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# Prognostic factors for survival after neoadjuvant chemotherapy in operable breast cancer: the role of clinical response

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**Abstract**

The aim of this retrospective study was to assess predictive factors for clinical response to preoperative chemotherapy and prognostic factors for survival. From 1981 to 1992, 936 patients with T2-T3, N0-N1 breast cancer who received 2–6 months (median 4) of preoperative chemotherapy were selected from the Institute Curie database. Preoperative treatment was followed by surgery and/or radiotherapy. Median follow-up was 8.5 years (range 7–211 months). The objective response rate before surgery and/or radiotherapy was 58.3%. In stepwise multivariate analysis (Cox model), favourable prognostic factors for survival were the absence of pathological axillary lymph node involvement (Relative Risk (RR) 1.54; $P=0.0004$), low histological tumour grade (RR = 1.54; $P=0.0017$), clinical response to preoperative chemotherapy (RR = 1.45, $P=0.0013$), positive progesterone receptor (PR) status (RR = 1.56; $P=0.0001$), smaller tumour size (RR = 1.37; $P=0.005$) and lack of clinical lymph node involvement (RR = 1.42; $P=0.007$). The association of clinical tumour response with survival is independent of the baseline characteristics of the tumour. Clinical response could be used as a surrogate marker for evaluation of the efficacy of neoadjuvant chemotherapy before assessment of the pathological response.


*Keywords:* Neoadjuvant chemotherapy; Prognostic factor; Breast cancer

## 1. Introduction

Neoadjuvant chemotherapy has become the standard of care for patients with locally advanced breast cancer and has rapidly come to the forefront among potential treatments for patients with earlier-stage operable disease [1,2]. 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 [3–9].The only demonstrated benefit in terms of treatment effects of neoadjuvant chemotherapy in operable breast cancer is the achievement of tumour shrinkage, which allows more conservative treatment in some patients [10]. The response of breast tumours to preoperative chemotherapy might also be predictive of the efficacy of therapy on distant micrometastatic disease and outcome. A possible advantage of primary systemic treatment is to test the *in vivo* tumour response in order to modify treatment or introduce new drugs postoperatively. However, the response of the primary breast tumour to preoperative chemotherapy could simply be associated with better prognostic factors. The standard predictive and prognostic factors established in primary breast cancer may not carry the same value in breast cancer patients initially treated with chemotherapy rather than surgery. The independent prognostic value of tumour response, distinct from that of other prognostic factors such as tumour size, tumour grade and hormone sensitivity, should be demonstrated.

Since 1981, at the Institut Curie, neoadjuvant chemotherapy has also been used in large operable breast cancers, prior to local regional treatment. The aim of this study was to retrospectively assess the prognostic value of clinical response after preoperative chemotherapy in

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breast cancers prospectively registered in the database of one institution.

## 2. Patients and methods

### 2.1. Patients

The present study was a retrospective analysis of the Institut Curie Breast Cancer database. This database was initiated in 1981 to prospectively register data for all patients treated for breast cancer at the Institut Curie [11]. The selection criteria were prior neoadjuvant chemotherapy for operable T2 or T3, N0 or N1 tumours. Patients with metastatic, locally advanced or inflammatory cancer were excluded, as were patients with bilateral tumours, prior cancer and male patients. Between 1981 and 1992, 936 patients who received neoadjuvant chemotherapy were registered and selected according to our criteria. Pathological diagnosis was performed in all patients on core needle biopsy specimens obtained before treatment. Histological grade was performed according to the Scarff, Bloom and Richardson (SBR) method. Steroid receptor levels were assessed by quantitative radioimmunoassays.

### 2.2. Evaluation procedures

Response was assessed after neoadjuvant chemotherapy and before local regional treatment, by clinical measurement by palpation of both the primary tumour and the axillary nodes by two or three examiners (medical oncologist, surgeon and radiotherapist). Response was scored according to the International Union Against Cancer (UICC) criteria. Complete response was defined as the total resolution of the breast mass and regional lymph adenopathy as determined by physical examination, partial response was defined as 50% or greater reduction in the product of the two largest perpendicular dimensions of the breast mass and regional lymph adenopathy and minor response was defined as less than a 50% reduction in the product of the two largest perpendicular dimensions. Stable disease was defined as no measurable change in the product of the two largest perpendicular dimensions, and progressive disease was defined as an increase of at least 25% in the product of the two largest perpendicular dimensions. Clinical response was defined as complete response (CR) or partial response $\geqslant 50\%$ (PR).

### 2.3. Treatment

All patients received a median of four (range: 1–6) cycles of neoadjuvant chemotherapy. From 1983 onwards, chemotherapy consisted of FAC or FEC with Adriamycin (A) (Doxorubicin) 25 mg/m$^2$ days 1 and 8 or Epirubicin (E) 50 mg/m$^2$ on day 1, Cyclophosphamide (C) 500 mg/m$^2$ on days 1 and 8, 5-Fluorouracil (F) 500 mg/m$^2$ on days 1, 3, 5 and 8. A few patients (6.9%) did not receive anthracyclines, but Thiotepa at a dose of 10 mg/m$^2$ on days 1 and 8, in one arm (CTF) of a randomised trial [12]. Before 1983, for 52 patients (5.5%), chemotherapy consisted of M2AC with doxorubicin 50 mg/m$^2$ on day 1, cyclophosphamide 500 mg/m$^2$ on day 1 and methotrexate 25 mg/m$^2$ days 2 and 9, mitomycin 6 mg/m$^2$ on day 1. Chemotherapy was administered intravenously (i.v.) at 28-day intervals or longer depending on bone marrow recovery. Fifty-two percent of the patients were included in three different prospective trials [3,12]. The data for the rest of the patients were also prospectively registered.

Local and/or regional treatment depended on tumour regression in response to chemotherapy. Conservative breast treatment, consisting of tumorectomy before or following radiotherapy, was performed in 303 patients (32.4%). In 367 patients (39.2%) no surgery was performed and local treatment consisted of radiotherapy alone. Mastectomy could not be avoided in 266 patients (28.4%) and was performed with radiotherapy in 192 patients. 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 a complete or almost complete response received a radiation boost to the tumour bed to achieve a total dose of 70–75 Gy.

Axillary dissection was performed in only one-half of 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. Pathological nodal status was then obtained in only 471 patients and has been previously reported in Ref. [13]. Radiotherapy alone was predominantly performed in good responders to chemotherapy and/or radiotherapy.

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

After completion of all treatments, patients were observed every 4 months for 2 years, every 6 months during the next 3 years and then at least yearly.

### 2.4. 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 curves were determined using a Kaplan–Meier product-limit method [14,15]. Statistical significance

between the response groups was assessed using the log-rank test. Multivariate analysis was carried out to assess the relative influence of prognostic factors on overall survival, using the Cox proportional hazards model in a forward stepwise procedure [16]. Missing values (tumour grade, receptor levels) were coded as separate variables (missing, not missing) and were retained in the model. The Cox models were therefore applied to the whole sample. $P$ values $<0.05$ were considered to be significant. Statistical analyses were performed by BMDP software (BMDP statistical software, Inc., Los Angeles, CA 925, USA, 1991).

## 3. Results

Pretreatment patient and tumour characteristics are summarised in Table 1. Median age was 47 years. Seventy-five percent of patients were premenopausal. Median tumour size was 4.5 cm (range: 2–12 cm). Sixty-five percent of the patients had clinical lymph node involvement. The pathological and laboratory characteristics of the tumours were as follows: 82% of tumours were grade II or III, 85% of tumours were ductal carcinomas, progesterone receptors (PR) were positive in 54% of patients and oestrogen receptors (ER) were positive in 58% of patients.

Table 1
Patients' characteristics

| | $n=936$ |
|---|---|
| Tumour size | |
| T2 | 574 (61%) |
| T3 | 362 (39%) |
| Median (range) (cm) | 4.5 (2–12) |
| Clinical lymph node status | |
| N0 | 324 (35%) |
| N1 | 612 (65%) |
| Age (years) | |
| Median (range) | 47 (24–74) |
| Tumour grade | |
| I | 145 (18%) |
| II | 469 (60%) |
| III | 173 (22%) |
| NA (16%) | |
| Histology | |
| Ductal | 746 (85%) |
| Lobular | 66 (8%) |
| Others | 68 (8%) |
| NA (6%) | |
| PR | |
| Negative | 375 (46%) |
| Positive | 434 (54%) |
| NA (14%) | |
| ER | |
| Negative | 305 (42%) |
| Positive | 422 (58%) |
| NA (22%) | |
| Pathological lymph node status | |
| pN0 | 214 (45%) |
| PN1 | 257 (55%) |
| NA (50%) | |

NA, not available; ER, oestrogen receptor; PR, progesterone receptor.

### 3.1. Tumour response to neoadjuvant chemotherapy

The objective response rate before local/regional treatment was 58.3%, with 15.5% complete responses. Another 30.1% of patients achieved a minor response. Only 1.0% of patients presented with tumour progression (Table 2). Mastectomy was avoided in 71.6% of patients in favour of lumpectomy combined with radiotherapy (Table 3). Conservative treatment was performed in a total of 459 (84.1%) of the 546 patients who achieved a major response. Conversely, mastectomy was avoided in only 54.1% of the patients who did not achieve an objective clinical response.

The clinical response rate was lower in larger ($>5$ cm), well differentiated (SBR I, ER- and PR-positive) tumours (Table 4). Age, nodal status and histology were not predictive of clinical response. However, the response rate in lobular carcinomas was slightly lower than in ductal carcinomas ($P=0.06$).

Median follow-up was 8.5 years (range: 7–211 months). To date, 330 deaths, 194 local relapses, 389 distant metastases and 459 events have occurred. The 5- and 10-year survival rates were 80.4% (95% Confidence Interval (CI): 77.8–82.9) and 59.7% (95% CI: 56–63.7), respectively, and the corresponding 5- and 10-year disease-free survival rates were 59.9% (95% CI: 56.8–63.2) and 46.1% (95% CI: 42.5–49.8), respectively. Local

Table 2
Clinical response

| Clinical response | $n=936$ | (%) | Objective response rate (%) | Tumour reduction (%) |
|---|---|---|---|---|
| Complete response (CR) | 145 | 15.5 | | |
| Partial response (PR) $\geqslant 50\%$ | 401 | 42.8 | 58.3 | 88.4 |
| Minor response (MR) $<50\%$ | 282 | 30.1 | | |
| Stable disease (SD) | 99 | 10.6 | | |
| Progression (PD) | 9 | 1.0 | | |

Table 3
Local/regional treatment

| | $n=936$ | (%) | Conservative treatment |
|---|---|---|---|
| Radiotherapy alone | 367 | 39.2 | |
| Lumpectomy and radiotherapy | 303 | 32.4 | 71.6 |
| Mastectomy and radiotherapy | 192 | 20.5 | |
| Mastectomy | 74 | 8.0 | |

Table 4
Correlation of clinical response to neoadjuvant chemotherapy with patient characteristics

| Characteristics $n=936$ | Objective clinical response rate (%) $n=546$ (58.3) | $P$ value |
|---|---|---|
| Tumour size | | |
| T2 | 63.4 | |
| T3 | 48.9 | <0.001 |
| NUICC | | |
| N0 | 60.7 | |
| N1 | 55.9 | NS |
| SBR | | |
| I | 48.3 | |
| II and III | 59.2 | 0.015 |
| Age (years) | | |
| ⩽40 | 64.5 | |
| >40 | 57.5 | NS |
| Histology | | |
| Ductal | 58.7 | |
| Lobular | 47.0 | 0.06 |
| ER | | |
| Negative | 63.6 | |
| Positive | 55.5 | 0.02 |
| PR | | |
| Negative | 64.0 | |
| Positive | 52.3 | 0.0008 |
| Histological lymph node status | | |
| pN0 | 57.9 | |
| pN1 | 50.2 | NS |
| Local/regional treatment | | |
| Conservative | 68.5 | |
| Mastectomy | 32.7 | <0.001 |
| Radiotherapy alone | | |
| Yes | 66.8 | |
| No | 52.9 | <0.001 |

relapse-free survival (LRFS) rates were 82.9% (95% CI: 81.2–84.6) at 5 years and 73.9% (95% CI: 71.3–76.5) at 10 years. LFRS was not significantly different between responders and non-responders ($P=0.49$).

In the univariate analysis, prognostic factors for survival were clinical tumour size, clinical nodal status, ER and PR status, tumour grade, pathologic nodal status and clinical tumour response (Table 5). Five and 10-year survival rates according to clinical tumour response are summarised in Table 6 and Figs. 1 and 2.

On forward stepwise multivariate analysis (Cox model), favourable prognostic factors for survival were the absence of pathological axillary lymph node involvement ($P=0.0004$), low histological tumour grade ($P=0.0017$), clinical response to preoperative chemotherapy (RR = 1.45, $P=0.0013$) positive PR status ($P=0.0001$) smaller tumour size ($P=0.005$) and lack of clinical lymph node involvement ($P=0.007$) (Table 7).

Table 5
Univariate analysis (overall survival)

| Patients' characteristics | 10-year survival (%) | Log-rank test |
|---|---|---|
| Tumour size | | |
| T2 | 63.9 | $P=0.002$ |
| T3 | 53.6 | |
| Clinical lymph node status | | |
| N0 | 67.4 | $P=0.0002$ |
| N1 | 55.8 | |
| Age (years) | | |
| ⩽40 | 60.7 | $P=0.21$ (NS) |
| >40 | 56.4 | |
| Tumour grade (SBR) | | |
| I and II | 63.8 | $P=0.0007$ |
| III | 47.7 | |
| ER | | |
| − | 52.9 | $P=0.0032$ |
| + | 60.9 | |
| PR | | |
| − | 52.1 | $P=0.0001$ |
| + | 66.2 | |
| Pathological lymph node status | | |
| No axillary dissection | 63.1 | $P=0.0001$ |
| | | $P<0.0001$ |
| pN0 | 68.1 | |
| 1–3 pN1 | 55.9 | |
| >3 pN1 | 32.6 | |
| Clinical response | | |
| yes | 65 | $P=0.001$ |
| no | 52.9 | |

Table 6
Overall survival according to clinical response

| Response | Patients $n$ (%) | 5-year survival (%) | S.D. | 10-year survival (%) | S.D. |
|---|---|---|---|---|---|
| CR | 145 (15.5) | 88.3 | 2.8 | 76.2 | 4.2 |
| PR⩾50% | 401 (42.8) | 80.9 | 2.0 | 60.7 | 3.0 |
| PR<50% | 282 (30.1) | 80.1 | 2.4 | 58.6 | 3.5 |
| SD | 99 (10.6) | 68.6 | 4.8 | 38.2 | 5.8 |
| PD | 9 (1.0) | 66.7 | 15.7 | 44.4 | 21.0 |
| Total | 936 | 80.4 | 1.3 | 59.7 | 1.9 |

S.D., standard deviation.

## 4. Discussion

As response to preoperative chemotherapy is correlated with survival, response could be used as an intermediate endpoint to determine the value of new chemotherapy regimens or new drugs administered after well-established regimens [17]. Since this intermediate endpoint can be achieved within weeks after starting preoperative chemotherapy, new regimens or new active agents could be evaluated promptly and useful conclusions could be drawn without a 5- to 10-year waiting

Table 7
Multivariate Cox analysis (overall survival) ($n = 936$, 330 deaths)

| | RR | $P$ value |
|---|---|---|
| Pathological lymph node status | | |
| pN0 | 1 | |
| pN1 | 1.54 | 0.0004 |
| Tumour grade | | |
| I–II | 1 | |
| III | 1.54 | 0.0017 |
| Clinical response | | |
| Responders | 1 | |
| Non-responders | 1.45 | 0.0013 |
| PR | | |
| Positive | 1 | |
| Negative | 1.56 | 0.0001 |
| Tumour size | | |
| T2 | 1 | |
| T3 | 1.37 | 0.005 |
| Clinical lymph node status | | |
| N0 | 1 | |
| N1 | 1.42 | 0.007 |

RR, relative risk.

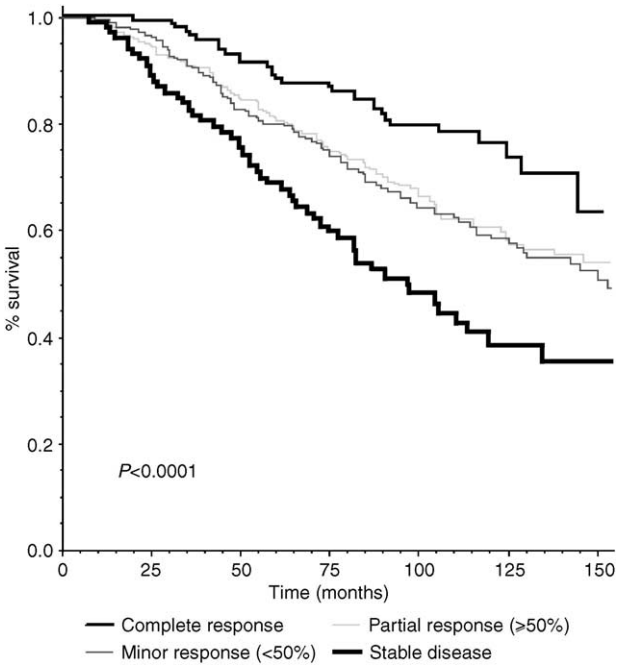


Fig. 1. Overall survival according to clinical response.

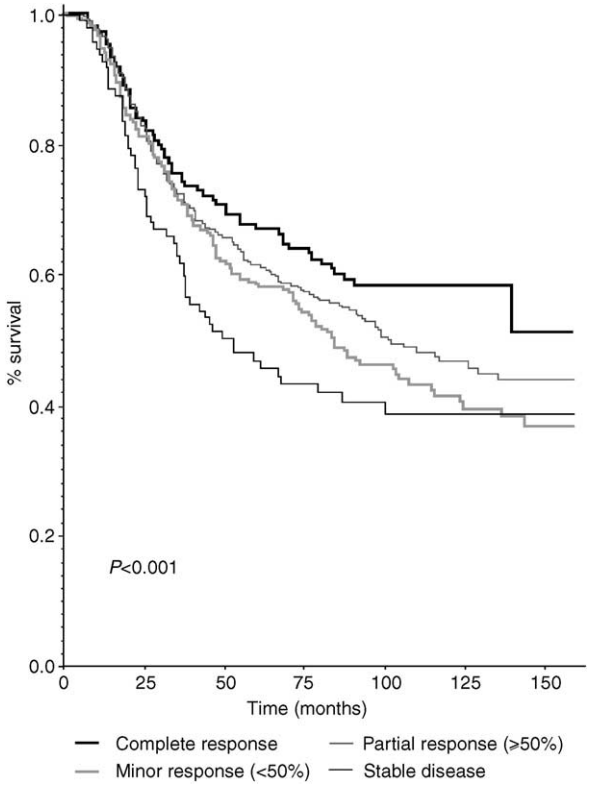


Fig. 2. Disease-free survival according to clinical response.

period, as is currently the case after the use of post-operative adjuvant therapy [18].

In our study, based on a review of data from a single institution with a long follow-up, the clinical response to neoadjuvant chemotherapy was an independent prognostic factor for survival in the multivariate analysis. We have previously reported this result in a smaller series from a trial performed in our institution [19]. The prognostic value of clinical response is variably appreciated and studies are reviewed in Table 8. It has been observed to be significant by several authors [20–22]. In the study by Ellis [23] on 185 patients, clinical responders had an improved DFS ($P = 0.009$) and OS ($P = 0.08$) compared with non-responders. There was no association between pathological complete remission (pCR) and survival. Clinical CR (cCR) does not define a more favourable subgroup compared with those not obtaining cCR. A recently published European Organization for Research and Treatment of Cancer (EORTC) trial did not find clinical objective response to be a significant prognostic factor in multivariate analysis [8]. Pathological tumour response has been reported to be a more powerful prognostic factor than clinical response in locally advanced breast cancer [24–26] and, more recently, in operable breast cancer [5,8,27]. We have previously reported the results in 488 patients treated surgically out of this series of 936 patients [13]. Pathological response was assessed and available in the 288 patients not irradiated prior to surgery. The pCR rate was 5% (14 patients) and was significantly correlated with the clinical response ($P = 0.047$). Only 1 patient, classified as a non-clinical responder, had a pCR.

Although pathological response is the strongest prognostic factor, discrepancies have been observed between the various classifications [24,25,28–31]. Response rates could vary according to various parameters, such as complete disappearance of tumour cells or 'nearly' CR, residual *in situ* carcinoma, dissociation between breast and axillary node responses and pathologist's experience.

Table 8
Prognostic value of response of patients with operable breast cancer treated with neoadjuvant chemotherapy-review of the literature

| Author [Ref.] | Year | Patients *n* | | % of response | DFS[a] | | OS[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Univariate | Multivariate | Univariate | Multivariate |
| Jacquillat [20] | 1991 | 250 | cCR | 30.0 | NA | NA | NA | NA |
| | | | pCR | NA | NA | NA | NA | NA |
| | | | cR | 71.0 | Yes | 0.028 | Yes | 0.005 |
| Scholl [19] | 1995 | 200 | cCR | 22.5 | NA | NA | NA | NA |
| | | | pCR | NA | NA | NA | NA | NA |
| | | | cR | 60.0 | No | Yes | 0.05 | Yes |
| Cameron [21] | 1997 | 47 | cCR | | | | | |
| | | | pCR | 17.0 | NA | NA | 0.005 | NA |
| | | | cR | 63.8 | NA | NA | 0.005 | NA |
| Ellis [23] | 1998 | 185 | cCR | 36.0 | No | No | No | No |
| | | | pCR | 9.1 | No | No | No | No |
| | | | cR | 82.0 | 0.009 | No | 0.08 | No |
| Bonnadonna [27] | 1998 | 536 | cCR | 16.0 | 0.001 | No | NA | NA |
| | | | pCR | 3.0 | 0.001 | 0.034 | NA | NA |
| | | | cR | 76.0 | | | | |
| Fisher [6] | 1998 | 747 | cCR | 36.0 | 0.0014 | NA | No (0.19) | NA |
| | | | pCR | 5.0 | 0.0001 | NA | 0.06 | NA |
| | | | cR | 80.0 | NA | NA | NA | NA |
| van der Hage [8] | 2001 | 350 | cCR | 6.6 | No | No | No | No |
| | | | pCR | 3.7 | NA | NA | 0.008 | NA |
| | | | cR | 49.0 | No | No | No | No |

cCR, clinical complete response; pCR, pathological complete response; cR, clinical response; NA, not available; DFS, disease-free survival; OS, overall survival.
[a] Numbers refer to *P* values from statistical tests.

Several studies have addressed the discrepancy between the clinical CR and pCR. Pathological response is associated with clinical response, but a poor correlation is observed with residual active invasive tumor in clinical complete responders: 4/11 (36%) in the study by Machiavelli [32], 16 out of 22 (73%) in the EORTC study [8], 159 out of 248 (64%) in the National Surgical Adjuvant Breast Project (NSABP)-B18 trial [6]. In Herrada's study, 100 patients with locally advanced breast cancer were registered and treated in prospective trials of neoadjuvant chemotherapy. These authors evaluated the correlation between physical examination and sonographic and mammographic measurements of breast tumours and regional lymph nodes with pathological findings [33]. In this study, physical examination was the best non-invasive predictor of the real pathological findings based on measurement of the primary tumour, whereas sonography was more closely correlated with the real dimensions of the axillary lymph nodes.

The development of a cCR with an incomplete pathological response following preoperative therapy may be associated with only partial eradication of occult metastases. Perhaps distant disease can only be eradicated by a preoperative regimen that completely eliminates the primary breast tumour. A pathological complete response to preoperative therapy should be of greater importance than a cCR. However, the great majority of pathological complete responders are observed among clinical complete responders and pCR is rarely observed in non-responders. In our series, complete responders clearly had a better outcome than the other patients. Interestingly, no survival difference was observed between objective responders (PR $\geqslant$50%) and minor responders (PR $<$50%) (Table 6). A clear cut-off in 10-year survival was observed only between three categories: complete responders with a 10-year survival of 76.2%, partial responders ($\geqslant$50% and $<$50%) with a 10-year survival of approximately 60% and non-responders with a 10-year survival of 38.2%.

As observed, tumour progression during preoperative chemotherapy is rare (1.0%) in our series and in other trials: 3% in the NSABP B18 [10] or 1.4% in the EORTC trial [8]. Non-responders to neoadjuvant chemotherapy have a poor outcome: 10-year survival of 38%. In a recent report from the M.D. Anderson Institute, the outcome of non-responders was even poorer in the subgroup of patients who also had pathologically-positive lymph nodes and ER-negative disease [34].

Tumour clinical response was also related to tumour size: clinical tumour shrinkage was more marked in smaller tumours, as reported in the Milan series [27]. PR

or ER expression, and SBR I grade correlated unfavourably with response to chemotherapy and favourably with survival. These well-differentiated tumours, with a usually low proliferation rate, are less sensitive to chemotherapy, but have a lower risk of relapse. These factors are favourable prognostic factors for survival and unfavourable predictive factors for response [35]. Ovarian suppressive effect of the preoperative chemotherapy or the later use of hormonal therapies as postoperative treatment could also contribute to the prognostic value of hormonal receptor status.

pCR is infrequent in the largest trials: 11% in the NSABP B18 and 4% in the EORTC 10902. This point emphasises the need for better therapies to increase the incidence of pCR. The efficacy of neoadjuvant chemotherapy should be increased. cCR rates of more than 60% have been obtained following continuous infusion of 5-fluorouracil associated with epirubicin and cisplatin [36]. New drugs such as the taxanes are currently under investigation in combination with anthracyclines as neoadjuvant treatment in order to increase the pathological complete response rate [30,37]. The role of docetaxel has been investigated before or after neoadjuvant chemotherapy in the NSABP trial B27 [18]. The addition of preoperative docetaxel (Taxotere) to preoperative doxorubicin and cyclophosphamide (AC) resulted in improved clinical and pathological tumour responses [38]. The Aberdeen Breast Group has reported the activity of neo-adjuvant docetaxel in patients with a poor response to anthracyline-based chemotherapy [31]. Patients with large and locally advanced breast cancers received four cycles of anthracycline-based chemotherapy. Responders were randomised to receive either another four cycles of CVAP or four cycles of docetaxel. All patients whose tumours failed to respond received a further four cycles of docetaxel. A significantly higher clinical response (94% versus 66%) and pCR (34% versus 16%) was seen in patients randomised to receive docetaxel and 3-year survival was better. Primary treatment with docetaxel following an anthracycline-based treatment regimen resulted in significantly increased survival rates and disease-free interval compared with continued anthracycline-based treatment [39].

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 [40], we feel that this strategy should be investigated in patients with a high S-phase content. High S phase is correlated with a clinical response to neoadjuvant chemotherapy [41,42]. It could also be proposed that pCR divides patients according to their already predetermined prognoses. Therefore, the hypothesis that stronger therapies may increase the response rate, and thereby survival should be further demonstrated.

In conclusion, the association of tumour response with survival is independent of the baseline characteristics of the tumour. Clinical response before assessment of pathological response could be used as a surrogate marker to evaluate the efficacy of neoadjuvant chemotherapy. More active systemic and local therapies are needed for patients with breast cancer refractory to neoadjuvant chemotherapy.

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