Multimodality Treatment of 128 Patients with Locally Advanced Breast Carcinoma in the Era of Mammography Screening Using Standard Polychemotherapy with 5-Fluorouracil, Epirubicin, and Cyclophosphamide

Prognostic and Therapeutic Implications

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BACKGROUND. Locally advanced breast carcinoma is associated with a poor prognosis. With single treatment modalities, i.e., surgery and/or radiation therapy, results have been consistently dismal. However, several earlier reports have indicated improvement in survival with a combined modality approach, i.e., the utilization of systemic therapy.

METHODS. Between 1991 and 1994, 128 patients with locally advanced noninflammatory or inflammatory breast carcinoma (LABC) were treated with a combined modality strategy consisting of 4–6 courses of preoperative 5-fluorouracil (600 mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) every 3 weeks, followed by modified radical mastectomy or sector resection with axillary dissection in combination with postoperative radiotherapy and concomitant cyclophosphamide (850 mg/m^2). Postoperatively, 3–5 adjuvant courses of FEC therapy were given. Nine percent of the patients received preoperative radiotherapy because the FEC therapy was not sufficiently effective. One-third of the patients were given tamoxifen (20 or 40 mg daily) at the end of the multimodal therapy.

RESULTS. Clinical responses were observed in 60% of the patients; 5% had complete responses (CR) and 55% had partial responses (PR). Stable disease (SD) was observed in 40%. No patient had progressive disease (PD) preoperatively. With a median follow-up of 37 months, the median disease free survival (DFS) and median overall survival (OS) were 29 and 54 months, respectively. The actuarial 5-year DFS and OS were 36% and 49%, respectively. The locoregional recurrence rate was 20%, and 53% of the patients experienced systemic relapse. Univariate analysis revealed a significant prognostic difference according to clinical stage of LABC in favor of less advanced stages. Clinical and biologic parameters linked to a significantly worse prognosis were the presence of inflammatory breast carcinoma and peau d'orange. There was a significant trend of worse prognosis for patients receiving below 60% and 75% of the intended dose intensity with reference to DFS and OS, respectively.

CONCLUSIONS. Standard dose preoperative and postoperative FEC therapy combined with surgery and radiotherapy in the era of mammography screening seem

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to yield results comparable to those achieved with other conventional strategies in the treatment of unscreened populations. ***Cancer* 1998;83:936–47.**

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Locally advanced breast carcinomas (LABCs) constitute 10–29% of all breast carcinomas in industrialized countries.[1,2] The corresponding figures for Sweden in the era of mammography screening were 6.0% and 4.4% in 1989 and 1995, respectively (unpublished data from the South Swedish Breast Cancer Registry). LABC, classified according to (UICC) criteria[3] as Stage IIB (T3N0 only), III, or IV (ipsilateral supraclavicular lymph nodes only), represents a heterogenous group of tumors with differences in locoregional extension, biologic behavior, and prognosis.[2,4,5] Patients with LABC have early relapse and poor survival when treated only with surgery and/or radiotherapy.[2,4] Five-year overall survival figures of 10–30% have been reported, with few patients surviving 10 years.[2] Inflammatory breast carcinoma (IBC), a subgroup of LABC, is a highly aggressive type of breast carcinoma; patients have a 5-year survival rate of 0–20% and a median survival of 4–29 months after receiving only locoregional therapy.[5,6] The incidence of IBC has been reported to represent 1–4% of overall breast carcinoma incidence in the Western world.[2,7]

Comparisons among studies are difficult due to major variations in diagnostics, eligibility and response criteria, tumor type, and the scheduling and duration of treatment modalities.[2,4,8] With the introduction of multimodality therapy, prognosis has improved for patients with LABC. Five-year disease free survival figures of 30–70% have been reported, with overall survival ranging from 35% to 80%.[2,4,8] Corresponding figures for IBC were 20–50% and 30–75%, respectively.[2,8] Although most data were derived from Phase II trials and retrospective studies, it is now widely considered acceptable to combine locoregional therapy modalities with systemic therapy to improve local control and eradicate distant micrometastases already present at diagnosis.[2,5,8–11]

In this article, we report on multimodal therapy for 128 patients with LABC who were treated with neoadjuvant chemotherapy consisting of standard dose FEC followed by surgery, radiotherapy, and further FEC therapy. The primary aim was to determine the objective response rate. Secondary aims were to study the frequency of local relapse as well as disease free survival (DFS) and overall survival (OS) in subsets of patients with LABC.

MATERIALS AND METHODS

Patients and Diagnostic Procedure

One hundred twenty-eight patients with cytologically and/or histopathologically proven locally advanced breast carcinoma were enrolled in the treatment protocol between May 1991 and December 1994 at eight oncology departments in Sweden.

The design was not randomized because the population was considered too limited to allow a randomized study within a reasonable time period, as well as for statistical reasons.

Baseline Investigations

Chest X-ray and blood chemistry were recommended (entry requirements: Hb >100 g/L; leukocyte count $>3.0 \times 10^9$/L; platelet count $>100 \times 10^9$/L; and S-albumin, renal, and hepatic functions within normal limits). Ultrasound or computed tomography (CT) of the liver was undertaken only if the laboratory values for the liver were abnormal. Mammography and bone scan were recommended. Hormone receptor and DNA analysis were performed if material was available. Estrogen and progesterone receptor status were analyzed with biochemical assays. Receptor positivity was defined as ≥10–15 fmol/mg protein or ≥0.1–0.3 fmol/μg DNA. DNA analyses (S-phase and ploidy) were performed by flow cytometry. High S-phase using flow cytometry was defined as ≥7% for diploid tumors and ≥12% for aneuploid tumors, except at 1 study center (with 15 participating patients), which defined high S-phase as ≥10% irrespective of ploidy. One center (with 20 patients) used a static single-cell measurement for DNA analysis; these data are not presented in this report.

Inclusion and Exclusion Criteria and Staging

Eligibility criteria included patients with Stage IIB (T3N0 only), III, and IV (ipsilateral supraclavicular lymph nodes only) according to UICC guidelines.[3] Criteria for inflammatory carcinoma were based on the clinical history and physical findings.[4]

A record of the complete medical history and a physical examination, including measurement of locoregional tumor extension, were performed on all patients. A history of other malignancy apart from basal cell carcinoma or in situ cervical carcinoma or a history of any other condition or disease preventing

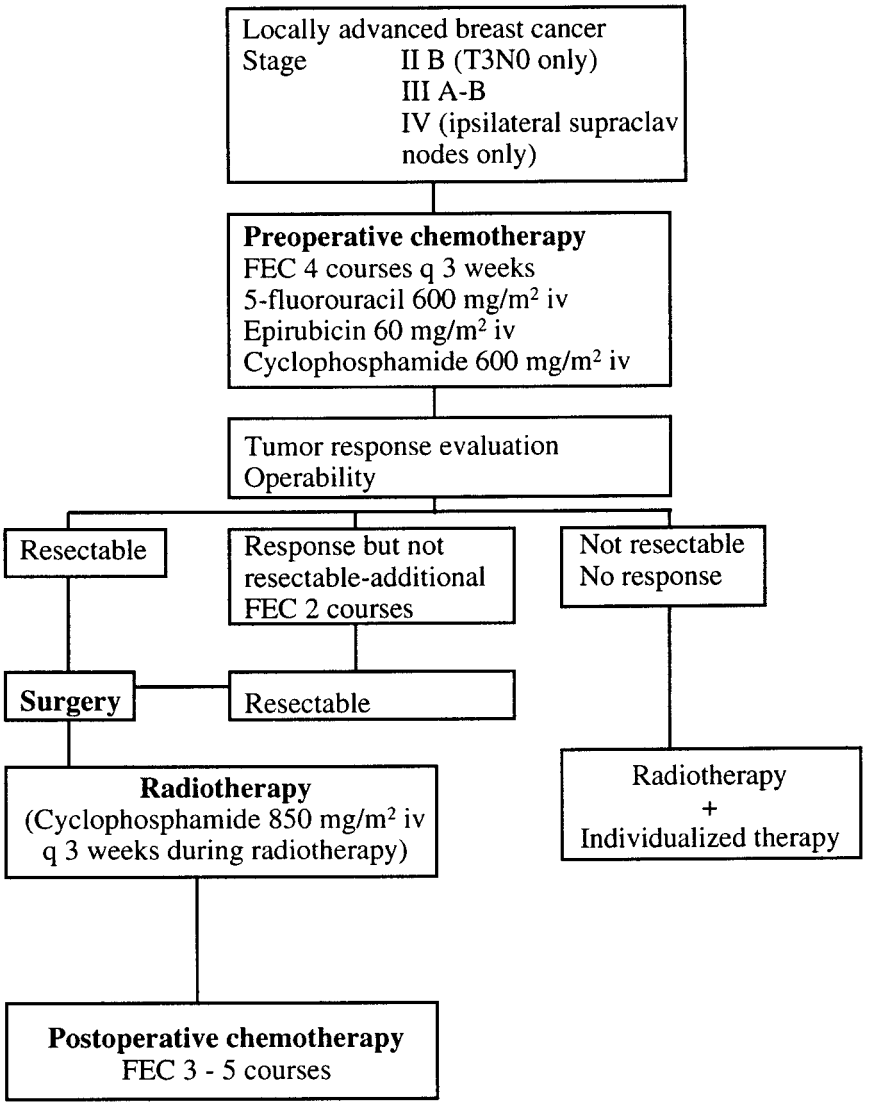


FIGURE 1. The protocol schedule for multimodal therapy of patients with locally advanced breast carcinoma is shown.

chemotherapy, including pregnancy, were exclusion criteria. There was no age limit per se. Oral informed consent was obtained from all patients.

Treatment Schedule

Pre- and postoperative FEC therapy

The treatment protocol is presented in Figure 1. After induction therapy with 5-fluorouracil (600 mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) every third week for 4 courses, a clinical examination was performed in which response and operability were evaluated. The degree of myelosuppression was based on blood counts taken on Days 1 and 21. Dose reduction was undertaken as follows: 100% was given if the leukocyte count was $>3.0 \times 10^9$ and the platelet count was $>100 \times 10^9$, 50% if the leukocyte count was $>2.0 \times 10^9$ and the platelet count was $>50 \times 10^9$. It was recommended that lower values result in 1 weeks' delay. If the patients were operable after 4 courses, they underwent surgery followed by locoregional radiotherapy and postoperative FEC therapy for 5 more courses. Patients with responding, but still not resectable, breast carcinomas were given 2 additional courses of FEC followed by surgery, locoregional radiotherapy, and further FEC for 3–5 courses. To avoid delay of systemic treatment during radiotherapy, cyclophosphamide (850 mg/m^2) was given concurrently every third week instead of FEC. If no response and no resectability were recorded, individualized therapy was implemented (in this situation, radiotherapy).

Surgery

The standard surgical procedure was modified radical mastectomy with axillary dissection. If the tumor size

was less than 3 cm after induction chemotherapy and the tumor was not fixated, sector resection or breast-conserving surgery with axillary dissection could be considered. The tumor was analyzed for histologic type and stage, hormone receptor status, and DNA status. It was recommended that tumor material be frozen for future analysis.

Radiotherapy

Radiotherapy, in which both photon and electron beams were used, was administered after mastectomy to the chest wall, ipsilateral axilla, supraclavicular fossa, and internal mammary lymph node chain. The dose per fraction varied between 2 and 4.5 gray (Gy); the total dose corresponded to a cumulative radiation effect (CRE) value[12] of at least 15.3 Gy. Preoperative radiotherapy was given to patients who did not respond to induction chemotherapy; it consisted of 2–3 Gy fractions to a total dose corresponding to a CRE value of 16.5. This technique, using tangential photon beams to the breast and ipsilateral axilla, was also used postoperatively to treat patients who underwent breast-conserving surgery.

Monitoring

Evaluation included clinical examination after 4 (6) FEC courses. The tumor size was estimated before and after primary chemotherapy. Estimation of tumor size in a breast containing an LABC is exceedingly difficult and does not make the application of UICC criteria[3] easy. Complete response (CR) was defined as no clinical evidence of residual tumor, and partial response (PR) as a $\geq$50% reduction in tumor size. A reduction in tumor size of less than 50% was defined as stable disease (SD). An increase of $\geq$25% in tumor size was defined as progressive disease (PD). Operability criteria of Haagensen and Stout were used.[13]

Follow-up after completed therapy included physical examination every 3–6 months during the first years and every 6–12 months thereafter. If clinical signs of recurrence appeared, X-ray examinations and blood chemistry tests were performed. Patients were monitored until death or last follow-up.

Statistical Methods

The Cox proportional hazards model and the chi-square and log rank tests were used to estimate and test the influence of the variables on the outcome.[14,15] The curves depicting DFS and OS were computed according to the Kaplan–Meier method and calculated from the time of diagnosis.[15] For survival analyses, an SPSS computer program was used (SPSS Inc., Cary, NC). Intended dose intensity was defined as scheduled dose every third week for nine courses for each cytotoxic agent.[16] Modification of the FEC courses, which involved modifying only the dosage of cyclophosphamide to 850 mg/m^2 every 3 weeks during radiotherapy, was not taken into account in the definition.

RESULTS

A total of 128 patients were included in the trial. Median follow-up was 37 months (range, 17–65 months). Four patients underwent high dose chemotherapy with autologous peripheral stem cell rescue after induction FEC therapy. They were not included in the statistical analyses of outcome.

Patient and Tumor Characteristics

Stage IIB (T3N0 only) was present in 8 patients (6%), IIIA in 30 patients (23%), IIIB in 82 patients (64%), and IV (ipsilateral supraclavicular metastases only) in 8 patients (6%). Of the 82 patients with Stage IIIB tumors, 57 (45%) had indirect or direct skin involvement, the tumors in 6 (5%) were fixed to the chest wall, and 3 (2%) had both these clinical findings. The clinical entity IBC was found in 22 patients (17%).

Median age was 53 years (range, 22–77 years). Fifty-nine percent of the patients were postmenopausal. Histology of the surgical specimens after induction FEC therapy demonstrated ductal carcinoma in 64 of 113 patients (57%). Hormone receptor status was known before chemotherapy for 50 patients (39%) and postoperatively for 77 patients (60%) (Table 1). For 29 patients (23%), hormone receptor status was known both before chemotherapy and postoperatively. Of these, 16 patients had positive receptor status (ER and/or PgR) before chemotherapy, which remained positive after induction chemotherapy in all cases (Table 1). Seventeen patients had tumors with negative receptor status before the start of FEC therapy; 9 of these remained negative, 4 breast carcinomas became positive, and 4 had unknown receptor status in the analysis based on the surgical specimens (Table 1). Aneuploid breast carcinomas were found in 8 of 10 tumors and 25 of 37 tumors, before chemotherapy and after induction FEC courses, respectively (Table 1). Figures for high S-phase before chemotherapy and after induction FEC courses were 7 of 9 patients and 26 of 40 patients, respectively (Table 1).

Treatment Schedule

Treatment of the patient population is summarized in Figure 2. One hundred four patients (81%) received 3–4 induction FEC courses, 11 (9%) were irradiated preoperatively after 4–9 preoperative FEC courses, 115 (90%) underwent modified radical mastectomy with axillary dissection, 5 (4%) did not undergo surgery,

TABLE 1
Characteristics of 128 Patients with LABC

Characteristics	No. (%) of patients	
	Pre-treatment	After induction FEC
Stage		
IIB	8 (6)	ND
IIIA	30 (23)	ND
IIIB	82 (64)	ND
IV	8 (6)	ND
Menopausal status		
Premenopausal	50 (39)	ND
Postmenopausal	73 (57)	ND
Unknown	5 (4)	ND
Hormone receptors (ER/PgR)		
Positive	33 (26)	40 (31)
Negative	17 (13)	37 (29)
Unknown	78 (61)	51 (40)
DNA index		
Diploid	2 (2)	12 (9)
Aneuploid	8 (6)	25 (20)
Unknown	118 (92)	91 (71)
S-phase[a]		
Low	2 (2)	14 (13)
High	7 (6)	26 (24)
Unknown	99 (92)	68 (63)
Histology		
Ductal	ND	64 (50)
Comedo type	ND	37 (29)
Lobular	ND	10 (8)
Tubular	ND	2 (2)
Unspecified	ND	15 (12)
Histologic differentiation		
Poor	ND	73 (57)
Moderate	ND	17 (13)
High	ND	1 (1)
Unspecified	ND	37 (29)

FEC: 5-fluorouricil, epirubicin, and cyclophosphamide; ER: estrogen receptors; PgR: progesterone receptors; ND: not done.
[a] Analyses based on 108 patients.

and 87 (68%) received a total of at least 9 FEC courses (Fig. 2). Of the 11 patients who were given preoperative radiotherapy, 10 had no response to induction chemotherapy, 8 then underwent surgery, and 2 were still not resectable. One patient had a PR and a CR after 3 and 9 FEC courses, respectively. This patient was then irradiated and did not undergo surgery. One hundred twenty-three patients (96%) were rendered disease free at the end of multimodal therapy.

After chemotherapy, adjuvant tamoxifen (20 or 40 mg daily) was given to 41 patients (32%). Of these, 28 were postmenopausal, 10 were premenopausal, and 3 were of unknown menopausal status. Tumors were positive for both ER and PgR in 16, positive for either ER or PgR in 9, negative for both ER and PgR in 11, and unknown in 5 of the 41 patients. Of the 128 patients, 39 were both ER and PgR positive pre- and/or postoperatively. Of these, 16 patients (41%) received adjuvant hormonal therapy.

Response

Clinical response to preoperative FEC therapy was observed in 77 patients (60%): CR in 6 (5%), and PR in 71 (55%). The remaining 51 patients (40%) had SD. PD was not observed in any of the patients during the preoperative treatment period (Table 2). Of the six patients with clinical CR, one refused surgery and any other further treatment. Of the remaining five patients with clinical CR, only two patients had pathologic CR.

Recurrence and Survival

Patient population

Of 128 patients, 1 patient with distant relapse was lost to follow-up after 28 months due to emigration.

Four patients, each of whom had a PR to induction FEC therapy, were not included in the analysis of outcome because they received high dose chemotherapy with autologous peripheral stem cell rescue after a total of 5–11 FEC courses. This was based on a high degree of pathologic lymph node involvement and/or aggressive tumor characteristics, although not defined in the protocol. These 4 patients had the following characteristics: One had clinical Stage IIIA (metastases to 21 of 21 lymph nodes), and the other 3 had clinical Stage IIIB with 8 of 10, 2 of 7, and 10 of 10 lymph nodes involved, respectively. The second and fourth patient had IBC. The first patient relapsed after 12 months and died after 21 months. The other three patients were alive and disease free after follow-up of 41, 27, and 22 months, respectively.

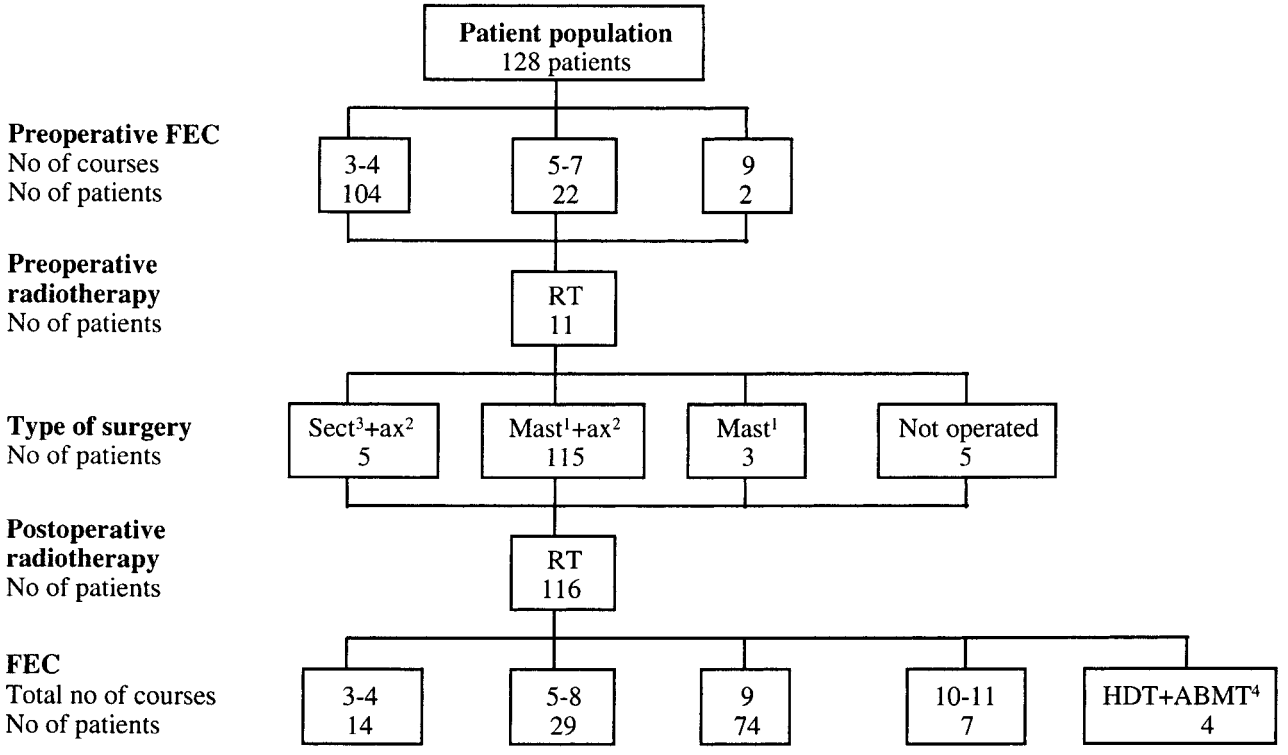
The median DFS and OS were 29 and 54 months, respectively (Fig. 3). The actuarial 5-year DFS and OS were 36% and 49%, respectively (Fig. 3). Local recurrence was seen in 25 of 124 patients (20%), whereas the distant failure rate was 66 of 124 (53%) (Tables 2 and 3).

Corresponding figures for patients with IBC were 6 of 20 (30%) and 16 of 20 (80%), respectively (Table 2). No patient was classified as having died of a cause other than breast carcinoma.

Systemic therapy after recurrence was given to 46 of 70 patients (66%). Of these patients, 24 (34%) received hormonal therapy, 13 (19%) received polychemotherapy, and 9 (13%) were treated with single-agent chemotherapy.

Clinical and Biologic Variables

Univariate analyses revealed significant differences in DFS among Stages IIIA, IIIB, and IV, with worse prognoses for the more advanced stages (Table 4). A sim-



Abbreviations: [1]Modified radical mastectomy, [2]Axillary dissection, [3]Sector resection, [4]High-dose chemotherapy supported by autologous stem cells

FIGURE 2. Patient distribution is shown, with reference to therapies actually given.

TABLE 2
Locoregional and Distant Relapses among 124 Patients with Locally Advanced Breast Carcinoma Divided into 2 Subgroups

Sites of relapse	No. of patients	%
Total with LABC	104	
Locoregional only	4	4
Distant only	35	34
Both sides 1[a]	15	14
Total relapses	54	52
Total with IBC	20	
Locoregional only	0	0
Distant only	10	50
Both sides 1[a]	6	30
Total relapses	16	80

LABC: locally advanced breast carcinoma; IBC: inflammatory breast carcinoma.
[a] Both locoregional and distant relapse.

ilar pattern was observed for OS, although this was not statistically significant (Table 4). When the results for the 8 patients with Stage IIB were added, the *P* values were 0.09 and 0.18 for DFS (Fig. 4) and OS, respectively.

Patients with IBC had significantly worse prognosis (Table 4, Fig. 5). The presence of peau d'orange changes was associated with worse prognosis; however, this did not reach the formal cutoff level of 5% for OS (Table 4). The other studied clinical signs were not significantly associated with worse prognosis (Table 4).

Based on symptoms and clinical signs, patients with inflammatory carcinoma were divided into two clinical subgroups, namely, IBC and LABC with secondary inflammatory signs. Patients with IBC had a short history of development of inflammatory signs in a major part of the breast, usually with no underlying palpable mass. This was observed in 22 patients and appeared more often in younger patients (median age, 48 years). Patients with IBC had worse prognoses than other women (DFS: $P = 0.002$ [chi-square test], relative risk 1.2, 95% CI 1.1–1.4; OS: $P = 0.003$, relative risk 1.25, 95% CI 1.1–1.5) (Fig. 5). The same pattern, although not significant, was observed when the two

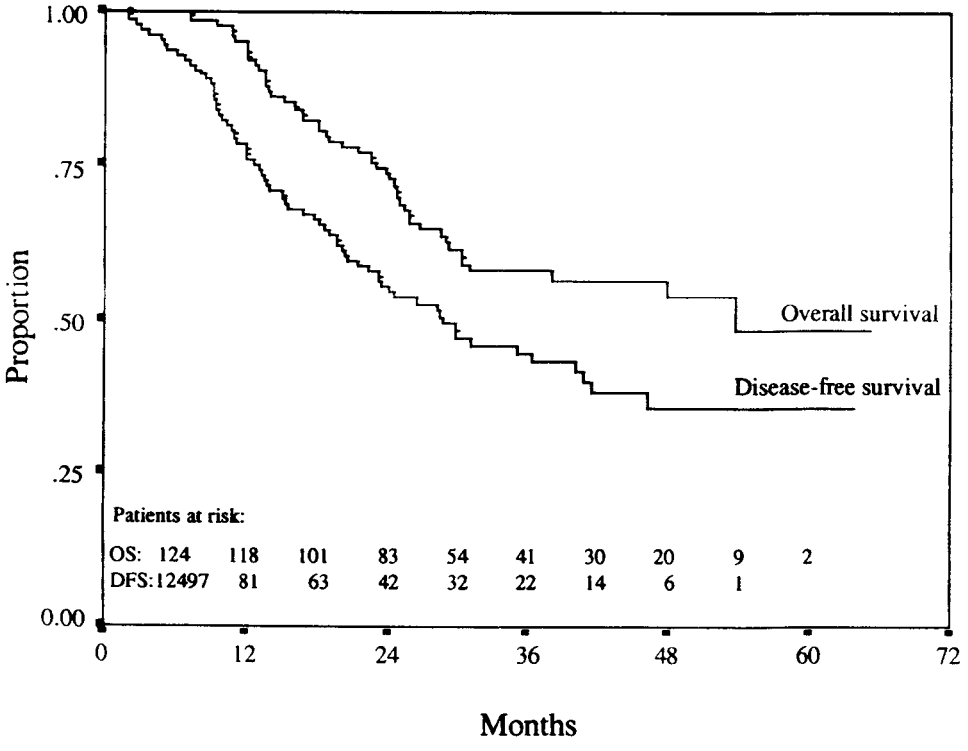


FIGURE 3. Disease-free survival (DFS) and overall survival (OS) are shown for 124 patients with locally advanced breast carcinoma.

TABLE 3
Sites of Relapse among 124 Patients with LABC

Site of relapse	No. of patients	%
Chest wall	17	14
Locoregional lymph nodes	9	7
Skin[a]	7	6
Lymph nodes 1[a]	17	14
Bone	34	27
Lung	21	17
Pleura	17	14
Liver	26	21
Other viscera	2	2
CNS	7	6
Contralateral breast	11	9

LABC: locally advanced breast carcinoma; CNS: central nervous system.
[a] Relapse occurred outside the locoregional area.

subgroups were compared (DFS: $P = 0.10$ [chi-square test], relative risk 1.2, 95% CI 1.0–1.5; OS: $P = 0.21$, relative risk 1.2, 95% CI 0.9–1.5). When the patients with secondary inflammatory signs were compared with other patients, there was no statistically significant difference, and the curves merged (DFS: $P = 0.69$ [chi-square test], relative risk 1.1, 95% CI 0.6–1.9; OS: $P = 0.44$, relative risk 1.3, 95% CI 0.7–2.4).

The analysis of the prognostic impact of response did not reach statistical significance. However, 4 of the 6 patients (67%) who had CR were still alive and disease free, compared with 42% and 43% of the patients with PR and SD, respectively.

We did not study the survival impact of menopausal and hormone receptor status because the subgroups were too small for statistically firm conclusions.

Dose Intensity

Data on 74 patients who received a total of 9 FEC courses were analyzed. Only this group was analyzed with reference to dose intensity, whereas the other subgroups were too small.

Median dose intensity was 68%, 67%, and 91% for 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide, respectively. The higher intensity noted for cyclophosphamide reflects the fact that doses were given during radiotherapy for this compound, which was not taken into account in the analysis. The number of single cyclophosphamide courses varied and was not separately registered. Accordingly, dose intensities for epirubicin and 5-FU were lower than for cyclophosphamide.

The material was separated into three dose levels per week (Table 5). There was a significant trend for both epirubicin and 5-FU with reference to DFS and OS in favor of patients who received higher doses. The critical levels were for DFS $\leq$60% (epirubicin: $P = 0.007$, 5-FU: $P = 0.002$, log rank test) and for OS $\leq$75%

TABLE 4
Influence of Clinical and Biological Variables on the Prognosis of Patients with LABC

Variable	No. of patients	DFS RR (95% CI)	*P*-value[a]	OS RR (95% CI)	*P*-value[a]
Stage					
IIIA	30	1.0	<0.05	1.0	0.14
IIIB	81	1.9 (1.0–3.5)		0.6 (0.3–1.0)	
IV	8	3.2 (1.2–8.6)		1.0 (0.6–1.5)	
Inflammatory carcinoma					
No	72	1.0	0.01	1.0	0.005
Yes	52	1.8 (1.1–3.0)		2.2 (1.3–3.9)	
Peau d'orange					
No	68	1.0	0.02	1.0	0.06
Yes	56	1.8 (1.1–2.9)		1.7 (1.0–3.0)	
Palpable lymph nodes					
No	26	1.0	0.36	1.0	0.29
Yes	97	1.3 (0.7–2.5)		1.5 (0.7–3.2)	
Fixed lymph nodes					
No	90	1.0	0.37	1.0	0.18
Yes	28	1.3 (0.7–2.3)		1.6 (0.8–3.0)	
Ulceration					
No	110	1.0	0.19	1.0	0.18
Yes	14	0.5 (0.2–1.4)		0.4 (0.1–1.4)	
Fixed tumor					
No	115	1.0	0.83	1.0	0.20
Yes	8	1.1 (0.4–2.7)		N/A[b]	
Periglandular growth					
No	55	1.0	0.23	1.0	0.15
Yes	58	1.4 (0.8–2.2)		1.6 (0.8–2.9)	
Grade of differentiation					
Moderate	17	1.0	0.08	1.0	0.35
Poor	74	2.2 (0.9–5.1)		1.6 (0.6–4.0)	

DFS: disease free survival; OS: overall survival; RR: relative risk; CI: confidence interval.

[a] P values were determined by the chi-square test.

[b] Data N/A (not available); the no. of patients was too small.

(epirubicin: $P = 0.05$, 5-FU: $P = 0.008$, log rank test). The patients who received the lowest doses showed a consistent pattern in all analyses of doing the worst.

Median cumulative doses for all 124 patients were 83%, 83%, and 97% for 5-FU, epirubicin, and cyclophosphamide, respectively.

Toxicity

Thirty-six of 124 patients (29%) had a leukocyte count of $<2.0 \times 10^9$ and 2 of 124 patients (2%) had a platelet count of $<50 \times 10^9$ during the treatment period (World Health Organization Grade 3–4 criteria). No treatment-related clinical cardiac failures or toxic deaths were recorded. Other nonhematologic toxicities were not studied in this protocol, but alopecia and nausea were observed.

DISCUSSION

In the present patient material, our response figures, with reference to response, with 5% CR and 55% PR after primary induction polychemotherapy, compared with other studies with multimodal therapy in LABC, tended to be in the lower range of other published response rates.[2,5,8] Notably, as many as 70% of the patients presented with advanced Stage IIIB or IV, including 17% with IBC, despite the fact that screening mammography programs were running in all but 2 of the participating regions. One may speculate that the patients whose disease was not detected in the screening program and who were thus deemed to have "interval cancers" may have presented with a biologically more aggressive phenotype. On the other hand, a patient's delay before initial diagnosis was not seldom observed. According to Valero et al., clinical response rates between 50% and 80% are common with different chemotherapy regimens, whereas clinical CRs vary between 5% and 20%.[2]

These authors also demonstrated that two-thirds of patients with a clinical CR had a pathologic CR as well. We had 2 of 5 with pathologic CR in our program, indicating the importance of histopathologic exami-

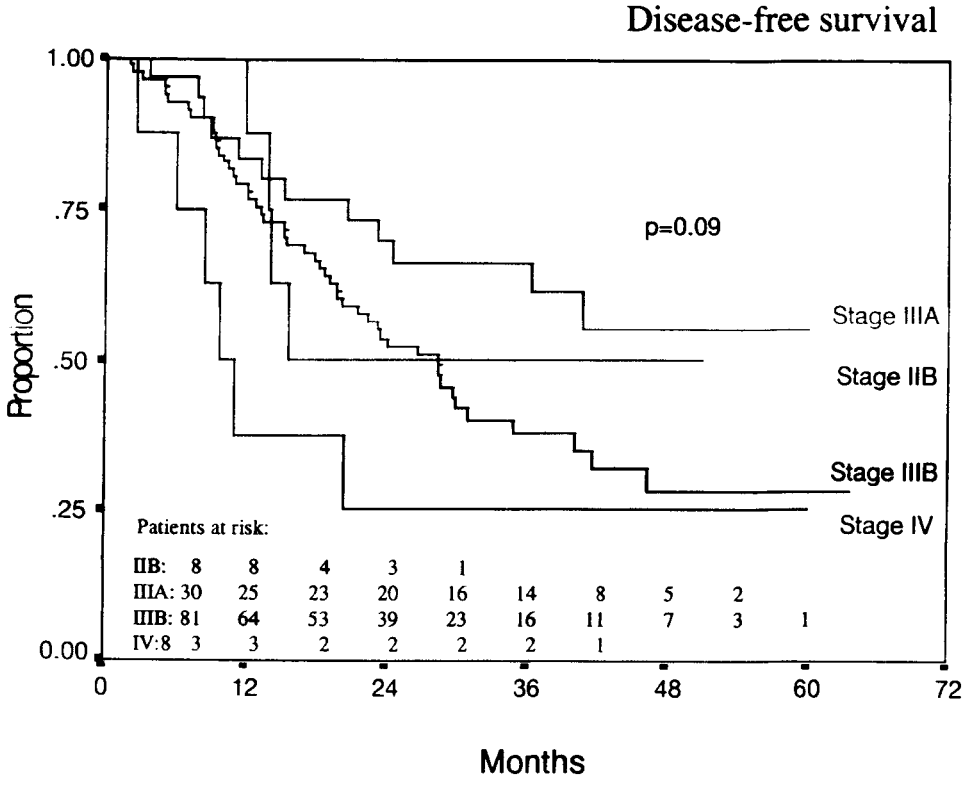


FIGURE 4. Disease free survival is shown for patients with different stages of locally advanced breast carcinoma.

nation of the whole breast and axilla for an accurate response evaluation of primary chemotherapy.[17]

The use of more effective induction chemotherapy will most likely increase the prospect of breast-conserving surgery.[18] However, some caution may be warranted in view of the work of Singletary et al., who presented a retrospective analysis suggesting more strict selection criteria for potential breast conservation.[19] This was based on clinical and mammographic responses to primary chemotherapy and histologic findings in mastectomy specimens from patients with LABC given multimodal therapy.[19]

Among our patients, the presence of peau d'orange and IBC revealed a significant impact on outcome; we assume that this was a reflection of biologically more aggressive behavior in the tumors. The importance of distinguishing IBC from LABC with secondary inflammatory changes has been emphasized.[2,4] Patients with the latter type of disease present with a longer clinical history and are more often elderly.[2,4] Our results confirm these previous observations.

The local control rate was 80% for LABC and 70% for IBC, whereas the distant failure rates were 53% and 80%, respectively. The actuarial 5-year DFS and OS figures (36% and 49%, respectively) were comparable to those for other similarly designed studies.[2,4,5,8] Local control rates of 60% to 80% after multimodal therapy have been reported.[2] The relapse frequency of 20% despite postoperative radiotherapy and pre- and postoperative FEC therapy indicate the need for better local therapy. The improvement of radiotherapy techniques have varied among treatment centers in Sweden since the completion of this protocol, with altered fraction schedules and the use of more risk organ-sparing techniques. The available data clearly emphasize the need for improved locoregional and systemic therapy for these patients.

The survival benefit (DFS as well as OS) and improved locoregional control by adding pre- and/or postoperative chemotherapy to locoregional therapy has been extensively presented in several retrospective analyses and Phase II studies of LABC and IBC.[2,4,5,8,10,20,21] Combined treatment with surgery and radiotherapy has been found to optimize locoregional control but has had little impact on survival compared with either therapy modality alone.[2,5,8] Multimodality treatment has been widely accepted, although the optimal locoregional therapy, drugs of choice, dose intensity, and sequence of modalities remain controversial and need to be studied further.[2,5,8]

Neoadjuvant chemotherapy allows assessment of tumor response, as previously discussed. Analyses of prognostic variables suggest a positive correlation between response and survival.[8,17,22] With different approaches to modulating neoadjuvant therapy, there is

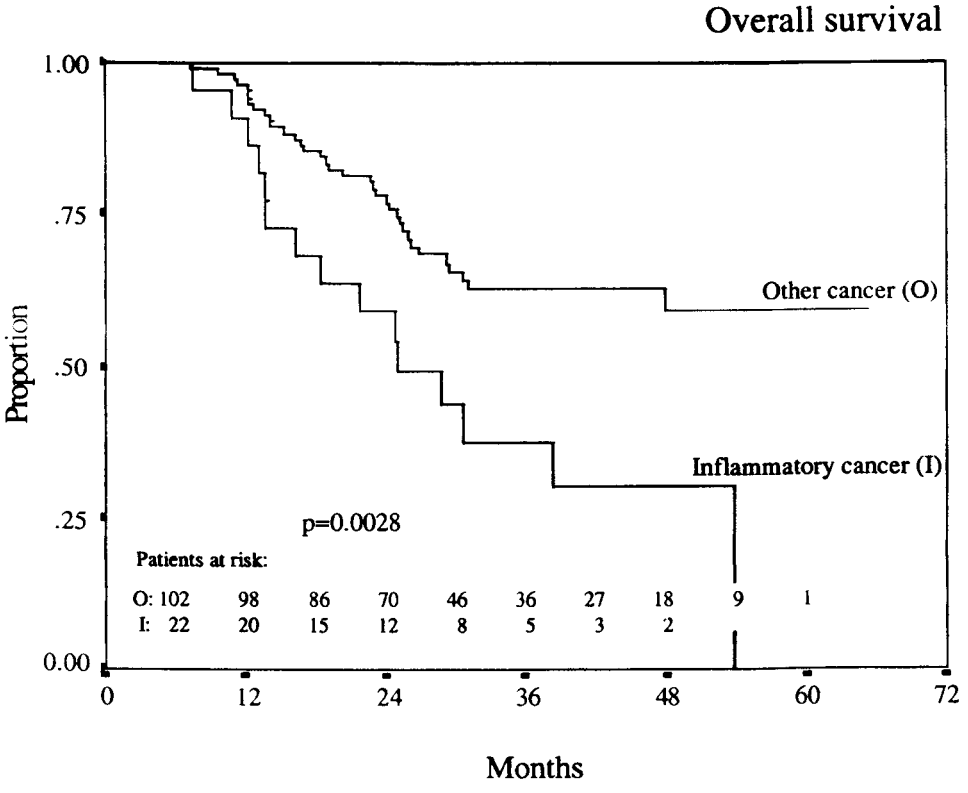


FIGURE 5. Overall survival of patients with inflammatory breast carcinoma (IBC) is compared with that of patients with other clinical stages of locally advanced breast carcinoma.

TABLE 5
Influence of Dose Intensity on the Prognosis of 74 Patients with LABC Given 9 Courses of Chemotherapy

Variable	No. of patients	% of intended dose intensity	Median DFS (mos)	*P* value[a]	Median OS (mos)	*P* value[a]
Dose intensity (mg/m^2/week)						
Epirubicin						
12.5	26	60	20.3	0.007	29.2	0.05
14.7	24	75	N/A[b]		53.8	
20.5	24	100	35.0		N/A[b]	
Cyclophosphamide						
168.3	24	85	29.8	0.69	53.8	0.83
197.7	25	100	N/A[b]		N/A[b]	
299.7	25	150	31.1		47.9	
5-Fluorouracil						
122.7	24	60	15.6	0.002	25.1	0.008
147.5	25	75	N/A[b]		53.8	
206.3	24	105	31.1		N/A[b]	
FEC						
308.8	27	75	23.3	0.20	30.6	0.28
355.8	22	85	35.0		N/A[b]	
454.1	24	110	N/A[b]		N/A[b]	

DFS: disease free survival; OS: overall survival; FEC: 5-fluorouracil, epirubicin, and cyclophsophamide.

[a] *P* values were determined by the log rank test.

[b] Data N/A (not available); the median survival time was not determined because too many cases were censored.

a trend toward greater emphasis on response benefit than on survival, which remains an intellectual challenge. Theoretically, remaining primary or drug-induced resistant cells could be present even in highly responsive tumors and affect long term outcome. Cellular drug-resistance mechanisms need further study,

preferably with repeated analyses to understand the changes of phenotype over time in tumor evolution from local to systemic disease.

The anthracycline dose intensity of our protocol was compromised when cyclophosphamide was given as a single agent during radiotherapy. It has been suggested that dose intensity is one of the important factors regarding outcome in breast carcinoma.[16,23–25] In our study, lower dose intensity of epirubicin and 5-FU, respectively, reflected significantly worse prognosis. Recent studies have indicated a dose-response correlation in the treatment of breast carcinoma, in both adjuvant and metastatic settings, which also has been demonstrated in the neoadjuvant setting for LABC.[17,26,27] In a prospective randomized study, Focan et al. disclosed a significant improvement in response rate and survival when they compared the effects of two different dose levels of epirubicin on previously untreated patients with advanced breast carcinoma.[28] This trend has been confirmed in other studies comparing different dose levels of epirubicin in the treatment of advanced breast carcinoma, although the impact on long term survival was not confirmed.[29–31]

Bezwoda et al. demonstrated, in a prospective randomized study, a superior survival of statistical significance for patients who received high dose therapy with autologous bone marrow support or peripheral blood stem cell rescue compared with patients given conventional doses.[32] Phase II data on high dose therapy in the adjuvant setting further supports the concept of a dose-response correlation; however, these findings are currently being investigated in randomized studies.[33]

The importance of drug scheduling was underlined by Blomkvist et al., who reported a randomized study with a significant survival benefit for patients who received FEC therapy every fourth week versus the same dose split into a weekly schedule.[34] The survival for the first group was 21 months, versus 12 months for those who received the weekly schedule.[34]

The benefit of adding hormonal therapy to cytotoxic agents for LABC has not been fully clarified.[10,21] Saarto et al. failed to demonstrate any survival benefit when they added adjuvant tamoxifen to a doxorubicin-based multimodal regimen for 2 years in the treatment of Stage IIIB breast carcinoma.[35] A recent study indicated a response benefit in the addition of hormonal synchronization to induction chemotherapy for patients with LABC.[36] However, other studies have failed to demonstrate any benefit in trying to synchronize the breast carcinoma cell prior to chemotherapy.[37] In treating elderly patients with hormone receptor positive LABC, it may be beneficial to use tamoxifen instead of polychemotherapy, based on the results of adjuvant therapy.[38] However, this issue needs to be investigated separately for the subset of patients who may benefit from endocrine treatment only.

In conclusion, this multimodal therapy strategy with standard FEC has been demonstrated to be feasible, although the majority of patients with LABC still succumb to distant metastases. Recent publications indicate a dose-response correlation and therefore support further investigations of dose-escalated chemotherapy for high risk patients with breast carcinoma. We have initiated a multicenter trial on individually tailored and G-CSF–supported FEC therapy, resulting in a considerably higher dose intensity.

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