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## ADJUVANT CYCLOPHOSPHAMIDE, METHOTREXATE, AND FLUOROURACIL IN NODE-POSITIVE BREAST CANCER

### The Results of 20 Years of Follow-up

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**Abstract Background.** Adjuvant combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil was administered after radical mastectomy for primary breast cancer with histologically positive axillary lymph nodes to assess whether it would improve treatment outcome as compared with surgery alone. Here we report a 20-year follow-up of this investigation.

**Methods.** In 1973 we began a trial involving 386 women who were randomly assigned to receive either no further treatment after radical mastectomy (179 women) or 12 monthly cycles of adjuvant combination chemotherapy (207 women). All patients were admitted to the Istituto Nazionale Tumori in Milan, Italy. Adjuvant chemotherapy was delivered in the outpatient clinic of the Division of Medical Oncology.

**Results.** After a median follow-up of 19.4 years, the

patients given adjuvant combination chemotherapy had significantly better rates of relapse-free survival (unadjusted relative risk of relapse, 0.71; 95 percent confidence interval, 0.56 to 0.90;  $P=0.004$ ; adjusted relative risk, 0.65; 95 percent confidence interval, 0.51 to 0.83;  $P<0.001$ ) and total survival (unadjusted relative risk of death, 0.78; 95 percent confidence interval, 0.62 to 0.99;  $P=0.04$ ; adjusted relative risk, 0.76; 95 percent confidence interval, 0.60 to 0.97;  $P=0.03$ ). With the exception of postmenopausal women, a benefit from adjuvant chemotherapy was evident in all subgroups of patients.

**Conclusions.** The long-term results of this trial of adjuvant combination chemotherapy confirm our preliminary observations of the effectiveness of the treatment in women with node-positive breast cancer. (N Engl J Med 1995; 332:901-6.)

IN 1975 we presented our first report on the efficacy of cyclophosphamide, methotrexate, and fluorouracil (CMF) as adjuvant treatment for node-positive breast cancer.<sup>1</sup> A subsequent report in the *Journal*,<sup>2</sup> along with the results of the National Surgical Adjuvant Breast and Bowel Project,<sup>3</sup> published in 1975, raised hopes that chemotherapy could have a more central role in the primary management of this common cancer. The ease of administration and the virtual absence of severe acute toxicity made CMF the most frequently used combination of drugs in clinical practice in oncology, as well as the regimen against which all new systemic adjuvant treatments were tested.<sup>4</sup>

In this paper we report the results of 20 years of follow-up of our original series of women who had had a radical mastectomy and who were randomly assigned to receive no further treatment or CMF chemotherapy for 12 monthly cycles. The long-term results continue to show a significant overall benefit for adjuvant chemotherapy. The findings support the strategy of early

systemic treatment of patients at high risk of micrometastases.

## METHODS

### Selection of Patients

The study group consisted of patients admitted to the Istituto Nazionale Tumori in Milan, Italy. All women 75 years of age or younger who had had a radical mastectomy (conventional or extended) for unilateral carcinoma of the breast and who had histologic evidence of involvement of one or more axillary nodes were considered for inclusion in the study. Patients with locally advanced or metastatic breast cancer, those whose tumors were fixed to the underlying pectoral fascia or muscle, those with a history of cancer, and those with concomitant severe nonmalignant systemic disease were not eligible for the study. The patients were told that they would be receiving either combination chemotherapy or no further treatment after mastectomy. The protocol design was approved by members of the institute's research and ethics committees.

### Study Design

The patients were stratified according to age ( $\leq 49$  years and 50 to 75 years), the number of axillary nodes involved (one to three and four or more), and the type of radical mastectomy (conventional or extended). The patients were then randomly assigned to receive either CMF for 12 cycles or no further treatment. No additional therapy was planned beyond that allowed in the protocol without documented evidence of treatment failure. In particular, no postoperative irradiation and no adjuvant endocrine therapy were administered.

From June 1, 1973, to September 11, 1975, a total of 391 patients

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were enrolled. Randomization was carried out by the central operations office; assignment was based on random-number tables and was balanced with a permuted-block design according to stratification. The median age of the control group was 52 years (range, 29 to 75), and of the CMF group, 51 years (range, 26 to 73). Of the original group of 391 patients, 5 patients could not be evaluated. One patient in each group died of cardiovascular disease within a few months of mastectomy, without evidence of treatment failure. The other three patients had protocol violations: one patient in each group was found to have had bone metastases at the time of mastectomy, and one patient (assigned to receive CMF) had had involvement of supraclavicular nodes at mastectomy. Interim analyses to verify the accrual of patients and drug tolerance were planned every four months. We initially decided that patients who declined to complete 12 cycles of CMF or who completed treatment with serious deviations from the protocol were to be considered unable to be evaluated and that we would rebalance the groups after excluding these patients. However, no such patients were excluded. Twenty-three women declined to complete all 12 cycles of CMF (median number of cycles completed, 5; range, 2 to 11), and six additional patients temporarily discontinued treatment with CMF for more than one month.

Treatment failure was considered to have occurred with the first documented evidence of new manifestations of disease in locoregional areas (including homolateral supraclavicular adenopathy), distant sites, the contralateral breast, or any combination of these sites. Neither second primary cancers nor deaths due to causes other than breast cancer were considered treatment failures.

#### Adjuvant Treatment

CMF treatment consisted of the cyclic administration of cyclophosphamide (100 mg per square meter of body-surface area orally from day 1 to 14), methotrexate (40 mg per square meter intravenously on days 1 and 8), and fluorouracil (600 mg per square meter intravenously on days 1 and 8). Each cycle was followed by a two-week rest period (day 15 to 28). The total dose of cyclophosphamide was adjusted upward or downward to the nearest 25 mg, since fractions of tablets could not be administered. In patients older than 60 years of age, the initial dose of methotrexate was reduced to 30 mg per square meter and that of fluorouracil to 400 mg per square meter. Chemotherapy was started two to four weeks after mastectomy. The dose was reduced if myelosuppression was present.<sup>2</sup>

#### Follow-up Study

Before surgery, all patients underwent a complete physical examination, x-ray study of the chest and skeleton (skull, spine, pelvis, and upper third of femurs), bilateral mammography, a differential blood count with platelet count, and biochemical tests. In the absence of symptoms, physical examination was performed every 3 weeks during the first year, every 6 months for the next 4 years, and every 12 months for the following 10 years. Biochemical tests, chest roentgenography, and bone roentgenography or bone scanning were performed every six to eight months during the first five years and once a year thereafter. Mammography was planned once a year. After the 15th year of follow-up, the patients were examined every 12 to 18 months. In patients with suspicious or controversial radiologic findings, examinations were performed more often. Liver ultrasonography was performed only if there were suspicious clinical or biochemical findings.

#### Percentage of Optimal Dose Received

The percentage of the optimal dose received was calculated as previously reported.<sup>3</sup> Briefly, for all patients, the total administered dose of each drug was calculated. For patients who either completed or refused to complete their treatment program, we calculated the total planned dose of each drug according to the protocol. In patients who had disease progression while receiving adjuvant chemotherapy, the total planned dose of each drug was calculated up to the day the last dose was received. For each drug, the total dose administered was di-

vided by the total planned dose. The percentage of the optimal dose received represented the average of all drugs given.

#### Statistical Analysis

Relapse-free survival was calculated from the date of surgery to the first documented evidence of treatment failure, whereas event-free survival was calculated from the date of surgery to the occurrence of any of the following: treatment failure, a second cancer, or death during complete clinical remission. Death from all causes was used as the end point for overall survival, which was also measured from the date of surgery. The Kaplan-Meier product-limit method<sup>6</sup> was adopted to estimate survival. The null hypothesis concerning the differential effects of treatment in univariate (unadjusted) analysis or after adjustment for prognostic factors (adjusted analysis) was tested by means of the log-rank test,<sup>7</sup> and all P values were two-tailed. In addition, Cox multiple regression analysis<sup>8</sup> was performed. The regression coefficients were estimated on the basis of maximum-likelihood criteria, and their significance was tested by the Wald test.<sup>9</sup> The relative risks were estimated as hazard rate ratios. The median follow-up at the time of the current analysis (August 1994) was 19.4 years. Only one patient in complete clinical remission was lost to follow-up, after 15.8 years; the minimal follow-up was 18.1 years.

#### RESULTS

At the 20-year analysis both relapse-free and overall survival remained significantly better in patients treated with surgery plus adjuvant chemotherapy than in patients treated with surgery alone (Fig. 1). In the control group the median time to relapse was 40 months, as compared with 83 months in the CMF group; the median lengths of overall survival were 104 and 137 months, respectively. It is worth emphasizing that most recurrences occurred within the first three years after radical mastectomy, but in the analysis of survival the two curves started diverging only after the seventh year. The median survival after the diagnosis of relapse was 36 months in the control group, as compared with 32 months in the CMF group. Eighteen years after relapse, and after receiving a variety of salvage treatments,<sup>10</sup> 4 percent of the women in the control group were alive with disease, as compared with 5 percent of the women in the CMF group. Thus, salvage therapy had the same palliative effect regardless of whether the patients received or did not receive initial adjuvant chemotherapy. These results reinforce the observation that the difference in overall survival was due to the adjuvant treatment and not to salvage therapy.

Table 1 outlines the main clinical characteristics of the women who entered the study. All medical records were reviewed, and some of these characteristics have changed slightly since our first report.<sup>1,2</sup> Two patients who underwent extended radical mastectomy — one in each group — were originally classified as having four positive axillary nodes, whereas our review showed that in each case three were axillary nodes and one was an internal mammary node. In addition, the definition of premenopausal now includes all perimenopausal patients — that is, women whose last menstrual period was within 12 months before the diagnosis of breast cancer and women less than 50 years of age who had had a hysterectomy before the diagnosis of breast can-

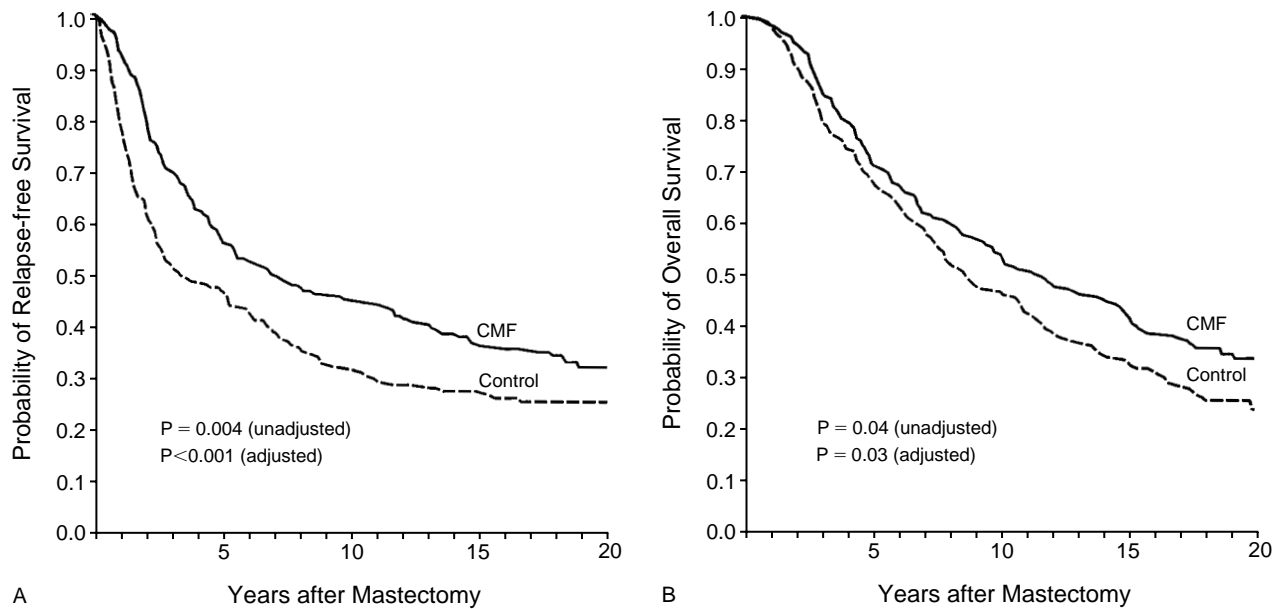


Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) According to Treatment Group.

With respect to relapse-free survival, 48 of 179 patients in the control group were disease-free at 20 years, as compared with 74 of 207 patients in the CMF group. With respect to overall survival, 44 of 179 patients in the control group were alive at 20 years, as compared with 70 of 207 patients in the CMF group.

cer. All these patients were previously considered postmenopausal. The main characteristics of the premenopausal and postmenopausal women were similar in the two treatment groups.

Table 1 also shows treatment outcome with respect to the main subgroups of patients. In all subgroups except postmenopausal women and patients with 4 to 10 positive nodes, a benefit from adjuvant CMF was evident, as reflected by either a lower rate of unfavorable events or longer survival. The greatest benefit of CMF treatment was among patients with one to three positive nodes (Table 1). Of the 9 women in the control group who presented with more than 10 positive lymph nodes, none were alive at 20 years, whereas 3 of 18 such patients in the CMF group were alive at 20 years, albeit with cancer. In this subgroup, the median length of relapse-free survival was 7 months in the control group and 36 months in the CMF group; the median lengths of overall survival were 27 and 78 months, respectively.

Table 1 shows rates of relapse-free survival and overall survival at 20 years according to menopausal status. At 20 years, there was still a sharp difference in the rates of both relapse-free and overall survival between premenopausal and

postmenopausal patients. After adjuvant chemotherapy with CMF, 47 percent of the premenopausal women were alive at 20 years, as compared with 22 percent of the postmenopausal women. Table 2 shows that the frequency of drug-induced amenorrhea (defined as the cessation of menses for at least three months during or soon after the administration of CMF) correlated with age. The latest analysis confirms our previous finding<sup>11</sup> that there is no significant difference in outcome between perimenopausal wom-

Table 1. Relapse-free and Overall Survival at 20 Years in the Two Groups of Patients, According to Their Characteristics at Entry into the Study.

CHARACTERISTIC	CONTROL GROUP (N = 179)	CMF GROUP (N = 207)	RELAPSE-FREE SURVIVAL*		OVERALL SURVIVAL†	
			CONTROL GROUP	CMF GROUP	CONTROL GROUP	CMF GROUP
	percent of total		percent			
Premenopausal	48	50	26	37	24	47
Postmenopausal	52	50	24	26	22	22
Tumor size‡						
≤2.0 cm	54	50	28	33	22	36
>2.0 cm	46	50	21	31	26	31
No. of involved nodes						
1-3	70	68	29	37	24	38
4-10	25	23	18	26	27	27
>10	5	9	0	0	0	17

\*In the analysis of relapse-free survival, second primary cancers and deaths due to other causes were not considered events. The rate of relapse-free survival was 25 percent in the control group as a whole and 32 percent in the CMF group as a whole (unadjusted relative risk, 0.71; 95 percent confidence interval, 0.56 to 0.90; P = 0.004; adjusted relative risk, 0.65; 95 percent confidence interval, 0.51 to 0.83; P < 0.001).

†The rate of overall survival was 23 percent in the control group as a whole and 34 percent in the CMF group as a whole (unadjusted relative risk, 0.78; 95 percent confidence interval, 0.62 to 0.99; P = 0.04; adjusted relative risk, 0.76; 95 percent confidence interval, 0.60 to 0.97; P = 0.03).

‡Tumor size on pathological analysis.

Table 2. Results of CMF Treatment at 20 Years in Premenopausal Patients According to Whether They Had Drug-Induced Amenorrhea.

CHARACTERISTIC	TOTAL (N = 103)	AGE ≤40 YR (N = 32)	AGE >40 YR (N = 71)	RELAPSE-FREE SURVIVAL*		
				TOTAL	AGE ≤40 YR	AGE >40 YR
				percent of total		
Total series	100	100	100	37	29	40
Amenorrhea	49	22	61	39	29	40
No amenorrhea	27	75	6	30	27	50†
Perimenopausal‡	24	3	33	41	NA	38

\*The 20-year rate of relapse-free survival was 26 percent in the control group as a whole, 17 percent in those ≤40 years of age, and 29 percent in those >40 years of age. NA denotes not assessable (only one patient was alive and disease-free).

†Two of four patients were alive and disease-free.

‡Women whose last menstrual period occurred within 12 months before the diagnosis of breast cancer and women less than 50 years of age who had had a hysterectomy before the diagnosis of breast cancer were considered perimenopausal.

en, women with drug-induced amenorrhea, and women without drug-induced amenorrhea.

Cox regression analysis, including all prognostic variables reported in Table 1, was carried out by resorting to a backward procedure. Relapse-free survival was significantly influenced only by the extent of nodal involvement and the treatment group. The number of involved nodes remained the most important prognostic factor (relative risk for women with >3 positive nodes, 1.74; 95 percent confidence interval, 1.44 to 2.11;  $P < 0.001$ ), followed by the type of treatment (relative

risk with adjuvant chemotherapy, 0.65; 95 percent confidence interval, 0.51 to 0.83;  $P < 0.001$ ). The most important variables influencing total survival were the extent of nodal involvement (relative risk for women with >3 positive nodes, 1.50; 95 percent confidence interval, 1.24 to 1.82;  $P < 0.001$ ), the type of treatment (relative risk with adjuvant chemotherapy, 0.76; 95 percent confidence interval, 0.60 to 0.97;  $P = 0.03$ ), and menopausal status (relative risk for postmenopausal women, 1.29; 95 percent confidence interval, 1.01 to 1.64;  $P = 0.04$ ).

Figure 2 shows the outcome according to the percentage of drugs received in the CMF protocol. In the 42 women who received at least 85 percent of the planned dose of CMF, the rate of relapse-free survival was 49 percent (median survival, 220 months) and the rate of overall survival was 52 percent.

Table 3 shows the rates of event-free survival in the two groups and the cumulative incidence of first relapse according to anatomical site. There were no important differences between groups in the incidence of locoregional relapse and relapse in the contralateral breast. The main therapeutic effect of adjuvant CMF was to reduce the incidence of distant metastases (10 percentage point difference at 20 years between patients who received CMF and those who did not).

Within 20 years after surgery second cancers were detected in 19 patients (5 in the control group and 12 in the CMF group). Various types were found in both groups, but no distinctive pattern prevailed. Similar results were found in 2465 patients treated with adjuvant

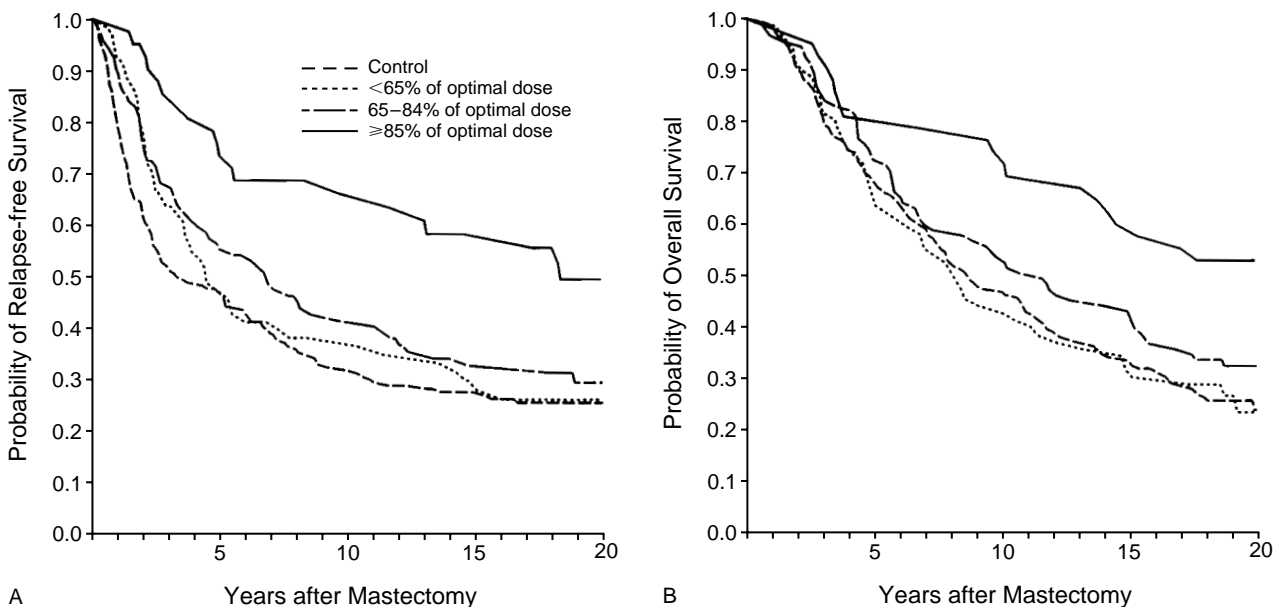


Figure 2. Relapse-free Survival (Panel A) and Overall Survival (Panel B) According to the Percentage of the Optimal Dose Administered.

With respect to relapse-free survival, 48 of 179 patients in the control group were disease-free at 20 years, as compared with 21 of 71 patients given <65 percent of the optimal dose of CMF, 31 of 94 patients given 65 to 84 percent of the optimal dose, and 22 of 42 patients given ≥85 percent of the optimal dose. With respect to overall survival, 44 of 179 patients in the control group were alive at 20 years, as compared with 18 of 71 patients given <65 percent of the optimal dose of CMF, 30 of 94 patients given 65 to 84 percent of the optimal dose, and 22 of 42 patients given ≥85 percent of the optimal dose.

Table 3. Cumulative Event-free Survival and the Incidence of First Relapse in the Two Groups of Patients at 5, 10, 15, and 20 Years.

VARIABLE	5 YEARS		10 YEARS		15 YEARS		20 YEARS	
	CONTROL GROUP	CMF GROUP	CONTROL GROUP	CMF GROUP	CONTROL GROUP	CMF GROUP	CONTROL GROUP	CMF GROUP
	<i>percent</i>							
Event-free survival	45	53*	29	40†	23	29*	18	23‡
Total 1st relapses	53	44	68	54	72	61	73	64
Locoregional	12	10	14	12	15	13	15	13
Contralateral breast	2	2	3	4	4	6	4	7
Distant	39	32	51	38	53	42	54	44
Soft tissue	3	1	4	1	4	1	4	1
Bone	18	12	22	15	23	17	24	17
Viscera	18	19	25	22	26	24	26	26

\*P=0.009.

†P=0.002.

‡P=0.01 (by univariate analysis).

CMF with or without doxorubicin.<sup>12</sup> Twenty-four women died without clinical or radiologic evidence of tumor recurrence (10 in the control group; median age at death, 76 years; 14 in the CMF group; median age at death, 67 years).

### DISCUSSION

Clinical studies<sup>2,3</sup> have established that node-positive breast cancer is not simply a localized disorder and that the prognosis of this disease could be improved by the administration of chemotherapy after surgical removal of the tumor by radical mastectomy. The effectiveness of various forms of adjuvant systemic therapy after 10 years of follow-up has been validated by an international overview.<sup>4</sup>

This long-term analysis of the trial we started two decades ago demonstrates a significant advantage of combination adjuvant chemotherapy that persists for at least 20 years after surgery. The effect was seen for both relapse-free and overall survival, though the magnitude of the changes differed among various subgroups of patients. Overall, the benefit translated into a 34 percent reduction in the relative risk of relapse and a 26 percent reduction in the relative risk of death.

As previously reported,<sup>13</sup> chemotherapy with CMF, as given in our study, failed to improve outcome significantly in postmenopausal women, particularly those older than 60 years of age. Many oncologists interpreted these results to mean that the predominant effect of chemotherapy was chemical castration. We have always maintained that the difference in the effectiveness of the regimen between premenopausal and postmenopausal women was mainly, if not exclusively, due to the low dose of chemotherapy that many postmenopausal patients received, either by protocol design or because of protocol violations, including lack of compliance with the regimen for oral cyclophosphamide.<sup>5</sup> Our results after 20 years of follow-up confirmed our initial observation. A recent study by the Cancer and Leukemia Group B<sup>14</sup> showed that both premenopausal and postmenopausal women given regimens involving high or moderate doses of cyclophosphamide, doxorubicin,

and fluorouracil had significantly better disease-free and overall survival than those given regimens involving low doses. Thus, recent, effective drug programs indicate that treatment outcome is very similar in premenopausal and postmenopausal women<sup>14-17</sup> and that drug-induced amenorrhea is not an important predictor of response.<sup>18</sup>

A recent analysis from the International Breast Cancer Study Group<sup>19</sup> concluded that adjuvant systemic treatments improved outcome mainly by reducing the incidence of first locoregional and distant soft-tissue relapses, whereas the incidence of first recurrences in bones and viscera was influenced much less.

Though our sample was smaller, we found that treatment with CMF resulted in a moderate suppression of micrometastases regardless of their anatomical sites. This observation motivated us to try new regimens — namely, one consisting of doxorubicin (Adriamycin) followed by CMF — to improve relapse-free and overall survival further in patients with more than three positive nodes.<sup>16</sup> Second cancers were not a major problem in the present study. In fact, the cumulative 20-year rate of second cancers in the absence of a relapse of breast cancer was 3 percent in the control group and 6 percent in the patients treated with CMF. In this study we did not observe any case of acute leukemia.

Our experience as well as that of other investigators<sup>14</sup> underlines the importance of avoiding reduced doses of chemotherapy if maximal benefit is to be achieved. These long-term results represent an important step in the contemporary evolution of breast-cancer treatment, which has expanded to include patients with node-negative cancer; new therapeutic choices, including anthracyclines; and the use of chemotherapy as the primary treatment.<sup>14,20,21</sup>

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