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Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer

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Summary Neoadjuvant chemotherapy is able to reduce the size of the majority of breast tumours and down-stage axillary-node status. The aim of this study was to assess the prognostic value of persistent node involvement after neoadjuvant chemotherapy. A total of 488 patients with T2–T3, N0–N1 breast cancer treated by neoadjuvant chemotherapy followed by tumour excision and axillary lymph-node dissection between 1981 and 1992 were selected from the Institut Curie database. Median follow-up was 7 years. Overall objective response rate before local treatment was 52% and breast tumour size was reduced in 83% of patients. No pathologic nodal involvement was observed in 46.5% of patients. Patients with ≥ eight positive nodes had a very poor median disease-free survival of only 20 months. Their 10-year disease-free survival rate was 7%, while the 10-year disease-free survival rate for patients with no node involvement was 64%. Median survival for patients with ≥ eight nodes positive was 48 months and the 10-year survival rate was 26% ($P < 0.0001$). On multivariate analysis, outcome was strongly correlated with pathological nodal status, tumour grade, hormonal receptor status and clinical response of the tumour. In conclusion, patients with extensive nodal involvement after neoadjuvant chemotherapy have a very poor outcome. Second-line treatment should be considered in this population. © 2000 Cancer Research Campaign http://www.bjcancer.com

Keywords: neoadjuvant chemotherapy; breast cancer; pathological nodal metastasis

The use of neoadjuvant chemotherapy in operable breast cancer may, at least in theory, eliminate early systemic micrometastases, avoid rapid growth of metastases after treatment of the primary site and hopefully prevent emergence of resistant clones (Bhalla and Harris, 1998). The only demonstrated benefit in terms of treatment effects is the achievement of tumour shrinkage, which allows more conservative treatment in some patients (Fisher et al, 1997). Several clinical trials have compared preoperative and postoperative chemotherapy in operable breast cancer, but no significant advantage in terms of long-term survival has been demonstrated to date (Scholl et al, 1994; Semiglazov et al, 1994; Powles et al, 1995; Fisher et al, 1998; Mauriac et al, 1999). The response of breast tumours to preoperative chemotherapy might also be predictive of efficacy of therapy on distant disease and outcome. A possible advantage of primary systemic treatment is to test in vivo tumour response in order to modify treatment or introduce new drugs postoperatively. Finally, the assessment of factors associated with clinical and pathological response is important for prognosis.

The NSABP B-18 trial showed that neoadjuvant chemotherapy was able to reduce the incidence of positive nodes (Fisher et al, 1997). The presence of axillary lymph-node metastases represents the single most important prognostic factor for patients undergoing surgery for primary breast cancer (Haagensen, 1977; Valagussa et al, 1978). The prognosis is also inversely related to the number of involved nodes (Nemoto et al, 1980; Fisher et al, 1983; Carter et al, 1989). Since neoadjuvant chemotherapy reduces node involvement, it could possibly modify the prognostic value of this parameter.

At the Institut Curie, primary radiotherapy for operable breast carcinoma, in order to allow conservative surgery, has been used for decades. Since 1981, neoadjuvant chemotherapy has also been used in large operable breast cancer, prior to local–regional treatment. The aim of this retrospective study was to assess the prognostic value of the persistence of positive axillary nodes after preoperative chemotherapy either by itself or in combination with other prognostic factors.

PATIENTS AND METHODS

Patient selection

The present study is a retrospective analysis of the Institut Curie Breast Cancer database. The selection criteria were prior neoadjuvant chemotherapy for operable T2 or T3, N0 or N1 tumours and surgery with axillary dissection. Patients with metastatic, locally advanced or inflammatory cancer were excluded, as were patients with bilateral tumours, prior cancer and male patients. Prognostic factors were assessed in patients with a follow-up greater than 5 years and for whom information was available about pathological axillary-node involvement.

Between 1981 and 1992, 936 patients who received neoadjuvant chemotherapy were registered and selected according to our

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criteria, except for axillary dissection. Response rates and survival data were assessed in the total population, as a 'reference group'. Axillary dissection was performed in only 507 of these patients. Radiotherapy was proposed as an alternative to surgery. Axillary dissection was performed in only one half of the patients selected in our retrospective study, because of various strategies for local–regional treatment according to patient and/or physician preference, controlled trial arm and tumour response. Radiotherapy alone was predominantly performed in good responders to chemotherapy and/or radiotherapy. In 19 patients, surgery with axillary dissection was performed at the time of local relapse and these patients were excluded from the analysis. Finally, 488 patients were fully eligible for analysis of the prognostic value of persistent node involvement following primary chemotherapy.

Pathological diagnosis and histological grading was performed in all patients on drill biopsy specimens. Steroid receptor levels were assessed by quantitative radioimmunoassay. From 1986 onwards, the cellular S-phase fraction (SPF) was determined in 225 tumours (46%), according to previously described techniques (Remvikos et al, 1993). The cut-off value was 5%, above which the proliferative index was considered to be high.

Treatment modalities

All patients received a median of four (1–6) cycles of neoadjuvant chemotherapy. From 1983 onwards, chemotherapy consisted of FAC or FEC with adriamycin (doxorubicin) 25 mg m^{-2} day 1 and day 8 or epirubicin 50 mg m^{-2} day 1, cyclophosphamide 500 mg m^{-2} day 1 and day 8, 5-fluorouracil 500 mg m^{-2} day 1, day 3, day 5 and day 8. Fifty nine (12%) of the 488 patients did not receive anthracyclines, but thiotepa at a dose of 10 mg m^{-2} day 1 and day 8, in one arm (CTF) of a randomized trial. Before 1983, i.e. for 32 patients (6.5%), chemotherapy consisted of M2AC with doxorubicin 50 mg m^{-2} day 1, cyclophosphamide 500 mg m^{-2} day 1 and methotrexate 25 mg m^{-2} day 2 and day 9. Chemotherapy was administered intravenously at 28-day intervals or longer depending on bone-marrow recovery. 278 (57%) of the 488 patients were included in three different prospective trials. The data for the rest of the patients were also prospectively registered.

After neoadjuvant chemotherapy and before local-regional treatment, response was assessed by clinical measurements of both the primary tumour and the axillary nodes. Response was scored according to the Eastern Cooperative Oncology Group (ECOG) criteria (Oken et al, 1982). A pathological complete response was characterized as pCR when there was no evidence of residual invasive tumour in the breast or axillary lymph nodes.

Local–regional treatment consisted of surgery with axillary dissection either alone or combined with radiotherapy. Conservative breast treatment consisting of tumourectomy before or following radiotherapy was performed in 236 patients (48.4%). Mastectomy could not be avoided in 252 patients (51.6%) and was associated with radiotherapy in 179 patients (71%). In 166 patients (34%), radiotherapy to the breast was performed before surgery in order to increase the chances of breast preservation. Radiotherapy was delivered at a mean dosage of 54 Gy over 6 weeks to the breast or chest wall and lymph-node areas. Patients with complete or almost complete response received a radiation boost to the tumour bed to achieve a total dose of 75–80 Gy.

In controlled trials, postoperative treatment was not planned. For patients who were not included in controlled trials, adjuvant tamoxifen could be given according to the hormonal status of the tumour.

Statistical methods

Survival time and disease-free survival time were measured from the date of diagnosis to the date of death or last follow-up. Differences between treatment groups were analysed by Chi-square tests for categorical variables and Student t-test for continuous variables. The survival and response duration curves were determined using a Kaplan – Meier product-limit method (Kaplan and Meier, 1958; Mantel, 1966). Statistical significance between treatment groups was assessed using the log-rank test. Multivariate analysis was carried out to assess the relative influence of prognostic factors on disease-free survival and overall survival, using the Cox proportional hazards model in a forward stepwise procedure (Cox, 1972). Missing values (tumour grade, receptor levels) were coded as separate variables (missing, not missing) and were retained in the model. So the Cox models were done on the whole sample. P values < 0.05 were considered as significant. Statistical analyses were performed by BMDP software (BMDP Statistical Software Inc, Los Angeles CA, USA).

Nodal extent was divided into 0, 1–3, 4–7, and ≥ 8 nodes in order to increase the number of patients in the last group and to permit comparison with a current French multicentric adjuvant trial in poor prognostic breast cancer patients (PEGASE 01).

RESULTS

Patient characteristics

Median age was 47 years and 75% of patients were premenopausal (Table 1). Median tumour size was 4.5 cm and 55% of patients had clinical lymph-node involvement. The pathological and laboratory characteristics of the tumours were as follows: 80% of tumours were grade 2 or 3, 87% of tumours were ductal carcinomas, progesterone receptors (PR) were positive in 52% of patients and oestrogen receptors (ER) were positive in 57% of patients, S phase was greater than 5% in 41% of patients. Patients who had received preoperative chemotherapy and radiotherapy had the same proportion of nodal involvement as those treated with preoperative chemotherapy only, particularly for women with ≥ 8 nodes positive (6% vs 7.5%; ns).

Tumour response to neoadjuvant chemotherapy

Objective clinical response rates immediately prior to local–regional therapy were 52% with only 7% complete responses. Another 31% of patients achieved a minor response. Only 2% of patients presented tumour progression (Table 2). One patient was lost to follow-up before response assessment. Mastectomy was avoided in 48% of the patients in favour of lumpectomy together with radiotherapy. Conservative treatment was performed in a total of 68.2% of the patients who achieved a major response. Conversely, mastectomy was avoided in only 27% of the patients who did not achieve an objective clinical response. Pathological response was assessed and available in the 288 patients not irradiated prior to surgery. The pathological complete response rate was 5% (14 patients) and was significantly correlated with clinical response ($P = 0.047$). Only one patient classified as a non-clinical responder had a pathological CR. The objective clinical response rate for the complete 'reference group'

Table 1 Patient characteristics

Patient characteristics	*n* (488)	
Tumour size		
T2	312	64%
T3	176	36%
Median (range)	4.5 cm	(2–12 cm)
Clinical lymph-node status		
N0–N1a	219	45%
N1b	269	55%
Age ≤ 40 years	107	21.9%
Median (range)	47 years	(24–71 years)
Premenopausal status	363	74.8%
SBR Grade		
I	85	20%
II	250	59%
III	88	21%
Histology		
ductal	420	87%
lobular	32	6.6%
others	30	6.4%
missing	6	–
Pregesterone receptors		
negative	202	47.6%
positive	222	52.4%
missing	64	–
Oestrogen receptors		
negative	165	42.8%
positive	220	57.2%
missing	103	–
S phase		
≤ 5%	132	58.6%
>5%	93	41.4%
missing	262	–

Table 2 Clinical response evaluated before local–regional treatment

	n (487)	Percentage	95% CI
Complete response	34	7.0%	4.7– 9.3
Partial response ≥ 50%	221	45.4%	41–49.8
Minor response < 50%	152	31.2%	27.1–35.3
Stabilization	70	14.4%	11.3–17.5
Progression	10	2.0%	0.8– 3.2

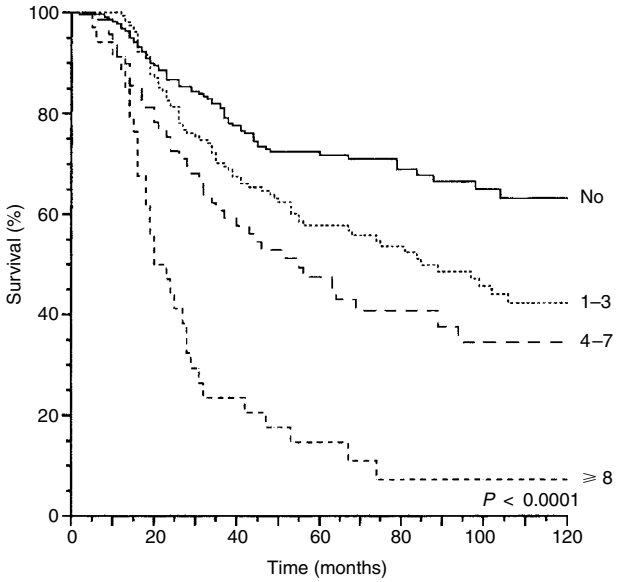

Figure 1 Disease-free survival according to node involvement (*n* = 487)

(936 patients), which included the 488 patients analysed in the present report, was 58.3% with 15.5% of complete clinical responses. The proportion of conservative treatment in the entire population was 71.6%.

Long-term outcome

Median follow-up was 7 years (85 months, range 7–181 months). 157 deaths, 61 local relapses, 191 distant metastases and 215 events have occurred to date. Overall 5-year and 10-year survival rates were 76% (95% CI, 71.8–79.8) and 55% (95% CI, 48.3–60.8), respectively (Table 3). The impact of persistent lymph-node involvement after neoadjuvant chemotherapy on disease-free survival was strongly correlated with the number of positive nodes on axillary dissection (Figure 1, Table 4). Only 15 patients had more than 10 involved nodes. The median disease-free survival was not reached at a median follow-up of 7 years, particularly in patients with no node involvement, who represented 46% of the total population. In contrast, the median disease-free survival for patients with eight or more positive nodes was only 20 months. The 10-year disease-free survival rate was 7% and a similar impact was observed on overall survival (Figure 2, Table 4). The 10-year disease-free survival rate for patients with no node involvement was 64%. Median survival for patients with eight or more positive nodes was 48 months and the 10-year survival rate was 26%. The same analysis was performed in the subgroup of 322 patients who had not received preoperative radiotherapy. The results concerning the impact of persistent pathological node involvement on outcome did not significantly different according to whether or not the patients had received preoperative radiotherapy (Table 5).

Table 3 Long-term survival

(*n* = 487)	3 years (%)	95% CI	5 years (%)	95% CI	10 years (%)	95% CI
Overall survival	88.2	85.2–91.1	75.8	71.8–79.8	54.6	48.3–60.8
Local relapse-free survival	91.2	88.6–93.8	87.9	84.8–91.1	81.8	76.9–86.7
Metastasis-free survival (median = 160 months)	73.6	69.6–77.6	64.3	59.8–68.7	53.1	47.4–58.7
Disease-free survival (median = 99 months)	70.4	66.3–74.6	59.6	55–64.1	47.6	41.9–53.2

Table 4 Survival according to lymph-node status

Nodes	Patients	DFS			OS		
		median (months)	5 years ± SD	10 years ± SD	median (months)	5 years ± SD	10 years ± SD
Total	487 (100%)	99	60 ± 2%	48 ± 3%	not reached	76 ± 2%	55 ± 3%
0	223 (45.8%)	not reached	72 ± 3%	63 ± 4%	not reached	83 ± 3%	64 ± 5%
1–3	159 (32.6%)	85	58 ± 4%	42 ± 5%	125	76 ± 4%	55 ± 5%
4–7	72 (14.8%)	55	47 ± 6%	35 ± 7%	91	68 ± 6%	43 ± 8%
≥ 8	34 (7%)	20	15 ± 6%	7 ± 5%	48	44 ± 9%	26 ± 8%
Logrank test			$P < 0.0001$			$P < 0.0001$	

Table 5 Disease-free survival (DFS) and overall survival (OS) according to lymph-node status and preoperative radiotherapy

Nodes	5-year DFS ± SD		5-year OS ± SD	
	woPRT (*n* = 322)	PRT (*n* = 166)	woPRT (*n* = 322)	PRT (*n* = 166)
0	76.9 ± 6.8%	60.1 ± 12.3%	86.5 ± 5.9%	75.4 ± 10.9%
1–3	61.8 ± 10.2%	52.1 ± 12.9%	83.1 ± 7.8%	66.6 ± 12.3%
4–7	49.1 ± 15.9%	44 ± 19.4%	63.9 ± 15.5%	53.1 ± 17.1%
≥ 8	12.5 ± 13.3%	20 ± 24.9%	54.2 ± 19.9%	20 ± 24.7%

woPRT = without preoperative radiotherapy; PRT = with preoperative radio therapy

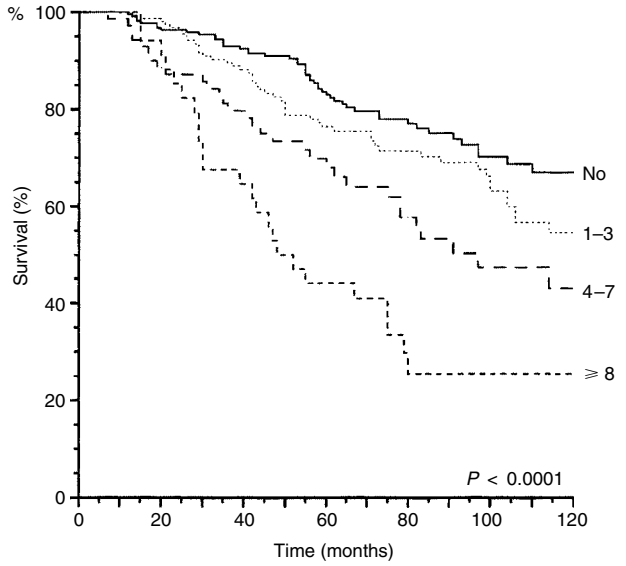

Figure 2 Overall survival according to node involvement (*n* = 487)

The 5-year and 10-year survival rates for the complete 'reference group' (936 patients) were 80.4% (95% CI, 77.8–83.1) and 59.7% (95% CI, 55.7–63.7), respectively, and the corresponding 5-year and 10-year disease-free survival rates were 59.5% (95% CI, 56.4–62.6) and 45.8% (95% Cl, 42–49.6), respectively.

Univariate and multivariate analysis

On univariate analysis, pathological node status was found to be correlated with both clinical lymph-node status before chemotherapy and clinical response of the primary tumour

Table 6 Correlation of histological lymph-node status and other prognostic factors (univariate analysis)

Patient characteristics	*n*	pN0 (*n* = 223)	pN1 (*n* = 265)	*P*
Clinical TUICC				
T2	312	47.4%	52.6%	
T3	176	42.6%	57.4%	ns
Clinical NUICC				
N0 N1a	219	68.5%	31.5%	< 0.0001
N1b	269	27.2%	72.8%	
SBR Grade				
I–II	335	46.3%	53.7%	
III	88	43.2%	56.8%	ns
unknown	65			
Age				
≤ 40 years	107	42.9%	57.1%	ns
> 40 years	381	46.5%	53.5%	
Histology				
ductal	420	44.7%	55.3%	
lobular	32	53.1%	46.9%	ns
others	30	53.4%	46.6%	
unknown	6			
Oestrogen receptors				
negative	165	49.7%	21.8%	ns
positive	220	42.7%	20.5%	
unknown	103			
Progesterone receptors				
negative	202	44.6%	55.4%	ns
positive	222	43.7%	56.3%	
unknown	64			
S Phase				
≤ 5%	132	49.2%	50.8%	
> 5%	93	50.5%	49.5%	ns
unknown	263			
Objective clinical response				
Yes	255	50.2%	49.8%	0.04
No	232	40.8%	59.2%	
Preoperative radiotherapy				
Yes	166	40.9%	59.1%	
No	321	48.0%	52.0%	ns

Table 7 Clinical response to chemotherapy (univariate analysis)

Characteristics	Objective clinical response	No response	P
TUICC			
T2	61.4% (191/311)	38.6% (120/311)	
T3	36.4% (64/176)	63.6% (112/176)	< 0.001
Mean tumour size	4.6 ± 1.5 cm	5.3 ± 1.9 cm	< 0.001[a]
NUICC			
N0 N1a	57.3% (125/218)	42.7% (93/218)	
N1b	48.3% (130/269)	51.7% (139/269)	0.05
SBR Grade			
I–II	51.5% (172/334)	48.5% (162/334)	
III	51.1% (45/88)	48.9% (43/88)	ns
Age			
≤ 40 years	52.3% (56/107)	47.7% (51/107)	
> 40 years	52.4% (199/380)	47.6% (181/380)	ns
Histology			
ductal	52.8% (222/420)	47.2% (198/420)	
lobular	45.1% (14/31)	54.9% (17/31)	
	50% (15/30)	50% (15/30)	ns
Oestrogen receptors			
negative	58.2% (96/165)	41.8% (69/165)	
positive	49.3% (108/219)	50.7% (111/219)	0.08
Pregesterone receptors			
negative	58.2% (117/201)	41.8% (84/201)	
positive	46.4% (103/222)	53.6% (119/222)	0.01
Histological lymph-node status			
pN0	57.4% (128/223)	42.6% (95/223)	
pN1	48.2% (127/265)	51.8% (138/265)	0.04
S Phase			
≤ 5%	53.8% (71/132)	46.2% (61/132)	
> 5%	67.8% (63/93)	32.2% (30/93)	0.03
Preoperative radiotherapy			
Yes	27.7% (46/166)	72.7% (120/166)	
No	65.1% (209/321)	34.9% (112)	< 0.001

[a]Student *t*-test.

(Table 6). 27% of patients diagnosed to have positive nodes on clinical examination prior to treatment were node-negative on pathological examination after chemotherapy and surgery. Clinical response was correlated with small tumour size, negative clinical lymph-node status, absence of progesterone receptors and high S-phase values (Table 7). Univariate analysis also showed that all of the usual prognostic parameters assessed in this study were correlated with disease-free survival and overall survival (Table 8). No correlation was demonstrated between histological response and survival, probably because pathological response was obtained in only 5% of patients. In a multivariate model (Table 9), outcome remained strongly correlated with pathological lymph-node status, with a 4.3-fold increased relative risk of death for patients with eight or more positive nodes. Tumour grade and hormonal receptor status were also associated with survival and disease-free survival. Young age was associated with a short disease-free survival. Preoperative radiotherapy was performed predominantly in poor responders to chemotherapy (72.7%) and therefore is associated to a poorer outcome in the univariate analysis for survival. On the multivariate analysis, the clinical response of the tumour was found to be an independent prognostic value of survival and preoperative radiotherapy had no more prognostic significance.

DISCUSSION

The increase in the number of positive nodes is almost linearly correlated with a decline in survival and the potential to achieve cure (Fisher et al, 1983). The prognostic value of persistent node involvement following neoadjuvant chemotherapy for locally advanced breast cancer has been evaluated in several studies (McCready et al, 1989; Gardin et al, 1995; Machiavelli et al, 1998; Kuerer et al, 1999*a*). Fewer reports have been published in operable breast cancer. Ellis et al (1998) showed that clinical but not pathological axillary-node status was a major predictor of outcome following primary chemotherapy. Conversely, pathological nodal status was reported by Bonadonna et al, 1998) and Cameron et al, (1997) to be the major prognostic factor associated with clinical response to treatment on multivariate analysis. In another smaller series, it was the only prognostic factor identified by a multivariate model (Botti et al, 1995). Data from the MD Anderson Hospital reported similar 10-year survival rates for primary doxorubicin-based chemotherapy. Women with stage III breast cancer had survival rates of 65%, 44%, 32% and 9%, when zero, 1–3, 4–9, and 10 nodes were still involved after chemotherapy, respectively (Frye et al, 1995).

It could be argued that the prognostic significance of the number of nodes still containing tumour after preoperative chemotherapy might simply reflect the number of nodes involved at presentation. However, in the NSABP B18 trial, a 37% increase in the incidence of pathologically negative nodes was seen following preoperative chemotherapy: 43% in the postoperative group compared to 59% in the preoperative group (Fisher et al, 1997). This decrease in pathological nodal involvement was equally distributed in all categories of node involvement (1–3, 4–9 or ≥ 10 positive nodes). However, it is not possible to separately identify those patients in whom all histologically involved nodes were cured by preoperative treatment. In our study, pathological nodal status was significantly correlated with clinical response ($P = 0.04$). The absence of involved nodes may therefore reflect drug sensitivity, at least in some cases, and Cox multivariate analysis revealed this factor to be a more sensitive marker than clinical tumour response.

Clinical response was an independent prognostic factor for survival in this study, as previously reported in other trials performed both in our institution (Scholl et al 1995) and by others (Cameron et al, 1997). In the present study, radiotherapy alone with a radiation boost to the tumour bed was proposed as sole local – regional treatment for very good responders. Consequently, no information was available about pathological axillary lymph-node status in these patients. Pathological tumour response has been reported to be a more powerful prognostic factor than clinical response in locally advanced breast cancer (Sataloff et al, 1995; Kuerer et al, 1999*b*) and more recently in operable breast cancer. The pathological complete response rate including pathological lymph-node status was 9% in the NSABP-B18 trial (Fisher et al, 1998) and quite low in the Milan experience (3%) (Bonadonna et al, 1998).

The persistence of nodal involvement after neo-adjuvant therapy may represent the existence of persistent systemic micrometastases which are ultimately responsible for the patient's demise. However, in the present study, one might expect that patients also given loco–regional radiotherapy would have less nodal involvement for the same degree of micrometastatic disease. The systemic disease had been exposed to identical anti-cancer therapy, but the local nodes would have received radiotherapy. There is a trend to a worse survival for patients who received preoperative radiotherapy for the same number of involved nodes. However, statistical comparisons were not significant.

Table 8 Disease-free survival (DFS) and overall survival (univariate analysis, $n = 487$)

Characteristics	*n*	DFS 5 years (%)	DFS 10 years (%)	Logrank	Overall survival 5 years (%)	Overall survival 10 years (%)	Logrank
TUICC							
T2	311	62.3	45.7		80.9	58.7	
T3	176	54.9	49.1	$P = 0.33$	67.4	47.7	$P = 0.01$
NUICC							
N0 N1a	218	71	59		83.2	63.3	
N1b	269	51	39	$P < 0.0001$	70.1	49.1	$P = 0.0012$
Age							
≤ 40 years	107	48	33		69	48	
> 40 years	380	63	53	$P = 0.0004$	78	57	$P = 0.06$
SBR Grade							
I–II	334	63	51		79.7	62	
III	88	47.7	36	$P = 0.001$	56.5	35.9	$P < 0.0001$
Histology							
Ductal	419	57.3	43.8		74.9	52.2	
Lobular	32	75.8	55.6	ns	86.9	81.8	ns
Progesterone receptors							
negative	201	52	39		66	41	
positive	221	65	52	$P = 0.005$	83	65	$P < 0.0001$
Oestrogen receptors							
negative	165	55	39		68	49	
positive	218	64	47	ns	82	57	$P = 0.02$
Node involvement							
pN0	223	71.8	63.3		83.1	64.4	
pN 1–3	158	57.8	42.3		76.4	54.6	
pN 4–7	72	47.5	34.5		68.1	43.1	
pN ≥ 8	34	14.7	7.3	$P < 0.0001$	44.1	25.5	$P < 0.0001$
Clinical response							
Yes	255	65.1	49.9		79.1	63.1	
No	231	53.3	44.7	$P = 0.04$	72.1	47.2	$P = 0.01$
Preoperative radiotherapy							
Yes	166	52.1	42.1		68.3	46.8	
No	321	63.5	50.4	$P = 0.04$	79.9	59.9	$P = 0.004$
S Phase							
≤ 5%	131	64.4	53.1		86.6	53.3	
> 5%	93	51.1	24.8	$P = 0.009$	66.7	38.4	$P = 0.009$

Prediction of response is important, as response to treatment constitutes a major prognostic factor. In the present study, tumour response was also related to tumour size and clinical tumour shrinkage was more marked in smaller tumours, as also reported in the Milan series (Bonadonna et al, 1998). The probability of axillary lymph-node involvement has been reported to progressively increase with increasing size of the tumour (Nemoto et al, 1980), but this relation was not observed in our study, possibly because only T2 and T3 tumours were analysed. In our experience, absent progesterone receptor (PR) expression correlated favourably with response to chemotherapy and unfavourably with survival. Colleoni had previously reported this correlation in a series of 73 patients receiving neoadjuvant chemotherapy (Colleoni et al, 1999). MacGrogan detected significant chemosensitivity for ER-negative tumours, but not for PR-negative tumours (MacGrogan et al, 1996), whereas other authors failed to observe a correlation between hormone-receptor expression and response to chemotherapy (Jain et al, 1996; Makris et al, 1997). One hypothesis could be that PR-negative tumours have high proliferation, since less differentiated. Therefore they relapse more rapidly but are equally more sensitive to chemotherapy. In more recent publications, patient selection according to biological predictive factors for response, including high S phase and c-erbB-2 overexpression, remains one of the most challenging issues in neoadjuvant chemotherapy (Colleoni et al, 1999). S phase was available in only a small fraction of the patients in this series. Nevertheless, high S phase remained predictive of clinical response to neoadjuvant chemotherapy on multivariate analysis as previously reported (Remvikos et al, 1989). Pathological lymph-node involvement may constitute a response criterion to determine the efficacy of neoadjuvant chemotherapy. The correlation between the risk of developing distant metastases and axillary content is consistent with the hypothesis that axillary involvement is an index of the capacity for tumour spread, but it is not the cause of dissemination and may not be a predictive marker of response to treatment.

How can the efficacy of neoadjuvant chemotherapy be increased? Complete clinical response rates of more than 60% have been obtained following continuous infusion of 5-fluorouracil associated with epirubicin and cisplatin (Smith et al, 1995). New drugs such as taxanes are currently under investigation in combination with anthracyclines as neoadjuvant treatment in order to increase the pathological complete response rate (Costa et al, 1999). The role of docetaxel is being investigated before or after neoadjuvant chemotherapy in the current NSABP trial B27 (Mamounas, 1998). One of the secondary objectives of this trial is to determine whether there might be a benefit from addition of postoperative docetaxel chemotherapy, particularly in a subgroup of patients such as those with residual positive nodes after a

Table 9 Multivariate analysis ($n = 487$)

	Disease free survival				Overall survival		
	n	**RR**	**95% CI**	***P***	**RR**	**95% CI**	***P***
Node involvement							
None	222	1	–		1	–	
1–3	159	1.6	1.2–2.3		1.3	0.9–1.9	
4–7	72	2.3	1.5–3.4	< 0.001	1.9	1.2–3.1	< 0.0001
≥8	34	6.3	4.1–9.7		4.3	2.6–7.1	
SBR Grade							
I–II	333	1	–		1	–	
III	88	1.6	1.2–2.2	< 0.01	1.9	1.4–2.9	0.005
Pregesterone receptors							
positive	221	1	–		1	–	
negative	201	1.4	1.1–2	< 0.05	2	1.4–3.3	< 0.01
Response							
Yes	255	–		1	–		
No	232	–	ns	1.5	1.1–2.1	0.01	
Age							
>40 years	380	1	–		–		
≤40 years	107	1.4	1.1–1.9	<0.05		–	ns

preoperative combination of doxorubicin and cyclophosphamide. The Aberdeen Breast Group has reported the activity of neo-adjuvant docetaxel in patients with a poor response to anthracyline-based chemotherapy (Hutcheon et al, 2000). Other second-line treatments with or without high-dose chemotherapy might also be considered in this population. Although recent studies have reported disappointing results of chemotherapy intensification (Pusztai and Hortobagyi, 1998), we feel that this strategy should be investigated in patients with a high S phase.

Although preoperative tumour debulking is considered to be a favourable prognostic factor, there is still a controversy concerning the need to perform axillary dissection following an excellent clinical response to systemic induction therapy. According to the results of the NSABP B18 trial, 26% of clinically node-negative patients with tumours ≤ 2 cm had pathologically positive nodes after preoperative chemotherapy (Fisher et al, 1997). Although preoperative therapy induces downstaging of axillary lymph-node status, persistent pathological node involvement is an unfavourable prognostic factor and does not argue in favour of elimination of axillary lymph-node dissection. Since the use of sentinel lymph-node biopsy as an alternative to axillary dissection is becoming increasingly popular (Krag et al, 1998), this procedure might be further investigated in patients receiving neoadjuvant chemotherapy (Kuerer et al, 1999*b*). Patients with locally advanced breast cancer and clinically positive axillary lymph nodes following neoadjuvant chemotherapy will benefit from axillary dissection to ensure local control (Kuerer et al, 1998). However, the benefit of axillary dissection in patients with a clinically negative axilla may be minimal and potentially harmful if the axilla is irradiated, particularly as pathological staging does not affect subsequent systemic treatment. A prospective randomized trial of axillary dissection vs axillary radiotherapy in patients with a clinically negative axilla following neoadjuvant chemotherapy is presently underway to evaluate this hypothesis (Kuerer et al, 1998).

In conclusion, pathological lymph-node status after neoadjuvant chemotherapy remains the major prognostic factor for survival in large operable breast cancers. Axillary lymph-node dissection should be considered to be an important component of combined modality therapy for patients with large resectable breast carcinoma, in order to identify subgroups of patients who may benefit from alternative treatments in the adjuvant setting. New strategies must be designed to increase the clinical response rate and pathological tumour sterilization rate. The poor prognosis of patients with extensive lymph-node involvement after preoperative therapy justifies the development of alternative treatment modalities.

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