Ten-Year Results of a Randomized Trial Evaluating Prolonged Low-Dose Adjuvant Chemotherapy in Node-Positive Breast Cancer: A Joint European Organization for Research and Treatment of Cancer–Dutch Breast Cancer Working Party Study

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Purpose: **To investigate whether treatment with prolonged low-dose adjuvant chemotherapy could improve survival of patients with axillary node-positive breast cancer.**

Patients and Methods: **Four hundred fifty-two patients with axillary node-positive breast cancer who received postoperative irradiation were prospectively randomized in a trial (European Organization for Research and Treatment of Cancer [EORTC] 09771) that compared surgery followed by prolonged low-dose chemotherapy versus surgery alone. Chemotherapy was given for a period of 2 years and consisted of monthly courses of cyclophosphamide 50 mg/m^2 orally on days 1 to 14, methotrexate 15 mg/m^2 intravenously on days 1 and 8, and fluorouracil 350 mg/m^2 intravenously on days 1 and 8 (CMF).**

Results: **At a median follow-up time of 10 years, the overall survival duration was significantly prolonged in the chemotherapy arm (hazards ratio, 0.75; 95% confidence interval, 0.56 to 0.99; $P = .04$). Ten-year overall survival rates (± SE) were 59% (± 3.6%) for the chemotherapy arm and 50% (± 3.7%) for the control arm. Time to local relapse was significantly prolonged in the chemotherapy arm (hazards ratio, 0.63; 95% confidence interval, 0.42 to 0.94; $P = .02$). Patients with one to three positive axillary nodes and patients with estrogen receptor-negative tumors especially benefited from chemotherapy. Toxicity was observed in 93% of patients.**

Conclusion: **We conclude that prolonged low-dose adjuvant CMF can significantly prolong overall survival in patients with node-positive breast cancer. However, considering the fact that toxicity was still considerable despite reducing the dose of chemotherapy by 50%, we believe that conventionally dosed short-term regimens are preferable in the treatment of node-positive breast cancer.**

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THE FIRST RANDOMIZED clinical trial on systemic therapy in breast cancer was initiated by Fisher et al[1] in 1958 and studied the issue of whether short-course adjuvant thiotepa could improve survival in early breast cancer. The rationale for this design was to determine whether tumor cells spread during the surgical procedure could be killed by chemotherapy administration during the first 72 hours after surgery. In 1968, Nissen-Meyer et al[2] used a similar design in a trial of patients with breast cancer who received a 6-day course of cyclophosphamide. Greenspan[3] was among the first to introduce successfully combination therapy in breast cancer in the early 1960s. After the discovery of the active regimen of vincristine, prednisone, cyclophosphamide, methotrexate and fluorouracil (CMFVP) in the treatment of metastatic disease by Cooper et al[4] in 1968, subsequent trials focused on the study of various combinations of these chemotherapeutic agents. The acceptance of the concept that in a large group of patients, foci of metastatic cells were already present at the time of diagnosis led to the conclusion that repetitive courses of drugs were required to destruct these tumor cells.[5-7] Furthermore, a review by DeVita et al[8] in 1975 showed that the results of combination chemotherapy were superior to those of single-agent therapy. When finally Bonadonna et al[9] initiated their study comparing CMF versus no therapy in 1973, this rapidly became one of the most widely studied regimens in the treatment of breast cancer. Results from several randomized clinical trials indicated that advantages were most pronounced in women less than 50 years of age.[10] To determine the optimal duration of chemotherapy became then the second-generation goal for investigators, and data from several investigators showed that regimens us-

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ing 4 to 6 months of therapy were likely to be as effective and were probably preferable to ≥ 12 months of therapy.[11] As a result, a recommendation was finally made at the Consensus Development Conference in 1986 that 6-month courses of CMF should become the standard treatment for women with axillary node-positive breast cancer younger than 50 years of age.[12]

However, at the time, when the first preliminary but promising results of adjuvant CMF in axillary node-positive breast cancer were published by Bonadonna et al[9] in 1976, many controversies were also raised about the effects of the regimen on overall survival and the concern whether short-term or long-term side effects could eventually be detrimental.

Therefore, a prospectively randomized trial was designed in the Netherlands (European Organization for Research and Treatment of Cancer [EORTC] 09771) to be performed under the auspices of the Breast Cancer Cooperative Group of the EORTC, comparing treatment with low-dose CMF administered over 2 years versus surgery alone. This design aimed to reduce toxicity while maintaining the same total dose of chemotherapy as was administered in the regimen used by Bonadonna et al.[9] The trial was started in 1976 and closed to patient entry in 1980. It included premenopausal and postmenopausal axillary node-positive patients with early breast cancer who underwent either a radical mastectomy or modified radical mastectomy before being randomized.

In the present 10-year follow-up report, we show that both overall survival and toxicity data were comparable with those of the conventional 12-month CMF regimen used by Bonadonna et al,[9] despite the fact that dosages were reduced by 50% and therapy was given over a period of 2 years.

PATIENTS AND METHODS

Trial Design

Women with axillary node-positive breast cancer from 20 different hospitals in the Netherlands were randomized in a multicenter phase III trial (EORTC 09771) comparing surgery followed by a prolonged regimen of low-dose adjuvant chemotherapy versus surgery alone.

Central randomization and registration were performed after surgery and histopathologic confirmation of positive axillary nodes by means of a telephone call to the EORTC Data Center in Brussels, Belgium. Randomization was based on random permuted blocks and was stratified for institution, menopausal status, and nodal status (one to three positive nodes or ≥ four positive nodes).

Patient Population

Trial entry criteria included informed consent given by the patient according to the institute's regulations, preoperatively staged and histologically confirmed diagnosis of T1a,2a,3aN0,1M0 breast cancer, surgery with curative intent, (modified) radical mastectomy, and one or more histopathologically confirmed positive axillary nodes.

Patients were ineligible if they were older than 70 years of age, had bilateral breast cancer, had a well documented history of another neoplasm (except basal cell carcinoma), had distant metastases, had metastases in the infraclavicular lymph nodes, had received previous treatment for breast cancer in addition to (modified) radical mastectomy, had a WBC count ≤ 4.0×10^9/L, had a platelet count ≤ 130×10^9/L, had a serum creatinine level more than 105 μmol/L, had an alkaline phosphatase level that had repeatedly been above the normal value, were conditionally or mentally unfit, or were pregnant or lactating at time of diagnosis.

Treatment

Surgery consisted of either radical or modified radical mastectomy (according to Madden[13]) that included a total axillary dissection in which the infraclavicular top nodes were separately marked.

Postoperative radiation therapy had to start within 6 weeks after surgery. In patients with one to three positive axillary nodes, internal mammary-chain irradiation with 40 Gy was administered over 4 weeks. In cases of four or more positive axillary nodes, supraclavicular and axillary nodes were irradiated using 50 Gy over 5 weeks, in addition to the parasternal irradiation.

After surgery, all patients were randomized either to receive 2 years of adjuvant chemotherapy or to be monitored by observation. Chemotherapy was given for a period of 2 years and consisted of monthly courses of cyclophosphamide 50 mg/m^2 orally on days 1 to 14, methotrexate 15 mg/m^2 intravenously on days 1 and 8, and fluorouracil 350 mg/m^2 intravenously on days 1 and 8. Between the completion of radiation therapy and the start of chemotherapy, patients were observed for a period of 7 to 10 days, which could be prolonged if the WBC count was less than 4.0×10^9/L. The dose reduction in case of World Health Organization (WHO) grade 1 hematologic toxicity was 50% for cyclophosphamide and methotrexate, whereas the dose of fluorouracil was not reduced in case of grade 1 toxicity. In case of WHO grade 2 hematologic toxicity, cycles of CMF were discontinued until grade 1 toxicity was reached. In case of serious gastrointestinal toxicity leading to mucosal lesions of the mouth and throat and/or watery diarrhea, fluorouracil and methotrexate were temporarily withdrawn. Cyclophosphamide treatment was interrupted when hemorrhagic cystitis occurred. In case of a serum creatinine level greater than 105 μmol/L, treatment with methotrexate was temporarily stopped. No additional hormonal treatment was given to any of the patients randomized.

Follow-Up Examinations

Follow-up examinations were requested every 3 months during the first 5 years after surgery. Minimal requirements were physical examination, performance scale assessment, and two serum liver tests. For trial purposes, a chest x-ray and a bone scan were performed every 6 months and a mammography was performed once per year. After 5 years, progress reports were sent once per year and contained information about the disease and survival status of the patients. All data were reviewed centrally by the study coordinators, a research fellow, and the data manager.

Criteria of Evaluation

Disease-free survival was defined as the time between the date of randomization and the date of disease progression or death, whichever came first.

Table 1. Characteristics of Eligible Patients According to Treatment

Characteristic	Total	Adjuvant Chemotherapy	Control
No. of patients	437	224	213
Menopausal status (%)			
Premenopausal	216	50.4	48.4
Postmenopausal	221	49.6	51.6
Surgical procedure (%)*			
Radical mastectomy	132	34.6	27.8
Modified radical mastectomy	284	63.6	71.2
Other	6	1.8	1.0
No. of invaded nodes (%)			
1-3	325	74.1	74.6
≥ 4	112	25.9	25.4
Estrogen receptor status (%)			
Negative	77	16.5	18.8
Borderline	25	7.1	4.2
Positive	147	33.0	34.3
Unknown	188	43.3	42.7
Tumor size (%)†			
≤ 2 cm	105	26.9	23.0
> 2 cm	315	73.1	77.0

* For 15 patients, information on surgical procedure was not available.
† For 17 patients, information on tumor size was not available.

Statistical Methods

Overall and disease-free survival curves were estimated using the Kaplan-Meier product-limit method[14] and compared using the log-rank test.[15] Estimates of hazards ratios, their 95% confidence intervals, and two-sided P values were calculated using both an unadjusted Cox proportional hazards regression model and a model stratified according to the number of positive axillary nodes (one to three or ≥ four) and including covariates for menopausal status, surgical procedure, estrogen receptor status, and clinical tumor size (if sufficient data were available for these covariates).[16]

RESULTS

From October 1976 to November 1980, 452 patients were randomized by 20 hospitals from the Netherlands. Of these 452 patients, 14 were ineligible for the study because they had an inadequate disease staging (n = 3), distant metastases (n = 7), previous treatment (n = 1), a second malignancy (n = 2), or were older than 70 years of age (n = 1). One patient could not be included in the statistical analyses because no follow-up data were available after randomization. The data of the remaining 437 patients (97%) were used in the analyses of this study. The cut-off date for this report was July 1993, when the median follow-up time was 10 years (maximum, 17 years).

The characteristics of eligible patients were well distributed among the two treatment arms (Table 1). The mean number of axillary nodes removed per patient was 11.9. Although not requested in the protocol, data on tumor estrogen receptor content could retrospectively be retrieved for 249 patients.

Table 2 lists the percentages of patients who were affected by toxicity on at least one occasion. Only 6% of patients had grade 3 (WHO) WBC counts and no grade 4 toxicity was observed. Likewise, for platelet counts, no grade 3 or 4 toxicity could be detected. In the majority of the patients, nausea and vomiting developed during the administration of chemotherapy. One third of patients had alopecia, while other side effects, such as infection, stomatitis, and cystitis, were relatively rare. Seven percent of patients had no toxicity recorded at all. No toxic deaths occurred among patients treated with prolonged low-dose chemotherapy.

Reliable data on the date of starting and ending chemotherapy, doses actually given, and toxicity could be collected for 142 of 224 patients in the chemotherapy arm. Of these, 114 (80.3%) received at least six cycles of chemotherapy, 103 (72.5%) received at least 12 cycles of chemotherapy, and 65 (45.8%) received 24 cycles of chemotherapy. The mean interval between surgery and initiation of chemotherapy was 62 days. The mean relative dose-intensities actually given and initially targeted were 0.33 and 0.45, respectively (calculated according to the method described by Hryniuk et al[17] and relative to the entire 36 weeks of the Cooper regimen[4]). No significant relationship between mean relative dose-intensity actually given or targeted and clinical outcome could be detected. When examining the duration of therapy, patients who had received 23 or more courses of chemotherapy had a significantly better overall survival than patients who had received less than 23 courses (P = .001). However, it should be noted that patients who received less courses of chemotherapy may have relapsed earlier and therefore had a worse survival.

Of 437 patients, 242 relapsed and 194 died. Time to

Table 2. Toxicity Among Patients Who Received Chemotherapy

Toxicity	No. of Patients	%
Hematologic*		
WBC	9	6.4
Platelets	0	0.0
Side effects		
Nausea	122	88.4
Vomiting	82	59.4
Infection	9	6.5
Stomatitis	27	19.6
Cystitis	7	5.1
Alopecia	49	35.3
Other	35	26.1
No toxicity	10	7.0

* WHO grade 3 or 4.

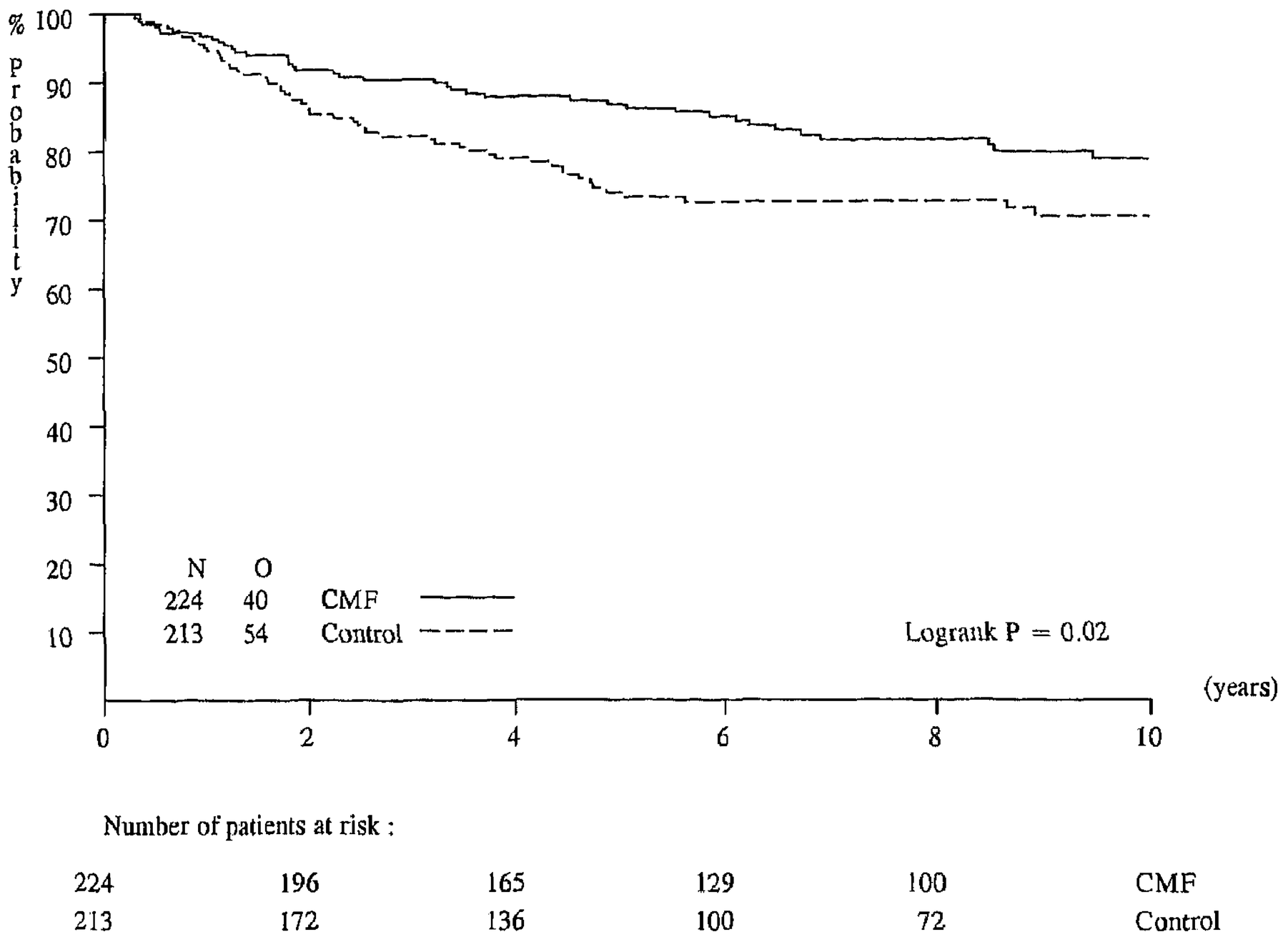

Fig 1. Time to local relapse among 437 patients with axillary node-positive breast cancer.

local relapse was significantly prolonged in the chemotherapy arm (hazards ratio, 0.63; 95% confidence interval, 0.42 to 0.94; $P = .02$) (Fig 1). However, this effect could not be demonstrated for time to distant metastases (hazards ratio, 0.89; 95% confidence interval, 0.68 to 1.18; $P = .43$) (Fig 2). There was a trend for treatment effect in favor of chemotherapy for disease-free survival (hazards ratio, 0.84; 95% confidence interval, 0.66 to 1.07; $P =$

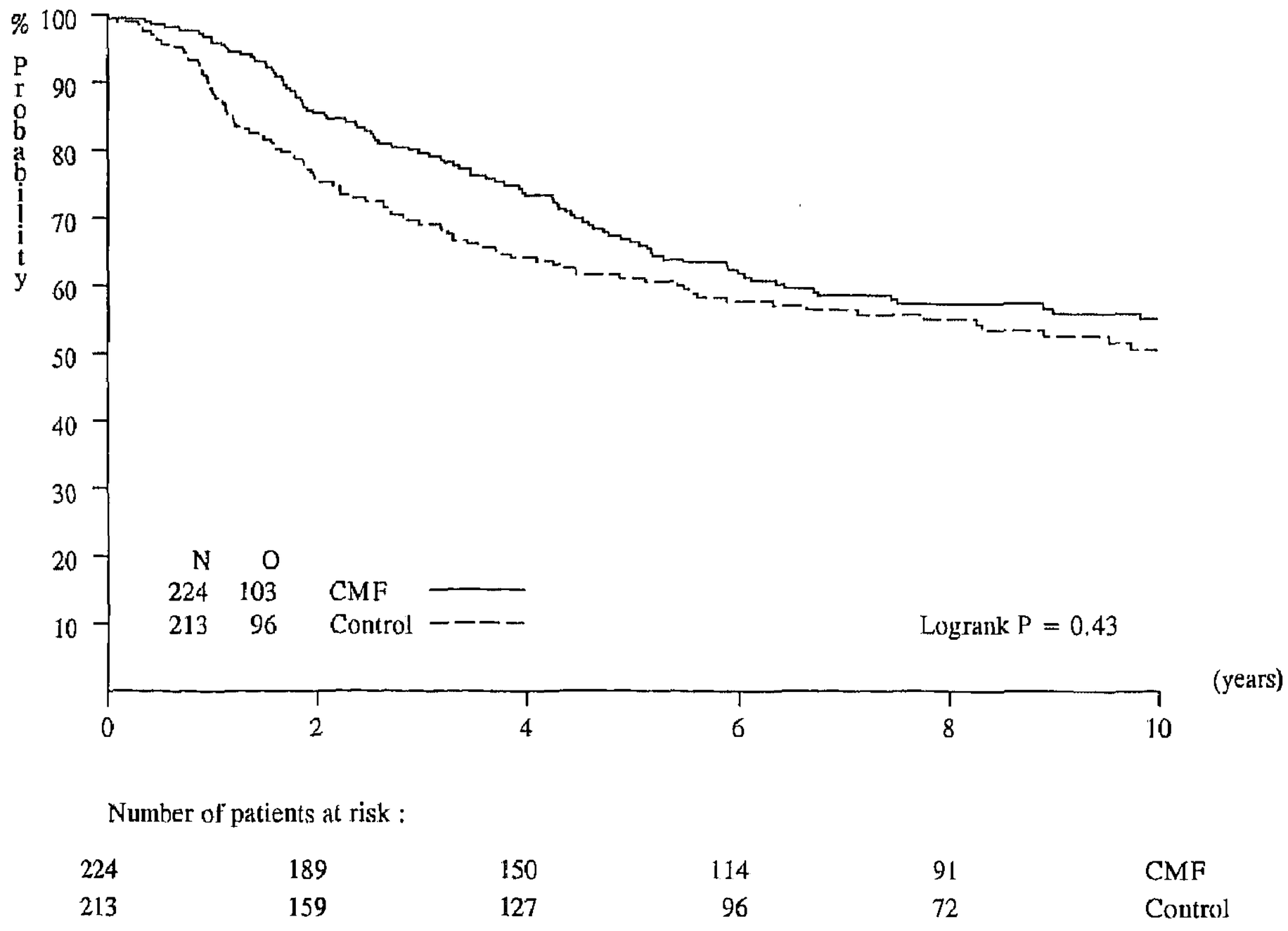

Fig 2. Time to distant metastases among 437 patients with axillary node-positive breast cancer.

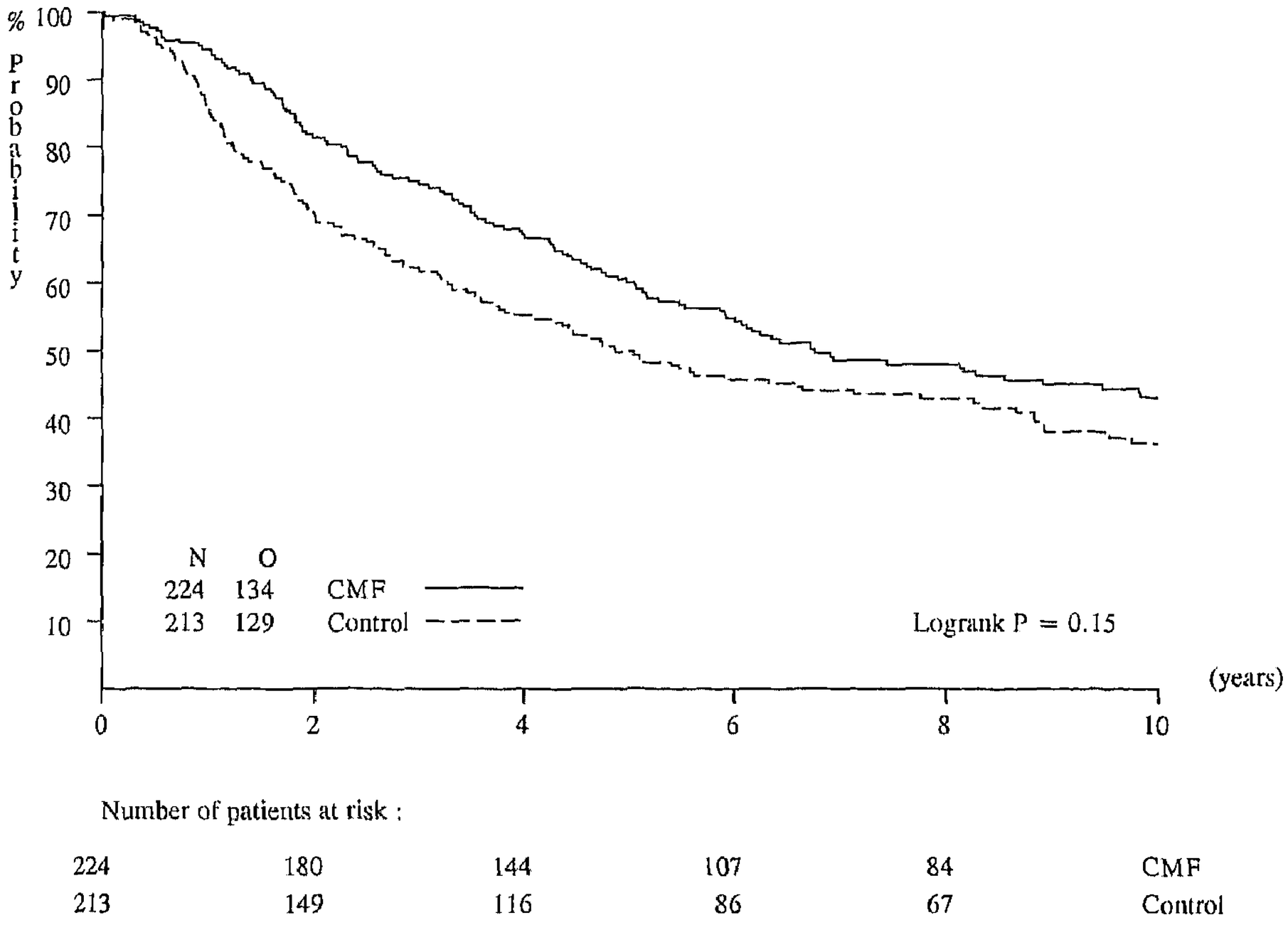

Fig 3. Disease-free survival among 437 patients with axillary node-positive breast cancer.

.15) (Fig 3). Ten-year disease-free survival rates (± SE) were 43% (± 3.5%) for the chemotherapy arm and 36% (± 3.6%) for the control arm.

Overall survival time was significantly prolonged in the chemotherapy arm (hazards ratio, 0.75; 95% confidence interval, 0.56 to 0.99; $P = .04$) (Fig 4). This advantage for the chemotherapy arm was due to a reduction in cancer deaths and no difference was found between the number of noncancer deaths in the two randomized treatment arms (data not shown). Ten-year overall survival rates (±

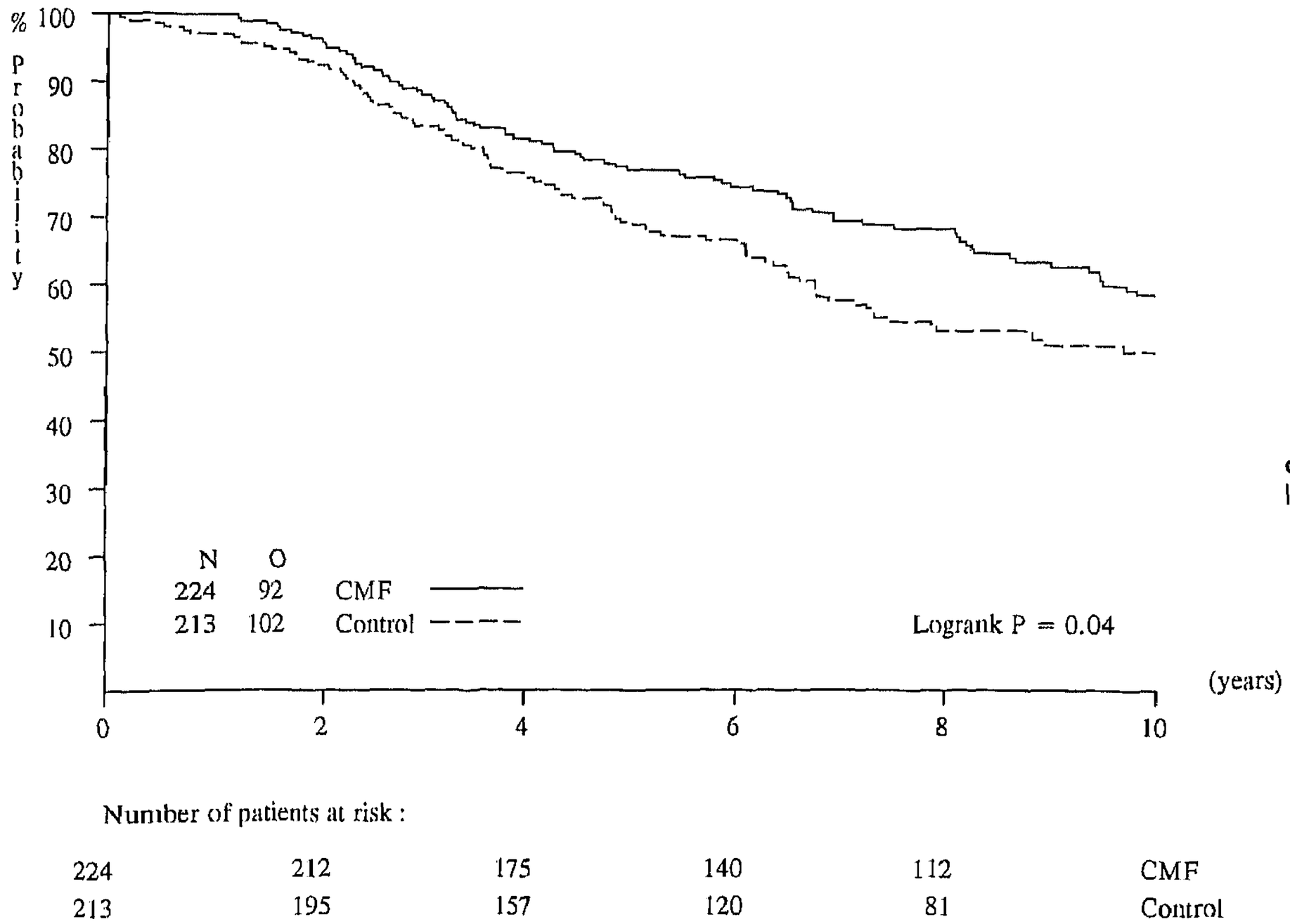

Fig 4. Overall survival among 437 patients with axillary node-positive breast cancer.

Table 3. Overall Survival Among 437 Patients With Node-Positive Breast Cancer, According to Treatment, Menopausal Status, Surgical Procedure, Number of Invaded Nodes, Estrogen Receptor Status, and Tumor Size

Variable	No. of Patients	No. of Events	10-Year Survival (%)	Hazards Ratio	95% CI	*P*
All patients						
Adjuvant chemotherapy	224	92	59	0.75	0.56-0.99	.04
Control	213	102	50			
Menopausal status						
Premenopausal						
Adjuvant chemotherapy	113	42	64	0.75	0.49-1.14	.17
Control	103	45	54			
1-3 positive nodes						
Adjuvant chemotherapy	85	28	68	0.65	0.39-1.08	.09
Control	79	33	55			
≥ 4 positive nodes						
Adjuvant chemotherapy	28	14	51	0.99	0.45-2.18	.98
Control	24	12	49			
Postmenopausal						
Adjuvant chemotherapy	111	50	53	0.76	0.52-1.11	.15
Control	110	57	46			
1-3 positive nodes						
Adjuvant chemotherapy	81	32	59	0.78	0.49-1.25	.30
Control	80	37	53			
≥ 4 positive nodes						
Adjuvant chemotherapy	30	18	41	0.69	0.36-1.31	.26
Control	30	20	30			
Surgical procedure						
Radical mastectomy						
Adjuvant chemotherapy	75	42	49	0.81	0.51-1.28	.36
Control	57	34	42			
Modified radical mastectomy						
Adjuvant chemotherapy	138	47	63	0.67	0.46-0.98	.04
Control	146	63	54			
Axillary nodal status						
1-3						
Adjuvant chemotherapy	166	60	64	0.71	0.50-1.00	.05
Control	159	70	54			
≥ 4						
Adjuvant chemotherapy	58	32	44	0.83	0.51-1.36	.45
Control	54	32	39			
Estrogen receptor status						
Negative						
Adjuvant chemotherapy	37	16	56	0.58	0.30-1.11	.10
Control	40	23	35			
Borderline						
Adjuvant chemotherapy	16	9	55	0.74	0.25-2.20	.59
Control	9	6	44			
Positive						
Adjuvant chemotherapy	74	33	48	1.05	0.64-1.70	.85
Control	73	32	58			
Unknown						
Adjuvant chemotherapy	97	34	66	0.67	0.42-1.06	.08
Control	91	41	51			
Tumor size (cm)						
≤ 2						
Adjuvant chemotherapy	58	23	63	0.71	0.39-1.30	.26
Control	47	20	51			
> 2						
Adjuvant chemotherapy	158	68	56	0.78	0.56-1.08	.13
Control	157	78	50			

NOTE. Hazards ratios, 95% confidence intervals, and *P* values were calculated using an unadjusted Cox proportional hazards model.
Abbreviation: CI, confidence interval.

SE) were 59% (± 3.6%) for the chemotherapy arm and 50% (± 3.7%) for the control arm. Table 3 list the hazards ratio and 10-year overall survival rates by treatment group according to different patient characteristics. The treatment effect appeared to be proportionally the same for premenopausal and postmenopausal patients, although differences between the chemotherapy group and the control group were no longer statistically significant. Patients with one to three positive axillary nodes benefited from chemotherapy, whereas this advantage was not observed for patients with four or more positive nodes. The magnitude of the treatment effect seemed to be the largest among the subgroups of premenopausal patients with one to three positive axillary nodes and patients with estrogen

receptor-negative tumors. A significant advantage in favor of chemotherapy was observed for the group of patients who had undergone modified radical mastectomy (hazards ratio, 0.67; 95% confidence interval, 0.46 to 0.98; $P = .04$). In patients who had undergone radical mastectomy, no advantage for chemotherapy could be observed. The effect of chemotherapy appeared to be the same for patients with tumors ≤ 2 cm and those with tumors greater than 2 cm. All of these results were confirmed by a multivariate analysis stratified for the number of positive axillary nodes and adjusted for the covariates menopausal status, surgical procedure, estrogen receptor status, and tumor size (data not shown). However, it should be noted that differences within these subsets could be due to chance. Moreover, statistical power is lost when multiple analyses are performed on smaller subgroups.

For 69 of 113 premenopausal patients randomized to the chemotherapy arm, reliable data were available concerning whether drug-induced cessation of menses had occurred. In this particular subgroup, no significant difference could be observed in overall or disease-free survival between patients with menses (n = 50) and those without menses (n = 19) (data not shown).

DISCUSSION

Our study showed that treatment with low-dose CMF continued for 2 years could significantly improve survival in patients with node-positive breast cancer. A search in the literature showed that our study was the only randomized trial until now to compare a low-dose CMF regimen with no further treatment in patients with node-positive breast cancer. Another low-dose adjuvant chemotherapy study that compared CMF with cyclophosphamide alone was performed in Denmark, but failed to demonstrate any difference in outcome between the two treatment arms (n = 805) at 6 years.[18]

Interestingly, we found a significant difference in overall survival in favor of chemotherapy, but this could not be shown for disease-free survival. We only observed a reduction in cancer deaths and, therefore, this finding was not due to differences in noncancer deaths. Although we are aware of the limitations of subgroup analyses, our results suggest that survival advantages for the chemotherapy treatment arm were most pronounced for premenopausal patients with one to three positive axillary nodes. Moreover, no advantage for chemotherapy was observed for patients with ≥ four positive nodes. These observations are in line with the conclusions from the overview of randomized clinical trials in early breast cancer.[19] Patients who underwent a modified radical mastectomy especially benefited from chemotherapy, whereas patients who underwent a radical mastectomy did not, a statistically significant difference that still existed after adjusting for tumor size. Although this difference in treatment effect was probably due to the smaller number of events in the radical mastectomy group, a similar observation was made in the first report of the Milan trial I, in which advantages for CMF were more pronounced in patients who underwent less extensive surgery.[9]

Our study showed a significant decrease in local relapses after 10 years, although a similar effect could not be demonstrated for distant metastases. In the majority of polychemotherapy studies in the past, investigators usually did not provide a breakdown for relapse-free survival by time to local relapse and time to distant metastases. Overgaard et al[20] conducted a study comparing chemotherapy with or without radiotherapy in high-risk breast cancer patients (T3-4 and/or node-positive). Reporting an extremely high number of locoregional recurrences, probably due to an inadequate method of axillary dissection (only a mean of 6.3 lymph nodes was removed), the investigators concluded that systemic therapy after nonradical mastectomy did not prevent locoregional recurrences. Another interesting observation was made in the trial conducted by Fisher et al,[21] who compared total mastectomy versus segmental mastectomy versus segmental mastectomy plus radiation therapy in a study in which all node-positive patients received chemotherapy. Although no information about time to local recurrence was given, distant metastases–free survival was not significantly different when total mastectomy versus segmental mastectomy and total mastectomy versus segmental mastectomy plus radiation therapy were compared. However, overall survival was borderline significantly different in favor of segmental mastectomy and segmental mastectomy plus radiation therapy, respectively.

Our observations indicated that there was a 40% reduction in the odds of local recurrence in the CMF arm, taking into consideration that all patients in both treatment arms had already received postoperative irradiation. This effect of chemotherapy on local relapse is still present and statistically significant at 10 years of follow-up. The proportionally small and nonsignificant effect on distant metastases in our study suggests that local control did have an impact on overall survival. On the other hand, the advantage for overall survival may also have been caused by an early prevention of distant metastases by chemotherapy. Future studies on chemotherapy and radiotherapy should address more precisely the question of whether therapy has an effect on local recurrence and distant metastases, which may help to study further the

relationship of these end points with overall survival. In addition, they should try to focus on the fact whether the sequence of chemotherapy and radiotherapy has any importance for the prevention of locoregional recurrences and distant metastases.

When the first results of the Milan trial I that studied 12-month cycles of CMF were published in 1976, an advantage in favor of chemotherapy could only be observed for disease-free survival, although toxicity was considerable.[9] However, 10-year results confirmed the effect on disease-free survival and showed a trend for overall survival in all patients ($P = .10$).[22] Both disease-free survival and overall survival benefits were significant in premenopausal women, and results were inversely related to the number of positive axillary nodes. Taking into consideration that our patient population contained a slightly larger proportion of premenopausal patients and patients with one to three positive axillary nodes, overall survival percentages in this trial are still highly comparable to those reported in the Milan trial I.[22] This result is particularly significant in view of the fact that our dose-intensities calculated according to the method reported by Hryniuk et al[17] were much lower than those obtained in the Milan trial I.

One of the objectives of the present trial was to study whether adjuvant treatment with a low-dose CMF regimen could also improve survival, but with less toxicity. Therefore, chemotherapy doses used in the present trial were approximately 50% of those used in Milan trial I.[9] Although it has been shown by Tancini et al[23] in 1983 that 6 months of CMF were equally effective as 12 months, the total dose of chemotherapy administered was considered to be important at the time this trial was designed. Therefore, treatment with low-dose CMF was continued for 2 years. The percentage of patients who completed all 24 cycles was 45.8%, which is comparable to the 44.9% who received the complete treatment of 12 cycles in the Milan trial I.[9] This suggests that there was no detrimental effect of a longer duration of chemotherapy on the number of courses that could be administered. However, despite the fact that chemotherapy doses were reduced by 50%, toxic side effects were still observed in 93% of patients, compared with a 96% toxicity rate reported in the Milan trial I. Although the method of reporting toxicity may have been different, this observation was probably partly related to the fact that in our trial design, treatment had to be continued for 2 years to obtain the same total dose of chemotherapy. Consequently, patients also had twice the chance to experience any toxicity, which might have hidden the possible beneficial effect of reducing the dosage of chemotherapy by 50%.

The conclusion that must be drawn from this study is that prolonged low-dose adjuvant CMF can significantly improve overall survival in patients with node-positive breast cancer. The lack of a standard-dose chemotherapy arm in this study limits the conclusions that can be made regarding the efficacy to standard-dose therapy. However, taking into consideration the long treatment duration and its considerable toxicity, it is likely that a cost-benefit comparison would show an advantage for short-term CMF regimens. Several randomized trials have already shown that shorter courses of polychemotherapy are as effective in prolonging survival as prolonged courses.[19] Moreover, results of the Cancer and Leukemia Group B 8541 trial have recently demonstrated that women who were treated with a high or moderate dose-intensity had a significantly better survival than those treated with a low dose-intensity.[24] In view of these data, we believe that conventionally dosed short-term chemotherapy regimens are preferable to prolonged low-dose regimens in the treatment of patients with axillary node-positive breast cancer.

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APPENDIX

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St Elisabeth Ziekenhuis, Leiderdorp
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