. After diagnosis of distant metastases patients were followed only to determine survival. Deaths attributed to breast cancer were confirmed by death certificates. The survival status of patients declared lost from the randomizing center at follow-up was checked with the city anagraphic office.

Statistical evaluations

In consideration of the age of the patients, mortality for reasons other than breast cancer was assumed to be around 10% at 5 years, contributing to dilute the efficacy of the anticancer treatment, thus deaths from any cause were considered events. Five-year survival in patients operated and in the tamoxifen-alone group was assumed to be similar and estimated at around 70%. The maximal acceptable difference between tamoxifen-alone and the standard treatment was fixed at 10%. With a power of 80% and one-sided $\alpha = 95\%$, we estimated that it would be necessary to recruit 570 patients.

Overall survival was computed from the time of randomization to the last available follow-up or death. The analysis of the metastases-free survival considered only the evidence of distant metastases. The analysis of the event-free survival considered the following events: (i) first local recurrence of disease (including any local progression in the tamoxifen-only group); (ii) locoregional progression; (iii) evidence of distant metastases; (iv) appearance of a second malignancy; and (v) death due to whatever cause. Patients lost at follow-up were included in the analysis up to the last available observation. Overall survival according to the extension of surgery in the surgical arm and local response in the tamoxifen-alone group were calculated according to treatment given. Breast cancer survival was computed considering death for any cause with prior distant metastasis. Overall survival, breast cancer survival, distant metastases and disease-free survival were estimated by the product-limit method, with failed observations censored to 0. The log-rank test was used to assess the statistical significance of treatment differences in event distribution. Differences in proportions of distant metastases were analyzed by means of the chi-square test. The *P* values were calculated according to a two-sided test of significance [20–22]. A Cox proportional model was used to relate some variable to overall and breast cancer survival [23]. Statistical calculations were performed using NCSS 2000 software (NCSS Statistical software, Kaysville, UT, USA).

Results

Between March 1987 and June 1992, 474 women aged over 70 years with operable breast cancer were recruited in this multicenter prospective randomized study, 239 in the surgical group and 235 in the tamoxifen-alone group. Ten and seven patients were considered ineligible and 16 and seven received the treatment planned for the opposite arm, respectively. Causes of inelegibility were similar in the two groups (Table 1).

Patient characteristics

The two groups were comparable for age, tumor size, clinical nodal status and performance status according to ECOG criteria. The median age is 76. The majority of tumors were T1 (55.2%); 41.5% of tumors were T2. As regarding nodal status, 60.3% of patients were N0 and 8.8% had clinically positive axillary nodes (Table 2). In the surgery plus tamoxifen arm 82% of patients were treated with radical surgery (30 patients, quadrantectomy with axilla clearance plus radiotherapy; 13 patients, Halstead mastectomy; 119 patients, Madden mastectomy). In this group receptor content was determined in 114/223 cases. In those patients 82 (72%) were estrogen receptor-positive and 74 (65%) progesteron receptor-positive. Ninety-four patients (82%) were positive for estrogen and/or progesteron receptors. The mean

Table 1. Study information

	Surgery plus tamoxifen	Tamoxifen
Randomized	239	235
Change of treatment after randomization	16	7
Ineligible	10	7
Causes of ineligibility		
Randomized with distant metastasis	1	1
No breast cancer	5	?
Age <70 years	1	4
Randomized and lost	3	3

level of estrogen receptors (RE plus patients only) was 174 fmol of protein.

Clinical efficacy

Local control. In the tamoxifen-alone group 21 patients (9.2%) (treatment given) had a clinical complete response (CR; complete disappearance of the tumor in mammography) and 74 (32.4%) a partial response (PR; a decrease of >50% of the product of the two major diameters of the tumor in mammography, compared with the basal), according to the best assessment, for a total of 95 (41.6%) responders (CR + PR). Median time to the best ever response was 5.1 months (95% CI 3.7–6.5) (Table 3).

Table 2. Patient characteristics

	Surgery plus tamoxifen	Tamoxifen	*P* value
Median age (range)	76 (69–90)	77 (65–88)	NS
Age groups, years (%)			NS
<75	87 (36.4)	66 (28.1)	
75–79	97 (40.6)	100 (42.6)	
>80	55 (23)	69 (29.4)	
ECOG performance status			NS
Unknown	2	0	
0	172	175	
1	65	60	
Tumor size (%)			NS
Unknown	6	4	
<2 cm	135 (57.9)	127 (55)	
2–5 cm	96 (41.2)	101 (43.7)	
>5 cm	2 (0.9)	3 (1.3)	
Clinical nodal status (%)			NS
Unknown	6 (2.5)	4 (1.7)	
N0	136 (56.9)	150 (63.8)	
N1a	69 (28.9)	66 (28.1)	
N1b	27 (11.3)	15 (6.4)	
N3	1 (0.4)	0	

NS, not significant.

At a median follow-up of 80 months 27 (11.2%) patients in the surgical arm and 106 (45.2%) in the tamoxifen-alone arm had a local progression; the difference is highly significant (P <0.0001) (intention to treat) (Table 4). The 14-year probability of local relapse is also significantly in favor of surgically treated patients (Figure 1).

Event-free survival

As shown in Table 4, 140 (58.5%) patients in the surgery plus tamoxifen group had an event, versus 188 (80%) patients in the tamoxifen-alone arm (P = 0.0001), with a median event-free survival of 61.6 and 40 months, respectively, (P <0.001). The 14-year probability of event-free survival is significantly better for surgically treated patients (log-rank P = 0.02).

Overall and breast cancer survival

There were 130 (54.4%) overall deaths in the surgery plus tamoxifen group and 144 (61.3%) in the tamoxifen-alone group (P = 0.1). No difference was found in long-term probability of overall survival (log-rank P = 0.89) (Figure 2). No difference was found in overall deaths between radical or minimal surgery in the surgery plus tamoxifen group according to a treatment given analysis (50.3% versus 60.4%; P = 0.2).

Table 3. Tumor response to tamoxifen alone (best ever response, treatment given)

	Nr (%)
Total evaluable	228
Not assessed	6 (2.6)
No change	125 (54.8)
Partial remission	74 (32.4)
Complete remission	21 (9.2)
Progression within 3 months	2 (0.8)
Median time to best response (months)	5.1
	(95% CI 3.7–6.5)
Median time to local relapse (months)	19.2
	(95% CI 15.4–30.1)

Nr, number of observed responses.

Table 4. Overall results at a median follow-up of 80 months

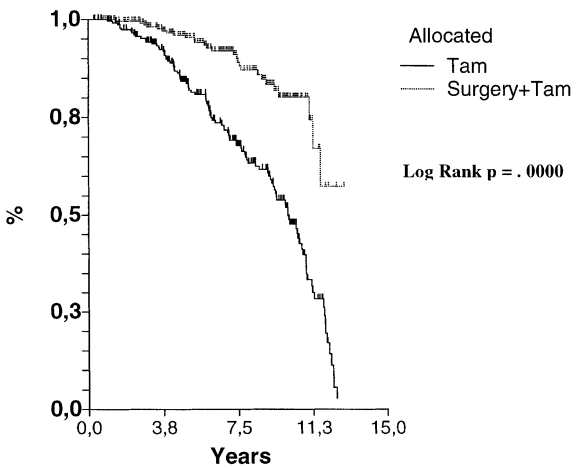
	Surgery plus tamoxifen	Tamoxifen	*P* value
Median follow-up (months)	79.6	80.1	NS
Local progression (%)	27 (11.2)	111 (47.2)	0.0001
Ipsilateral breast	20	2	
Other locoreginal	7	104	
Median event-free survival (months)	61.6	40	<0.001
Total events (%)	140 (58.5)	188 (80)	0.0001
First local progression	27 (11.3)	95 (40.4)	0.0001
First distant metastasis	0	10 (4.3)	NS
Second cancer	8 (3.3)	8 (3.4)	NS
Death from any cause	105 (43.9)	75 (31.9)	0.009
Median distant metastases event-free survival (months)	32.2	46.3	0.04
Distant metastases rate (%)	59 (24.7)	51 (21.7)	NS
Median overall survival (months)	70.9	71.2	NS
Survival rate (%)			
Overall deaths	130 (54.4)	144 (61.3)	NS
Breast cancer-related deaths	55 (23)	56 (23.8)	NS

NS, not significant.

No difference in breast cancer deaths was found between the two groups of treatment: 55 deaths (23%) in the surgical group versus 56 (23.8%) in the conservative group (Table 4). No difference emerged in the 14-year probability of breast cancer survival (log-rank $P = 0.18$) (Figure 3), or when evaluated for local progression as first event (log-rank $P = 0.38$) (Figure 4).

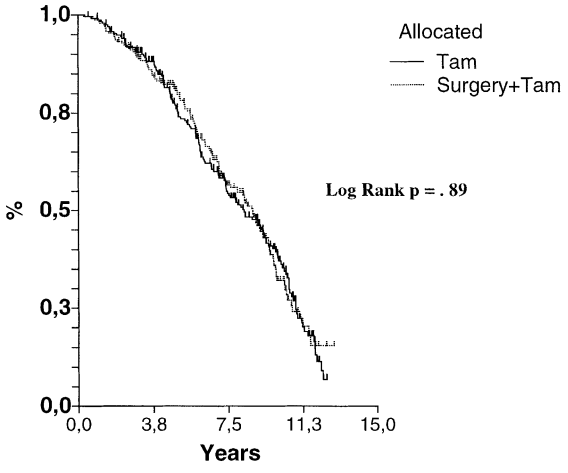
In the conservative group there is a trend for better breast cancer survival in patients with a clinical CR to initial tamoxifen, but the difference is not significant (log-rank $P = 0.59$, analysis for treatment given) (Figure 5). At a median follow-up of 80 months the distant metastases rate was 9.09% (2/21) in patients with CR and 23% (46/199) in patients with PR or stable disease, and this difference is near to a significant level ($P = 0.06$).

When a Cox proportional hazard model was constructed considering treatment allocation, age and tumor size as possible independent prognostic factors, the relative risk (RR) for overall death for treatment allocation was 1.02 (95% CI 0.8–1.3, $P = 0.8$), for age was 1.06 (95% CI 1.03–1.09, $P < 0.0001$) and for tumor size 1.01 (95% CI 1.00–1.03, $P = 0.01$). The relative risk for breast cancer death for treatment allocation was 1.38 (95% CI



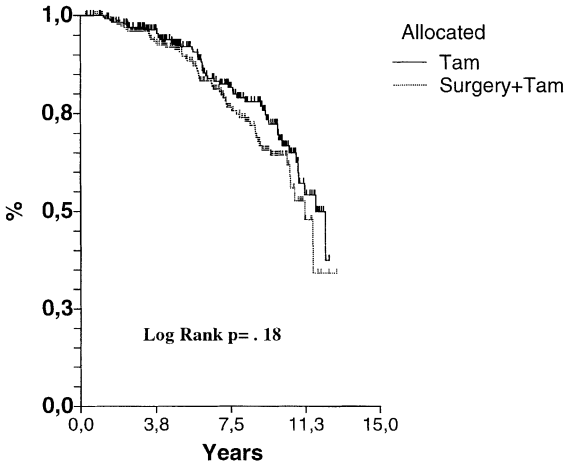
Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
Tam	232	193	138	78	20
Surg+Tam	228	184	136	73	10

Figure 1. Probability of being local relapse free.



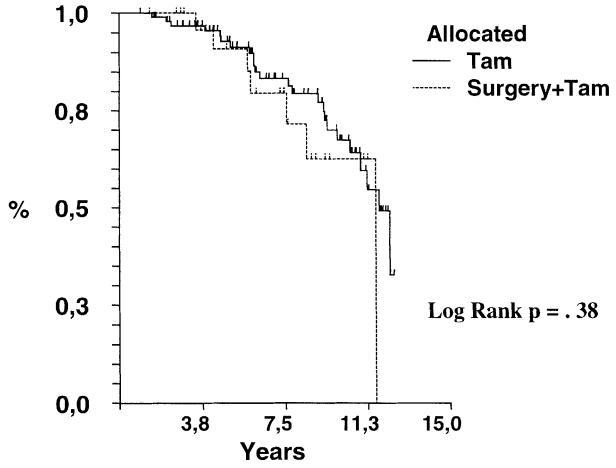
Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
Tam	233	193	141	78	20
Surg+Tam	236	187	141	73	11

Figure 2. Probability of overall survival.



Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
Tam	230	187	141	71	19
Surg+Tam	230	187	141	73	11

Figure 3. Probability of breast cancer survival.



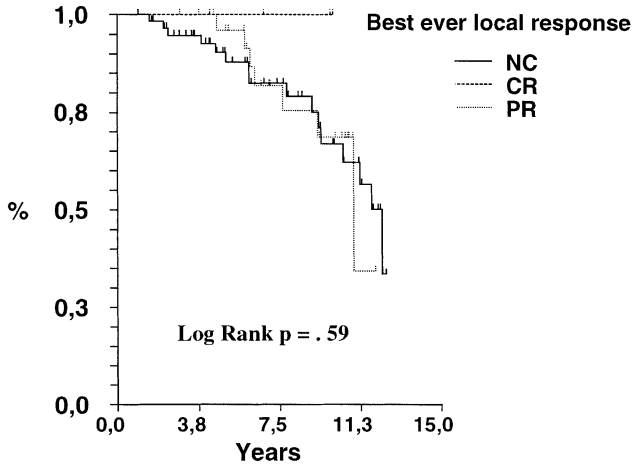
Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
Tam	94	78	60	35	12
Surg+Tam	23	23	16	8	0

Figure 4. Probability of breast cancer survival for local progression as first event.

0.94–2.04, P = 0.09), for age was 1.04 (95% CI 0.99–1.08, P = 0.06) and for tumor size 1.04 (95% CI 1.02–1.06, P <0.0001). The data confirm that treatment allocation is not related to overall and breast cancer survival, younger age is an independent prognostic factor for a longer overall survival only and tumor size for both overall and breast cancer survival.

Safety

There was no operative mortality in the surgery group. No difference between groups was found in toxicity nor in causes of death different from breast cancer. Fifty per cent of patients without recurrence died for cardiovascular reasons (Table 5).



Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
No Change	59	45	32	20	11
Partial Response	25	25	21	13	2
Complete Response	0	0	0	0	0

Figure 5. Probability of breast cancer survival according to initial response to tamoxifen.

Table 5. Causes of death in non-relapsed patients

	Nr (%)
Overall (P = 0.6)	
Surgery plus tamoxifen	72/239 (30)
Tamoxifen alone	83/235 (35)
Causes (both groups)	
CHF	34 (21.9)
Myocardial infarction	16 (10.3)
Stroke	28 (18)
Senectus	14 (9)
Other	63 (40.6)

NR, number of observed responses.

Discussion

Although several authors have reported the use of tamoxifen as a sole treatment for operable breast cancer in elderly patients [6–13], no definitive conclusion on this treatment has been reported so far. It is an important issue because for elderly women with breast cancer deaths are more often non-cancer-specific.

We have reported the results of the Italian multicenter prospective randomized trial, GRETA, comparing the use of tamoxifen alone versus surgery plus adjuvant tamoxifen in the elderly. On the basis of the recent overview of 113 randomized tamoxifen trials [5], showing that adjuvant tamoxifen has definite benefits with little toxicity in postmenopausal patients compared with surgery alone, we consider this as the more adequate comparison.

The number of recruited patients is smaller than planned because of a reduction in recruitment with time; none the less our study remains the largest phase III trial on this topic. Further-

more, 5-year survival is around 80% in both arms, instead of the assumed 70% when planning the study; standard error of the observed survival and standard deviation of the log-rank test are similar and very small, the number of events is similar at any specific time. The revised power of the study with the recruited number of patients, as regards the main end point, which is survival, is 0.804.

At 13 years, we found no difference in the actuarial overall survival whether performing surgery or not as primary treatment for operable breast cancer in the elderly. This is in agreement with the conclusions of other authors comparing tamoxifen alone with surgery alone [9, 11], with a final report of the Robertson study comparing tamoxifen alone with surgery plus tamoxifen [24] and with the preliminary results of our study, the Cancer Resesarch Campaign trial and the meta-analysis of the two [13, 14, 16, 17].

As expected in older people, age is significantly related to a better overall survival. Tumor size is confirmed as a strong predictor of both overall and breast cancer survival. Despite the lack of difference in the overall survival, the event-free survival was significantly better in the surgery plus tamoxifen arm. This difference is attributable to a significantly better local disease control obtained with the combination therapy compared with tamoxifen alone. These findings confirm previous preliminary reports from other authors [9–12].

In contrast to our results, the Cancer Resesarch Campaign UK trial showed a better breast cancer survival in the surgical group [13] and, at a longer follow-up, an advantage in overall survival [25]. A possible explanation could be the proportion of small tumors (<2 cm) in the Italian trial (55%), which was much higher than in the Cancer Resesarch Campaign trial (23.4%) [13]. It is thus possible to argue that surgery plays an important role only in more advanced cancers, perhaps in relation to the natural life span in this class of age.

The distant metastasis incidence showed a trend in favor of the tamoxifen-alone treatment in the first 4 years, perhaps related to the loading dose. At a median follow-up of 80 months, we still found a significantly longer distant metastases-free survival in favor of the tamoxifen-alone group (46.3 versus 32.2 months, $P = 0.04$). This is consistent with other reported effects of high-dose tamoxifen such as induction of TGF-β overexpression (TGF-β is a potent inhibitor of epithelial cell growth) [26], induction of apoptosis [27] and a decrease of the Ki-67 labeling index [28, 29]. Nevertheless there is no improved breast cancer-specific survival.

The proportion of patients with positive estrogen or progesteron receptors in the surgical arm of our study was very high (82%), as expected when planning the trial. Prior assessment of receptor status, which was not requested at the time in any of the published studies, is obviously mandatory today. Unfortunately ER status cannot be measured in retrospect in the tamoxifen-alone arm because in the majority of cases the diagnosis was based on a fine needle aspiration.

Our final results confirm that minimal surgery followed by adjuvant tamoxifen is the most appropriate treatment in older patients with operable breast cancer. Perhaps a neoadjuvant treatment, starting with a loading dose, could be beneficial. A delayed second-line surgical treatment after a primary therapy with tamoxifen alone does not prejudice the overall survival of the elderly patient.

Tamoxifen alone is an adequate alternative as sole first-line treatment only in frail patients unfit for surgery or in cases of refusal of surgery, providing that a strict follow-up is planned and a higher risk of local recurrence is accepted. Our results with tamoxifen alone could be useful in relation to the increasing interest in neoadjuvant endocrine treatments, as illustrated in a recent review [30] and in two phase III trials [33–35].

Since the median time to achieve the best response to tamoxifen in our study was 5.1 months (95% CI 3.7–6.5), it is our opinion that the optimal duration of neoadjuvant endocrine treatment should be 6 months. Eiermann reported in a phase III trial a response rate (mammography) of 25% with tamoxifen and 35% with letrozole, both given for 3 months [33, 34]. Similarly, Ellis treated 324 patients for 4 months with letrozole or tamoxifen before surgery, reporting 38% and 20% response rates (mammography), respectively [35]. Thus, a longer treatment may lead to a better response rate.

Currently there is debate over whether a neoadjuvant response to an endocrine agent predicts the outcome of adjuvant therapy. In our study, patients with mammographic CR show a trend in favor of a better breast cancer survival and for a lower rate of distant metastases at a median follow-up of 80 months.The number of observed CRs is too small to speculate on this outcome but the observed trend is very suggestive.

Another pivotal question is which breast cancer patients should be treated with neoadjuvant endocrine therapy? In women suitable for neoadjuvant chemotherapy, the probability of downstaging of the tumor and subsequent conservative treatment is much higher with chemotherapy when compared with tamoxifen [31, 32] or with aromatase inhibitors [33–35] also in tumors that are rich in estrogen receptors. Another crucial point in favor of neoadjuvant chemotherapy is that pathological complete response (pCR) is related to a better prognosis [36–40] and recent trials reported a pCR rate of 10–34% [38–40]. The pCR rate reported with endocrine neoadjuvant treatment is 1.4% and 42% of patients were younger than 70 years [34]. Thus we think that endocrine neoadjuvant therapy should only be recommended for older patients.

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