

# Long-term prognostic and predictive factors in 107 stage II/III breast cancer patients treated with anthracycline-based neoadjuvant chemotherapy

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**Summary** The heterogeneity of therapeutic modalities and eligibility criteria and the lack of long-term follow-up in most reports of neoadjuvant chemotherapy for breast cancer preclude us from drawing conclusions about its value in clinically relevant patient subgroups. The present study aims to identify predictive and prognostic factors in 107 non-inflammatory stage II/III breast cancer patients treated between November 1980 and October 1991 with an anthracycline-based induction regimen before locoregional surgery. Preoperative chemotherapy comprised 3–6 cycles of doxorubicin (pirarubicin after 1986), vindesine, cyclophosphamide and 5-fluorouracil. Type of subsequent surgery and adjuvant treatment were decided individually. In analysis of outcome, univariate comparisons of end points were made using the log-rank test, and significant ( $P \leq 0.05$ ) pre- and post-therapeutic factors were incorporated in a Cox multivariate analysis. With a median follow-up of 81 months (range 32–164+ months), the median disease-free survival (DFS) is 90.5 months while median overall survival has not yet been reached. Cytoprognostic grade and histopathological response in both the primary and lymph nodes were independent covariates associated with locoregional relapse with or without DFS and overall survival. Eleven patients with pathological complete response remain free of disease with a 68-month median follow-up, while the 18 with residual microscopic disease on the specimen showed a 60% cumulative incidence of locoregional recurrence. Despite encouraging response rates based on clinical or radiological evaluation (87% or 70%), neither method showed any significant correlation with pathological response and failed to contribute prognostic information on patients' outcome. Pathological evaluation of antitumoral activity of primary chemotherapy remains a major source of prognostic information and might be used to select patients in need of additional adjuvant treatment.

**Keywords:** breast cancer; primary chemotherapy; prognostic factors

Neoadjuvant chemotherapy was introduced in the management of patients with locoregionally advanced breast carcinoma [i.e. stage III Union Internationale Contre le Cancer (UICC) (Beahrs et al, 1993)] in the 1970 decade (De Lena et al, 1978) as these patients had a poor prognosis with 5-year survival rates of 10–20% if treated with surgery and/or radiotherapy alone (Fletcher, 1972; Zucali et al, 1976). According to the concept of relationship between tumour burden and curability, this strategy was based on the theoretical advantage of acting without delay on potential systemic disease and added to the arguments for *in vivo* chemosensitivity testing (Feldman et al, 1986) and for better cosmetic and psychological results as a result of conservative breast surgery procedures (Hortobagyi et al, 1988; Valagussa et al, 1990; Fisher and Mamounas, 1995). Adjuvant chemotherapy was simultaneously developed, and the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG, 1992) confirmed its interest in stage I/II tumours – clinical staging and number of axillar lymph nodes involved still remaining the most determinant in the systemic adjuvant treatment selection (Henderson, 1991).

Most neoadjuvant chemotherapy data in breast cancer are single-center experiences, often lacking long-term follow-up (Swain et al, 1987; Mansi et al, 1989; Bonadonna et al, 1990; Valagussa et al, 1990; Mauriac et al, 1991; Fisher et al, 1994; Schwartz et al, 1994; Semiglazov et al, 1994; Smith et al, 1995; van der Wall et al, 1996). In spite of cosmetic advantages and gratifying clinical response rates, evaluation and comparison of these results remain difficult on account of heterogeneous populations, sometimes including inflammatory breast cancer in their cohorts, with different response evaluation methods (combination of physical examination, mammography and echography) and adjuvant treatment selections (Schaaqe-Koning et al, 1985; Feldman et al, 1986; Rouëssé et al, 1986; Swain et al, 1987; Mansi et al, 1989; Jacquillat et al, 1990; Maloïsel et al, 1990; Valagussa et al, 1990; van der Wall et al, 1996). Furthermore systematic pathological assessment of chemotherapy results in the primary tumour has often been limited (Jacquillat et al, 1990; Mauriac et al, 1991) or obtained by multiple biopsies (Feldman et al, 1986; Swain et al, 1987; Mansi et al, 1989; Smith et al, 1995). Consequently, there are neither acknowledged techniques for evaluation of the response nor established prognostic variable consensus for this modality of primary management, nor any validated means to gauge its real contribution to end points as time to progression, disease-free survival (DFS) and overall survival (OS) (Fisher and Mamounas, 1995).

We present a retrospective analysis on 107 women with stage II/III non-inflammatory breast carcinoma treated between November 1980 and October 1991 with an anthracycline-based

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neoadjuvant chemotherapy followed by surgery. As assessment of antitumoral activity was clinical, radiological and histopathological, the study allowed comparisons of their respective value. These results, added to the 7-year median duration of follow-up, make this analysis important in identification of predictive and prognostic parameters likely to assist in the prospective evaluation design of primary cytoreduction in clinically defined localized breast cancer.

## PATIENTS AND METHODS

### Patients

Candidates to neoadjuvant chemotherapy were patients with cytologically or histologically confirmed stage I/III (UICC) breast carcinoma. Premenopausal and perimenopausal women, defined respectively by regular menstrual cycles and amenorrhoea for less than 1 year, were included in the same group of patients for the purposes of this analysis. Informed consent was obtained in all cases according to institutional guidelines.

### Pretreatment evaluation

Patients had a detailed clinical history and physical examination. Diagnosis was usually performed on fine-needle aspiration cytology. Whenever possible, steroid hormone receptor status (oestrogen receptor, ER and progesterone receptor, PR) was established. Cytoprognostic grade was determined on an accepted and validated correspondence with the Scarff, Bloom and Richardson histopathological grading (De Maublanc, 1991). Absence of clinical metastasis was ascertained through a systematic work-up consisting of chest roentgenogram, bone scan and liver ultrasonography. Bilateral mammography completed clinical staging. Electrocardiogram, haemogram and blood biochemistry with liver function tests were performed before starting induction chemotherapy.

### Treatment

Neoadjuvant chemotherapy was based on an AVCF-type regimen (Rouëssé et al, 1986): doxorubicin 40 mg m<sup>-2</sup> day 1, vindesine 2 mg m<sup>-2</sup> day 2, cyclophosphamide 350 mg m<sup>-2</sup> day<sup>-1</sup> and fluorouracil 400 mg m<sup>-3</sup> day<sup>-1</sup> by short (20–60 min) i.v. in fusion from day 1 to day 4. Folinic acid 150 mg m<sup>-2</sup> day<sup>-1</sup> preceded the fluorouracil administration in 50% of patients. After 1986, doxorubicin was replaced by an analogue: pirarubicin (Théprubicine, Bellon, Neuilly/Seine, France) 20 mg m<sup>-2</sup> day<sup>-1</sup> given day 1 to day 3. In absence of progression, patients were given chemotherapy every 4 weeks until no additional objective decrease in clinical size of tumour or nodes occurred. The protocol planned a maximum amount of six cycles before surgery. In case of World Health Organisation (WHO) grade III/IV extra-haematological side-effects (Miller et al, 1981), chemotherapy had to be discontinued and patients had to undergo surgery.

After primary chemotherapy completion, the choice of surgical procedure [modified radical mastectomy (MRM) or partial mastectomy] was decided individually by the collaborating surgeon. Homolateral axillary lymph node dissection was required. If breast-conservation surgical procedure was chosen, frozen-section examination informed of resection margins to provide 2-cm clearance and to remain cosmetically acceptable. If

impossible on account of the width of the excision required, mastectomy was chosen.

Post-operative treatment was the responsibility of the individual, participating oncologists and there were no imposed guidelines. However, generally post-menopausal women received adjuvant tamoxifen for 2 years, while premenopausal patients with ER+ were subjected to hormonal (LHRH agonists) or surgical castration. Depending on the number of courses administered during primary chemotherapy, two or three cycles of the same combination could be given as adjuvant treatment, mainly in responding patients with positive lymph nodes. The decision to undertake locoregional radiotherapy (remaining breast and lymph nodes areas) was left to the responsible oncologist.

### Evaluation of response

Clinical patients' status was assessed at each chemotherapy session and before surgery as specified by WHO guidelines (Miller et al, 1981). Mammography was performed at the beginning and at the end of induction treatment. A partial remission (PR) implied a greater than 50% reduction of the product of the largest perpendicular diameters of measurable lesions, without the appearance of new lesions. Complete response (CR) was defined as complete disappearance of the initial tumour mass. Patients not fulfilling the criteria for CR or PR and without evidence of increase in tumour size or new areas of involvement had stable disease (SD).

We described histopathological response according to the Postsurgical Treatment Pathologic Classification given by the UICC (Beahrs et al, 1993), distinguishing pathological complete response (pCR) in primary (pTO) and lymph nodes (pNO) from other responses (pT+ or pT1–pT4, pN+). However, in some cases, we could not classify response in the primary tumour within the categories of the above-mentioned guidelines as their specimens showed residual tumour consisting of persistence of more or less diffuse scattered tumour cells microfoci with massive tumoral necrosis and areas of fibrosis. We coded such reports as pT9 in our database.

### Follow-up study

After completion of all treatment, patients were carefully followed up every 3 months for 3 years, every 6 months during the next 2 years, then at least yearly. Work-up including mammography and chest radiographs was carried out every 6 months at the beginning, then once a year. Sites of initial tumour relapse were classified as locoregional (whether exclusive or associated to distant recurrence) and distant (isolated and mixed). The database update was closed on 30 June 1994, at which time all living patients had been seen during the previous year.

### Method of analysis

Correlations between histopathological response, recurrence and main patient and tumoral characteristics were assessed with the Pearson Chi-square test. Estimates for local, metastatic and overall DFS, and OS were calculated from the date of diagnosis using the method of Kaplan and Meier (Kaplan and Meier, 1958). Univariate comparisons of end points were made with the log-rank statistic (Mantel, 1966), and a Cox survival model (Cox, 1972) was used to estimate the hazard ratio of events.

**Table 1** Pretreatment patient characteristics (n = 107)

Characteristics	No. of patients (%)
Median age (years)(range)	52 (28–78)
Menopausal status	
Premenopausal <sup>a</sup>	50 (46.7)
Post-menopausal	57 (53.3)
Clinical size of tumour	
T1	3 (2.8)
T2	51 (47.7)
T3	44 (41.1)
T4	8 (7.5)
Tx	1 (0.9)
Clinical lymph node status	
N0	60 (56.1)
N1	37 (34.6)
N2	10 (9.3)
Clinical stage of the disease	
IIA	39 (36.4)
IIB	33 (30.8)
IIIA	26 (24.3)
IIIB	8 (7.5)
X	1 (0.9)
Cytoprognostic grade	
1	14 (13.1)
2	43 (40.2)
3	33 (30.8)
Not available	17 (15.9)
Hormonal receptor status	
ER-PR-	32 (29.9)
ER-PR+	4 (3.7)
ER+PR+	38 (35.5)
ER+PR-	18 (16.8)
Not available	15 (14.0)

<sup>a</sup>Including five perimenopausal patients.

## RESULTS

### Patient characteristics

From November 1980 to October 1991, 125 women were entered in this study, of whom only three had stage I tumours and eight presented inflammatory breast cancer. These patients were excluded from analysis on account of their different natural history and prognosis (Henderson, 1991), in addition to seven other patients refusing surgery after induction chemotherapy. Thus, of 125 patients, 107 (86%) with stage II/III non-inflammatory breast carcinoma and who underwent primary chemotherapy plus surgery are considered in this report. Table 1 summarizes their main characteristics.

### Treatment and toxicity

The median number of cycles of induction chemotherapy administered every 4 weeks per patient was six (range two to six), without dose reduction in > 90% of patients. Except in cases in which patients developed severe extra haematological toxicity (24 patients), surgery was done at the maximal clinical response recording time, i.e. after 2, 3, 4, 5 and 6 cycles in 1, 11 (10.3%), 19 (17.8%), 17 (15.9%) and 59 (55.1%) patients respectively. Grade III/IV myelosuppression complicated with fever requiring hospitalization was seen in 15 patients (14%), two patients developed

**Table 2** Distribution of patient characteristics according to different histopathological responses in the primary tumour (n = 105)

Characteristic	pT0	pT1–pT3	pT9 <sup>a</sup>	Total
No. of patients	11	76	18	105 <sup>b</sup>
Menopausal status				
Premenopausal	5	35	10	50
Post-menopausal	6	41	8	55
Initial clinical T				
T1	0	1	2	3
T2	9	39	2	50
T3	1	30	13	44
T4	0	6	1	7
Tx	1	0	0	1
Initial clinical N				
N0	11	40	8	59
N1	0	28	8	36
N2	0	8	2	10
Initial clinical stage				
IIA	9	27	3	39
IIB	1	24	7	32
III	0	25	8	33
X	1	0	0	1
Cytoprognostic grade				
1	1	12	1	14
2	6	31	4	41
3	1	22	10	33
Not available	3	11	3	17
Oestrogen receptor status				
ER-	4	23	9	36
ER+	4	46	5	55
Not available	3	7	4	14
Clinical response				
Complete	6	11	8	25
Partial	5	52	9	66
Stable	0	11	1	12
Not available	0	2	0	2
Radiological response				
Complete	2	0	2	4
Partial	3	40	10	53
Stable	1	22	2	25
Not available	5	14	4	23
Pathological N				
pN0	11	41	11	63
pN+	0	35	7	42

<sup>a</sup>pT9, pathological response not able to be classed within categories of the Postsurgical Treatment Pathologic Classification given by the UICC (Beahrs et al, 1993) and consisting of tumoral necrosis, areas of fibrosis with persistence of microscopic nests and/or diffuse scattered tumour cells foci.

<sup>b</sup>Pathological tumour size assessment lacking in two patients (i.e. pTx).

grade III acral paraesthesias to vindesine, and asymptomatic decline in left ventricular ejection fraction in three patients motivated cessation of chemotherapy after five cycles. Digestive tolerance was good except in four patients who presented severe vomiting (grade IV). Despite application of refrigerated cap, alopecia of some degree was observed in most patients. Partial mastectomy was the chosen surgical procedure in 37 patients (34.6%) while 70 (65.4%) underwent MRM. After surgery, all patients were free of disease.

Adjuvant treatment included hormonotherapy with tamoxifen in 47 of 57 post-menopausal women (82.5%). Seventeen of

**Table 3** Disease outcome in patients with stage II/III breast cancer (univariate analysis)

Variable	n	LRFa (%)	P-value	Mb (%)	P-value	Deaths (%)	P-value
Clinical T							
T1/T2	54	10 (18.5)		5 (9.3)		8 (14.8)	
T3/T4	52	20 (38.5)	<b>0.008</b>	22 (42.3)	<b>0.00001</b>	23 (44.2)	<b>0.001</b>
Clinical N							
N0	60	9 (15.0)		7 (11.7)		6 (10.0)	
N1/N2	47	21 (44.7)	<b>0.00001</b>	20 (42.6)	<b>0.00001</b>	25 (53.2)	<b>0.00001</b>
Clinical stage							
IIA	39	5 (12.8)		3 (7.7)		4 (10.3)	
IIB	33	8 (24.2)		7 (21.2)		8 (24.2)	
III	34	17 (50.0)	<b>0.0002</b>	17 (50.0)	<b>0.00001</b>	19 (55.9)	<b>0.00001</b>
Oestrogen receptor							
ER+	56	13 (23.2)		11 (19.6)		12 (21.4)	
ER-	36	10 (27.8)	>0.5	12 (33.3)	0.078	16 (44.4)	<b>0.02</b>
Cytoprognostic grade							
1-2	57	7 (12.3)		10 (17.5)		10 (17.5)	
3	33	15 (45.5)	<b>0.0001</b>	10 (30.3)	<b>0.039</b>	16 (48.5)	<b>0.0004</b>
Clinical response							
CR	26	7 (26.9)		4 (15.4)		5 (19.2)	
PR	67	19 (28.4)		19 (28.4)		22 (32.8)	
SD	12	4 (33.3)	>0.5	4 (33.3)	>0.5	4 (33.3)	>0.5
Time to clinical response/C <sup>c</sup>							
≤ C3	68	19 (27.9)		17 (25.0)		20 (29.4)	
> C3	25	7 (28.0)	>0.5	6 (24.0)	>0.5	7 (28.0)	>0.5
Pathological T							
pT0	11	0 (0.00)		0 (0.00)		0 (0.00)	
pT1-3	76	19 (25.0)		21 (27.6)		22 (28.9)	
pT9	18	11 (61.1)	<b>0.0009</b>	6 (33.3)	0.19	9 (50.0)	0.099
Pathological N							
pN0	63	11 (17.5)		10 (15.9)		8 (12.7)	
pN+	42	18 (42.9)	<b>0.0008</b>	17 (40.5)	<b>0.0008</b>	22 (52.4)	<b>0.00001</b>

<sup>a</sup>LRF, locoregional failures (whether exclusive or associated to distant recurrence). <sup>b</sup>M, distant metastasis (whether exclusive or associated to locoregional recurrence). <sup>c</sup>C, cycle.

twenty-four (70.8%) premenopausal patients with ER+ underwent castration. Locoregional irradiation was carried out in 35 patients; in 32 of 96 (33.3%) patients showing viable tumoral cells on the surgical specimen after either conservative surgery [16/32 women (50%) or MRM [16/64 (25%)] and in 3 of 11 patients with a pCR. In patients receiving radiotherapy, no chest wall infection or moist desquamation was observed. Adjuvant chemotherapy was delivered to 30 women; in 14 of 33 (42.4%) women with cytoprognostic grade 3 tumours, in 13 of 36 (36.1%) with ER- and in 23 of 42 (54.8%) with pN+. In all, adjuvant hormone therapy was given to 77 patients (72%) and, in 17 instances, with concurrent chemotherapy.

### Clinical and radiological response

No tumoral progression occurred during chemotherapy. In 26 patients (24.3%), a clinical CR was documented, whereas 67 patients (62.6%) presented a PR. This clinical response occurred before the third cycle in 68 patients (64%). Stable disease was observed in 12 patients (11.2%) (data lacking for two patients).

Radiological response assessment was available in 84 women. Among them, five (6%) were classified as CR, whereas PR was

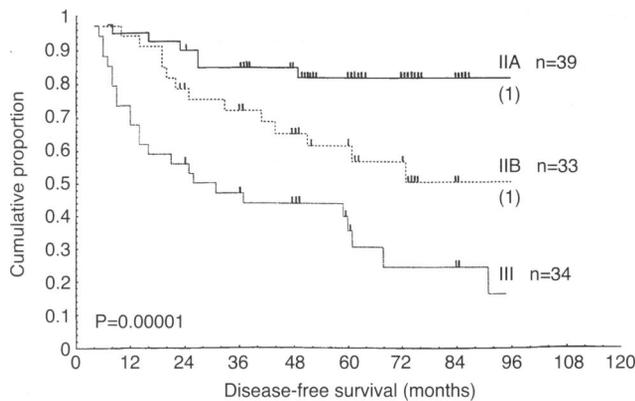
recorded in 54 others (64.3%). Of 18 patients with clinical CR and mammographic assessment available, only five (27.8%) showed a simultaneous radiological CR, illustrating the lack of correlation between radiological and clinical evaluations.

Clinical and radiological responses were not related to menopausal and ER status nor to cytoprognostic grade (data not shown). There was also no significant difference according to the anthracyclin used or initial TNM. Among 54 T1/T2 tumours, 17 (31.5%) achieved clinical CR and 28 (51.9%) PR, while CR and PR were documented respectively in 9 (17.3%) and 38 (73.1%) of the 52 T3/T4 tumours ( $P > 0.5$ ).

### Pathological response (Table 2)

Histopathological response assessment in both the primary (pT) and lymph nodes (pN) was available in 105 of 107 (98.1%) patients (data incomplete in two patients). Ductal carcinoma in situ alone was never seen, whereas 19 specimens showed coexistence of residual invasive tumour (pT+) and small foci of intraductal carcinoma.

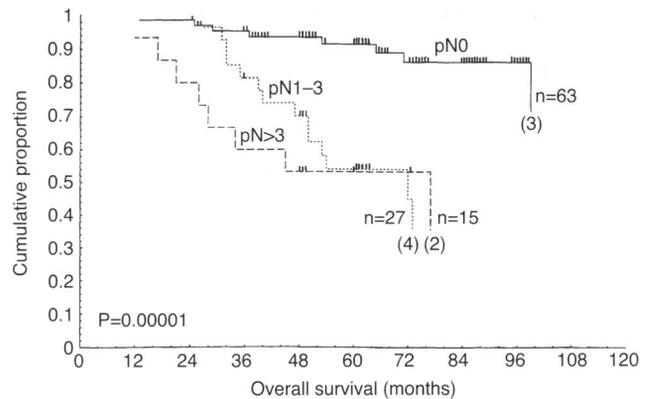
We observed 11 pCR (10.3%) in the primary tumour (pT0), in all cases without microscopically involved lymph nodes (pN0).



**Figure 1** Disease-free survival according to initial clinical stage (median follow-up 81 months). The differences between the three curves are statistically significant (log-rank  $P = 0.00001$ ). Straight sticks represent patients at risk. Numbers in brackets are patients remaining at risk at the end of the curves

Six of those eleven patients had been assessed as clinical CR, five had been clinically classified as PR, only two showing radiological CR. Initial clinical T and N were significantly correlated to the attainment of a pTO status ( $P \leq .005$ ), which was observed mostly in early stage tumours (IIA), all with initial NO disease.

In 18 patients, pathological assessment could not be classified within the pT categories according to the Postsurgical Treatment Pathological Classification. Their residual tumour histopathological pattern was coded as pT9 (see Patients and methods). Among them, we documented 11 pNO (61.1%) (Table 2). In this small sample, pT9 pathological assessment was found to be unrelated to any factor other than large tumours (T3).



**Figure 2** Overall survival according to histological axillary node dissection results (median follow-up 81 months). The difference between the curves of the two groups of women, with or without lymph nodes involvement, is statistically significant (log-rank  $P = 0.00001$ ). Straight sticks represent patients at risk. Numbers in brackets are patients remaining at risk at the end of the curves

Of 60 women with clinical NO, 13 (21.7%) had pN+ after primary chemotherapy (11 of them with more than three involved nodes). Of 37 women with N1 disease, 21 (56.8%) had pN+. Eight of ten patients with N2 disease had pN+. Overall, 15 patients (14%) had more than three involved nodes. The total of women with pNO was 63 (58.9%).

When logistic regression analysis was performed with pretherapy patient characteristics, clinical and radiological responses, only clinical stage IIA appeared significantly correlated with either pNO ( $P = 0.0001$ ) or pTO ( $P = 0.004$ ). Of note, there was no correlation between pathological response and clinical or radiological response.

**Table 4** Multivariate analysis according to Cox model

End points	Significant prognostic factors <sup>a</sup>	P-value	Relative risk	95% CI
Cumulative incidence of LRF <sup>b</sup>	Cytoprognostic grade (1–2/3)	0.014	3.7	1.3–10.7
	pT (pT0/pT1–pT3/pT9)	0.004	4.6	1.6–13.2
	pN (pN0/pN+)	0.0008	7.7	2.3–25.6
Cumulative incidence of M <sup>c</sup>	Cytoprognostic grade (1–2/3)	0.06	2.6	0.9–7.10
	T (T1–T2/T3–T4)	0.002	7.6	2–28.0
	N (N0/N1–N2)	0.009	4.5	1.5–13.8
DFS	Cytoprognostic grade (1–2/3)	0.009	2.8	1.2–6.03
	T (T1–T2/T3–T4)	0.014	11.5	1.6–80.5
	N (N0/N1–N2)	0.008	5.4	1.5–18.7
	pN (pN0/pN+)	0.004	4.6	1.6–13.1
OS	Cytoprognostic grade (1–2/3)	0.005	4.1	1.5–10.8
	T (T1–T2/T3–T4)	0.012	22.4	1.9–256
	N (N0/N1–N2)	0.001	15.2	2.9–77.7
	pN (pN0/pN+)	0.034	5.4	1.1–25.4

<sup>a</sup>Not significant prognostic factors (1) for cumulative incidence of LRF: ER status, T, N and stage; (2) for cumulative incidence of M: ER status, stage, pT and pN; (3) for DFS and OS: ER status, stage and pT. <sup>b</sup>LRF, locoregional failures (whether exclusive or associated to distant recurrence). <sup>c</sup>M, distant metastasis (whether exclusive or associated to locoregional recurrence).

## Tumour recurrence and survival

With a median follow-up of 81 months (range 32–164+ months), we have observed 46 relapses (43%). Local relapse alone occurred in 19 women (17.8%) (including two patients who developed contralateral breast cancer for the purposes of the analysis); 16 (15%) developed distant metastasis as the first sign of disease relapse, while synchronous detection of distant metastasis and locoregional failure was seen in 11 patients (10.3%). Thirty-one patients (29%) have died of metastatic breast cancer. We registered no other causes of death. The median DFS for the cohort is 90.5 months, while median OS has not been yet reached.

### Univariate analysis

Recurrence and its type and death rate were significantly related to well-established variables such as T, N, stage and cytoprognostic grade (Table 3), unlike menopausal status (data not shown). ER status showed a significant correlation only with survival ( $P = 0.02$ ). Of note, clinical response (as well as radiological) and time to clinical response did not reach a statistically significant value on failure rate. Relapse and OS were significantly related to pN (Table 3). Among 42 patients with pN+, 17 (40.5%) developed metastasis and 20 (47.6%) are still alive, compared with 10 (15.9%) metastatic relapses and eight (12.7%) deaths in 63 women with pNO ( $P < 0.001$ ).

Locoregional failure was significantly correlated to pT, being unfavourable to the 18 patients with a pT9 assessment: 11 (61.1%) developed local relapse compared with only 19 of 76 (25%) with pT1–pT3 response ( $P = 0.0009$ ). Although pT failed to significantly correlate with metastasis likelihood or survival (Table 3), all pT<sub>0</sub>pNO patients remain free of recurrence with a median observation time of 68 months (range 38–148+ months). One of them developed ovarian cancer after 130 months of follow-up. Presence of intraductal carcinoma was not associated with incidence of local recurrence; of 19 patients with this histological pattern plus residual invasive tumour (pT+) on the surgical specimen, five developed local relapse (26.3%) compared with 23 in the 77 other pT+ patients (29.9%) without any intraductal component ( $P > 0.5$ ).

The type of surgery and adjuvant radiotherapy does not seem to have influenced locoregional recurrence rate. Of 32 pT+ patients after conservative surgery, 16 only received local radiotherapy. However, the rate of local relapse was the same whether they had received it or not (5 of 16 in both groups, 31.3%). The same remark is valid for adjuvant radiotherapy in the group of pT+ patients after MRM (data not shown). On the other hand, the ones who underwent radiotherapy in this group had more often more than three involved nodes (7 of 16 patients) compared with the others (6 of 48). In patients who received adjuvant chemotherapy (30 women), 12 (40%) developed distant metastasis compared with 15 in 77 (19.5%) without post-surgical chemotherapy. Within these two groups of patients, the former showed a relative high frequency of tumours with ER– (43.3%), cytoprognostic grade 3 (46.7%) and/or pN+ (76.7%) compared with the second (respective rates of 29.9%, 24.7% and 26%). The same proportion of distant metastasis was seen in women receiving adjuvant hormone therapy (19 of 77 patients) or not (8 of 30).

In patients having undergone breast conservation procedure initially, total mastectomy seemed the mainstay treatment for locoregional relapse alone (8 of 17 patients, not including the two patients with contralateral breast cancer). All had salvage mastectomy and radiotherapy was performed in one patient. Five patients

remain free of second failure, while three have developed distant metastasis, their median second relapse-free interval being 15 months (range 2–44+ months). After MRM and in case of local failure (9 of 17 patients), treatment consisted of either surgery (two patients), radiotherapy (three patients) or a combination of radiotherapy and surgery (three patients). One patient refused any treatment and died later of metastatic disease. This salvage treatment prevented later recurrence in only one of these women, the others developing relapse with a median interval of 6 months (range 2–50 months).

Figure 1 shows the actuarial DFS according to clinical staging. Both the 5- and 10-year DFS rates are 81% for 39 stage IIA tumours, whereas the 5-year DFS rate is 61% for 33 patients with stage IIB tumours. Women with stage III tumours (34 patients) have a 5-year DFS rate of 40%, and their median value for DFS is 33 months. The differences between the three curves are statistically significant ( $P = 0.00001$ ). In Figure 2, survival according pN status shows 5- and 10-year OS rates of 92% and 75%, respectively, in patients with pNO, while for those with either  $\leq 3$  or  $> 3$  involved nodes actuarial OS curves meet at 54 months, 5-year OS rate is 54% and median values for OS reach about 70 months ( $P = 0.00001$ ).

### Multivariate analysis

As shown in Table 4, we failed to correlate ER status and clinical stage with either locoregional failure rate, metastasis rate, DFS or OS. Multivariate analysis preserved the significance of cytoprognostic grade to the four above mentioned end points. Both pT and pN were significantly correlated with locoregional failure, while only pN contributed further information to DFS and OS. Clinical T and N were the other significant factors associated with incidence of metastasis, DFS and OS.

## DISCUSSION

Although primary chemotherapy limits the possibility to study the initial biological characteristics of the tumour, it has gained popularity in locally advanced breast cancer in the past 15 years, increasing potential for breast preservation (Fisher and Mamounas, 1995). During this time, adjuvant chemotherapy proved itself gradually (EBCTCG, 1992), and several groups chose to deliver it in neoadjuvant setting for earlier stages (Jacquillat et al, 1990; Fisher et al, 1994; Schwartz et al, 1994; Semiglazov et al, 1994). Our group has been involved in this strategy since 1980, resorting to an anthracycline-based regimen, in agreement with its initial experience which favours their use in adjuvant setting for premenopausal patients with pN+ (Misset et al, 1996). After 1986, the search for new anthracyclines less cardiotoxic than doxorubicin resulted, in France, in the availability of pirarubicin, which was chosen according to encouraging early results (Chevallier et al, 1992).

Our results on survival for stage II/III tumours are similar to data from published series of preoperative chemotherapy (Hortobagyi et al, 1988; Jacquillat et al, 1990; Schwartz et al, 1994). Furthermore, the value of DFS and OS for patients with stage II tumours seems to favour the use of neoadjuvant chemotherapy, with at least a delay in disease progression parameters, when compared with historical experiences of post-operative chemotherapy for primary operated patients (i.e. patients with early breast cancer). The 5- and 10-year DFS rates are both 81% for stage IIA, the 5-year rate is 61% for stage IIB, which compares

favourably with the outcome of the first CMF adjuvant programme of the Milan Cancer Institute (Bonadonna, 1992). Nevertheless, this comparison must be interpreted cautiously as the exact initial pN was not known in our study, while all women included in the Italian trial were pN+. Moreover, only a few reports have addressed the role of neoadjuvant chemotherapy in stage II breast cancer (67% of our patients' population) (Jacquillat et al, 1990; Schwartz et al, 1994; Semiglazov et al, 1994).

Recognition of histopathological response as a significant parameter in determining long-term prognosis of women submitted to primary chemotherapy appears to be the most important contribution of the present report, strengthening the conclusions of several authors (Feldman et al, 1986; Hortobagyi et al, 1988; Maloisel et al, 1990; Ragaz et al, 1994; Frye et al, 1995). Obtaining a simultaneous pCR in primary and lymph nodes seems a valid surrogate end point for long-term relapse-free status. Although pT did not reach a significant value on DFS in multivariate analysis, none of the 11 women who achieved pT<sub>0</sub>pN<sub>0</sub> status has relapsed with a median follow-up of 5.7 years. They did not show a specific pretreatment characteristics distribution other than clinical stage, all but two being stage IIA. The British Columbia Cancer Agency reported 16 pCR (21.6%) obtained in 74 stage III tumour patients after a 6-month ACMF induction regimen (Ragaz et al, 1994). Among these 16 patients, they observed four relapses (25%). Nevertheless, the significant contribution to survival of pCR remains considerable in these locally advanced tumours as 60% of the 58 remaining patients developed recurrence. These results are reinforced by a Russian randomized trial comparing neoadjuvant chemotherapy combined to radiotherapy with radiotherapy alone before mastectomy in 271 patients with stage IIB/IIIA breast cancer (Semiglazov et al, 1994). In the arm with both induction treatments, they observed 30% pCR, 95% remaining free of relapse with a median follow-up time of 53 months. However, both studies report induction chemotherapy combined to radiotherapy, which makes it difficult to elicit the respective roles of both modalities in obtaining a pCR.

Our data also indicate that one should consider carefully the method used for the pathological response evaluation. Multiple biopsies or fine-needle aspirations as done by several investigators (Feldman et al, 1986; Swain et al, 1987; Briffod et al, 1989; Mansi et al, 1989; Smith et al, 1995) may be insufficient. It could preclude identification of a clinical subpopulation with, in particular, a high cumulative incidence of locoregional relapse, which is reflected in our multivariate analysis giving high significance to pT for locoregional failure rate ( $P = 0.004$ ). Thus, in 18 patients (classified as pT<sub>9</sub>), despite significant chemosensitivity pathological marks, we observed residual scattered tumoral cells microfoci, which may reveal a contingent of tumoral cells resistant to chemotherapy. Of these patients, 60% developed local recurrence, and 50% have died from metastatic breast cancer, even when pN<sub>0</sub> was documented. This last point is noteworthy as pN<sub>0</sub> was a highly significant predictive factor for long DFS and OS both in univariate and multivariate analysis. The assessment of residual microscopic disease might erase the benefit in obtaining pN<sub>0</sub>, and the incorporation of these pT<sub>9</sub> patients to the group with putatively beneficial histopathological downstaging, as advocated by others (Smith et al, 1995), may still be arguable. Although the impact of axillary lymph node dissection on survival is often questioned in primary operated patients (Lin et al, 1993), our study emphasizes its major prognostic information for women submitted to primary chemotherapy, as in the last report from the MD Anderson

Hospital (Frye et al, 1995). On the other hand, presence of an intraductal component with residual invasive tumour was not a predictor of local relapse, contrasting with conclusions of others (Schnitt et al, 1984). In this last report, patients had earlier stage tumours, and treatment consisted of local excision plus radiotherapy, which may explain the different observations.

Non-invasive methods for response evaluation (clinical and radiological measurements) did not show any significant prognostic value on patient outcome. However, the only published report (Jacquillat et al, 1990) showing improved DFS for patients who had a major clinical tumour regression following primary chemotherapy cannot be compared with our study as locoregional treatment excluded surgery. Correlation between clinical and radiological response were partial and inaccurate. Like other investigators (Feldman et al, 1986; Fisher et al, 1994; van der Wall et al, 1996), we failed to establish any correlation between any of these two response evaluation methods and pT or pN. This incites us to warn against the exclusive use of both these techniques for evaluation of the tumour response to primary chemotherapy.

In conclusion, the timing of chemotherapy for non-metastatic breast cancer is still debated, and results of a randomized NSABP B-18 trial comparing four cycles of cyclophosphamide and doxorubicin before or after surgery are eagerly awaited (Fisher et al, 1994). However, our study supports that a pCR in both the primary tumour and lymph nodes has a major prognostic value in patients being treated with neoadjuvant chemotherapy for breast cancer. The role of surgery of the primary tumour and lymph nodes as an evaluation tool should be considered before further assumptions are made of its exclusion in programmes of primary chemotherapy for breast cancer.

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