
DILEMMAS IN BREAST DISEASE

Locally Advanced Breast Cancer: Is Surgery Necessary?

Anne M. Favret, MD,* Robert W. Carlson, MD,* Donald R. Goffinet, MD,[†]
Stefanie S. Jeffrey, MD,[‡] Frederick M. Dirbas, MD,[‡]
and Frank E. Stockdale, MD, PhD*

**Departments of Medicine, [†]Radiation Oncology, and [‡]Surgery,
Stanford University Medical Center, Stanford, California*

■ **Abstract:** A retrospective analysis of the treatment of locally advanced breast cancer (LABC) was undertaken at Stanford Medical Center to assess the outcome of patients who did not undergo surgical removal of their tumors. Between 1981 and 1998, 64 patients with locally advanced breast cancer were treated with induction chemotherapy, radiation with or without breast surgery, and additional chemotherapy. Sixty-two (97%) patients received cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) induction chemotherapy. Induction chemotherapy was followed by local radiotherapy in 59 (92%) patients. Based on the clinical response to chemotherapy and patient preference, 44 (69%) patients received no local breast surgery. Radiotherapy was followed by an additional, non-doxorubicin-containing chemotherapy in all patients. The mean age of patients was 49 years. Of the 65 locally advanced breast cancers in 64 patients, 26 (41%) were stage IIIA, 35 (55%) were stage IIIB, and 4 (6%) were stage IV (supraclavicular lymph nodes only). Response to induction chemotherapy was seen in 59 patients (92%), with 29 (45%) achieving a complete clinical response and 30 (47%) a partial clinical response. With a mean follow-up of 51 months (range 7–187 months), 43 patients (67.2%) have no evidence of recurrent disease. Eight (12.5%) have recurred locally, and 21

(32.8%) have recurred with distant metastasis. Actuarial 5-year survival is 75%, disease-free survival is 58%, and local control rate is 87.5%. These data indicate that the routine inclusion of breast surgery in a combined modality treatment program for LABC does not appear necessary for the majority of patients who experience a response to induction chemotherapy. ■

Key Words: induction chemotherapy, inflammatory breast cancer

Optimal management of patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. Patients within this category represent TNM stage III and IV disease, which includes inflammatory breast cancer, tumors larger than 5 cm, bulky and matted lymph nodes, and patients with isolated ipsilateral supraclavicular lymph nodes as their only metastatic site. LABC represents 5–20% of newly diagnosed breast cancers in the United States, with a higher incidence in medically underserved areas (1).

In the past, patients with LABC underwent a radical mastectomy, which resulted in both poor local control and overall survival. Haagensen (2) first identified clinical features defining inoperability, including inflammatory carcinoma, skin edema, involved supraclavicular lymph nodes, satellite nodules, and arm edema. No pa-

Address correspondence and reprint requests to: Frank E. Stockdale, MD, PhD, Department of Medicine/Oncology, CCSR Building, Stanford University School of Medicine, Stanford, CA 94305-5115, U.S.A.

tient with these features in the Haagensen series survived disease-free 5 years after radical mastectomy. Subsequently external breast irradiation, either as primary treatment or following mastectomy, was used to improve local control (3–5). Although the combination of surgery and radiotherapy often improved local control, overall survival rates remained low. Most patients failed because the subclinical metastases they harbored at diagnosis were responsible for distant relapse and overall poor survival.

As early as 1973, investigators reported that combination chemotherapy prior to local treatment could decrease tumor burden, allowing for more effective local control with either surgery or radiation (6). In addition, systemic chemotherapy following the combination of neoadjuvant chemotherapy and local treatment could improve disease-free and overall survival. Subsequently multiple studies have demonstrated the benefit of systemic chemotherapy for treating patients with LABC (4,7–18).

While most LABC patients receive neoadjuvant chemotherapy followed by mastectomy, axillary dissection, and radiation with or without consolidative chemotherapy, most patients continue to succumb to distant metastases. Thus the justification of continuing to perform mastectomy or lumpectomy for patients with LABC rests principally on the belief that it increases local control. In the series of patients reported here, we demonstrate that an intensive program combining neoadjuvant chemotherapy with high-dose radiation to the breast followed by maintenance chemotherapy, results in high rates of local control and overall survival that are equivalent to those obtained by programs using mastectomy.

In this article, the Stanford University experience is reported, employing neoadjuvant doxorubicin-containing chemotherapy followed by high-dose external irradiation to the breast and chest wall, followed by additional chemotherapy.

MATERIALS AND METHODS

Eligibility

Between 1981 and 1998, 64 patients received treatment for 65 LABCs in the outpatient clinic at the Stanford University Medical Center. LABC, as defined by the 1997 Tumor, Nodes, and Metastasis (TNM) AJC Classification includes patients with stages IIIA, IIIB, and IV tumors if the ipsilateral supraclavicular lymph node is the only site of metastatic involvement (19). Stage IIIA includes patients with a primary tumor larger

than 5 cm and fixed or matted axillary lymph nodes without involvement of skin or fixation to the chest wall. Stage IIIB includes those patients with tumors directly involving the skin or with tumors fixed to the chest wall. Stage IV includes those patients with LABC within their breast and an involved supraclavicular lymph node as their only site of metastatic disease. Histologic diagnosis was confirmed by either fine needle aspiration (FNA), core needle biopsy, or limited incisional biopsy. Hormone receptor analysis was performed in 48% of patients. There was no evaluation of nuclear grade, S-phase, or DNA index. Patients who received primary mastectomy are not included in this analysis.

Pretreatment Evaluation and Follow-Up

All patients had pathologic diagnosis of breast cancer, a history and physical examination, a complete blood count (CBC) with differential and platelet count, biochemical survey, chest radiograph, and a bone scan. No patients were included who had distant metastases other than ipsilateral involved supraclavicular lymph nodes.

Treatment Plan

After an initial evaluation, induction chemotherapy was given. Sixty-two patients received CAF (cyclophosphamide 100 mg/m² by mouth for 14 days, doxorubicin 30 or 40 mg/m² intravenously on day 1 and day 8, and 5-fluorouracil (5-FU) 500 or 600 mg/m² intravenously on day 1 and day 8) on a 28-day cycle and were treated to maximal clinical response (three to six cycles). In 28 patients, the initiation of CAF was preceded by a loading dose of oral cyclophosphamide (8 mg/kg for 5 days). Two patients received cyclophosphamide (100 mg/m² by mouth for 14 days), methotrexate (40 mg/m² intravenously on day 1 and day 8) and 5-FU (500 or 600 mg/m² intravenously on day 1 and day 8) as induction therapy. In addition to an interval history and physical examination, a CBC was obtained prior to each cycle of chemotherapy. Standard criteria of tumor response were utilized as described elsewhere (20).

Patients were treated to maximal clinical response or six cycles of chemotherapy. This was followed by radiotherapy. In general, patients received a 5040 cGy external beam irradiation dose to the involved breast, supraclavicular, and axillary lymph nodes over 5 weeks in 180 cGy daily fractions, 5 days a week. On completion of this course, a boost was delivered to the tumor bed with either reduced-size tangential fields or an electron beam technique, giving up to an additional 1960 cGy to

this site (21,22). There was no substantially greater toxicity or cosmetic compromise with this dose of radiation.

Response Evaluation

The response to induction therapy was evaluated by physical examination before each cycle of therapy and more recently, by a combination of physical examination and repeat mammogram, ultrasound, and/or magnetic resonance imaging (MRI). Based on clinical assessment of a poor response to chemotherapy and/or radiotherapy, or patient personal preference, 20 patients underwent a surgical procedure—16 modified radical mastectomies and 4 lumpectomies with axillary node dissections.

Following radiation therapy or breast surgery, all patients received consolidative chemotherapy, most often consisting of oral cyclophosphamide on days 1–14 (100 mg/m²), intravenous methotrexate (40 mg/m²) on days 1 and 8, and 5-FU (600 mg/m²) on days 1 and 8. Consolidative therapy was given for four to eight cycles. Chemotherapy was followed by tamoxifen (20 mg/day) in 35 patients. Use of hormonal therapy was not based on hormonal receptor status (Table 1).

Disease-free survival and overall survival were measured in months from the date of diagnosis. The Kaplan and Meier (23) method was used to calculate survival curves. Survival was calculated in months from the date of diagnosis to death, or to the date of last follow-up of those patients still alive.

RESULTS

Sixty-four patients were included in this review. The mean age was 49 years (range 25–76 years). Thirty-three patients (52%) were premenopausal and 31 (48%) were postmenopausal. The majority had stage IIIB breast cancers [35 (55%)], of which more than half [20 (57%)] were classified as inflammatory based on clinical or pathologic criteria. Four patients with LABC and involved ipsilateral supraclavicular lymph nodes were clas-

Table 1. Treatment Plan: CAF → XRT ± SURGERY → CMF

Number of patients	Treatment received
62	CAF for two to six cycles
59	Local XRT
20	Surgery
	breast-conserving surgeries (4)
	mastectomies (16)
64	Consolidative chemotherapy

Two patients received CMF as neoadjuvant chemotherapy. Five patients had surgery without radiotherapy for their local treatment. All patients received consolidative therapy.

Table 2. Patient Characteristics

Characteristics	Number of patients
Total number of patients	64
Total number tumors	65
Age	
Median (range)	49 (25–76) years
<50 years	33
≥50 years	31
Initial stage	
IIIA	26
IIIB	35
Inflammatory	20
IV	4
Histology	
Lobular	4
Ductal	56
Both	1
Unknown	4
Hormone status	
ER positive	15
ER negative	16
Unknown	33

Patient characteristics of age, stage, histology, and receptor status. The patients with inflammatory disease comprise a subset of the stage IIIB patients.

sified as stage IV. Forty-one percent of patients had stage IIIA breast cancers. Fifty-six (86%) patients had infiltrating ductal carcinoma, while 4 (6%) had invasive lobular carcinoma. One patient had both invasive ductal and invasive lobular carcinomas and the histologic type was unknown in four patients. Of the 31 patients in whom a receptor assay was performed, 52% were estrogen receptor (ER)-positive and 48% were ER negative (Table 2).

Response to induction therapy was based on physical examination after induction chemotherapy and radiotherapy. An objective response [complete response (CR) and partial response (PR)] to induction therapy occurred in 59 patients (92%). Forty-five percent of patients had a CR, with those patients with stage IIIA having a higher rate of CR (61% versus 45% for stage IIIB and 25% for state IV). One patient with stage IIIA and two patients with stage IIIB had no significant response to induction chemotherapy (Table 3). In none of the patients did the tumor initially progress during induction chemotherapy.

Table 3. Clinical Response After Induction Chemotherapy

Response	All patients (%)	IIIA (%)	IIIB (%)	IV (%)
Complete	29 (45)	16 (61)	13 (37)	1 (25)
Partial	30 (47)	9 (35)	18 (51)	3 (75)
None	3 (5)	1 (4)	2 (6)	
Unknown	2 (3)		2 (6)	

Response of tumors in the breast to induction chemotherapy based on clinical examination, prior to local treatment. One patient had both a stage IIIA and IIIB tumor.

Table 4. Patients Who Received Surgery

Clinical response	Number of patients
Complete	4
Partial	12
None	2
Unknown	2

Surgery, either modified radical mastectomy or lumpectomy plus axillary dissection following radiotherapy, was performed in 20 patients based on tumor response to neoadjuvant therapy or personal preference. There were 16 modified radical mastectomies and 4 breast-conserving surgeries. Of those undergoing surgery, 10 were stage IIIA, 9 were stage IIIB, and 1 was stage IV. Most of the patients who underwent breast surgery had had a partial response to induction therapy (60%). There were four patients (20%) who had a complete response and two (10%) who had no response before undergoing surgery. The response of two (10%) patients is unknown (Table 4).

At the time of analysis, 43 patients (67.2%) had no evidence of recurrence with a mean follow-up of 51 months. Eight patients (12.5%) had recurred locally and 21 patients (33%) relapsed in distant sites (Table 5). In the radiation alone group, the rate of local recurrence was 9.3% and the rate of distant metastasis was 32.5%. In the group who received surgery, the local recurrence rate was 20% and the rate of distant metastasis was 35%. Overall 5-year survival for the 64 patients was 75% (Fig. 1) and disease-free survival was 58% (Fig. 2).

Table 5. Recurrence

	Total	Radiation alone	Radiation + surgery
Number of patients	64	44	20
No recurrence	43 (67.2%)	30 (68.2%)	13 (65%)
Distant metastasis	21 (33.0%)	14 (32.5%)	7 (35%)
Local recurrence	8 (12.5%)	4 (9.3%)	4 (20%)

Follow-up = 51 months (range 7–187 months)

Recurrences for the entire group, patients who received radiation as their local treatment, and patients who underwent a surgical procedure. All patients who had a local recurrence in addition to a distant metastasis are counted twice in this table.

DISCUSSION

Although combined modality treatment for LABC is currently the accepted standard of care, the choice of local treatment and the type and duration of induction and maintenance chemotherapy remain unclear. The experience at Stanford University over the past 17 years follows a paradigm using induction doxorubicin, cyclophosphamide, and 5-FU, radiotherapy for local control, followed by maintenance chemotherapy. If one assumes that most patients with LABC have poor outcomes because of micrometastatic disease, the two critical issues are (a) overall survival and (b) local control. Three- to five-year survival rates for LABC reported in the literature vary from 37 to 85% (12,24–27). Local control rates in patients receiving induction chemotherapy, radiotherapy, and maintenance chemotherapy when they had a surgical procedure ranged from 63 to 85% (4,10,12,28–31). Our local control rate of 87.5% and 5-year overall survival of 75% suggest that radiation without a surgical procedure achieves comparable rates of local recurrence or overall survival.

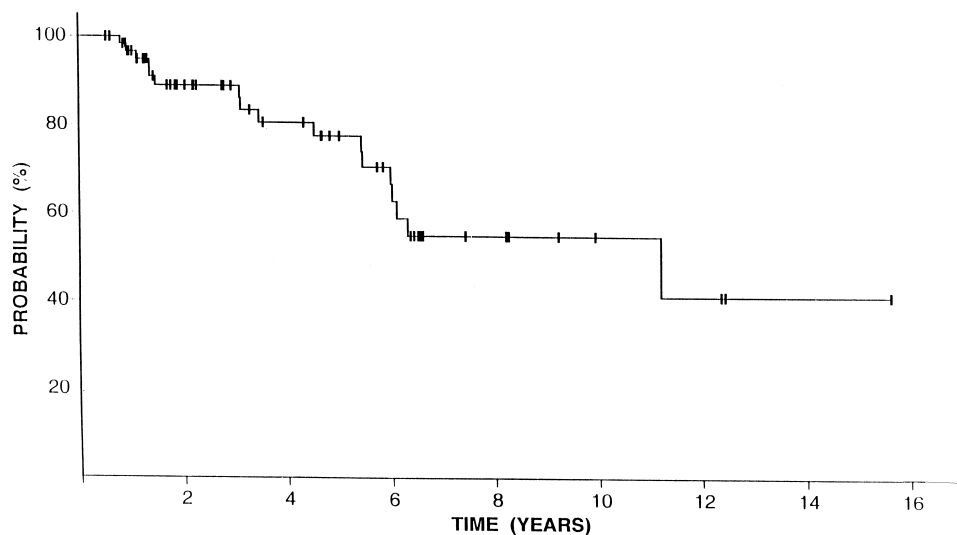


Figure 1. The probability (in percent) of overall survival in 64 patients with locally advanced breast cancer.

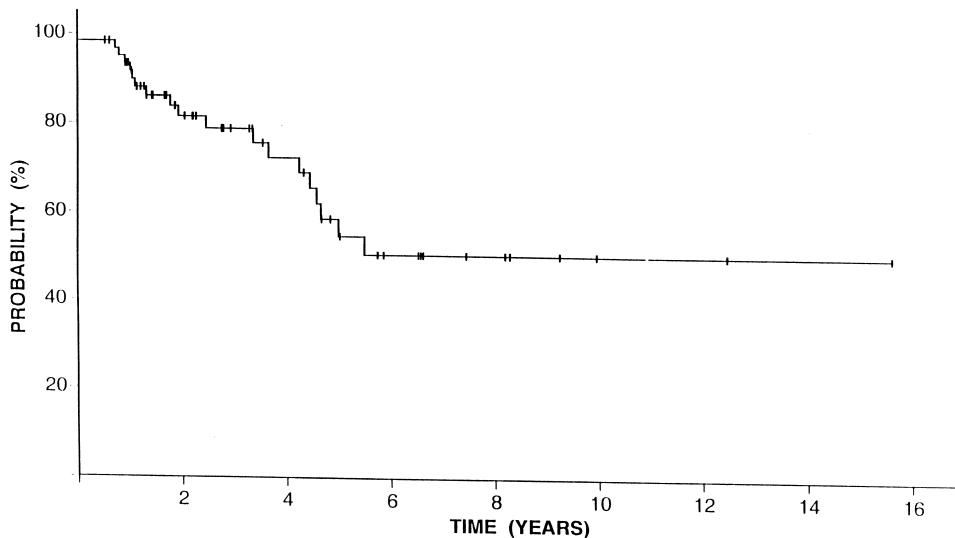


Figure 2. The probability (in percent) of disease-free survival in 64 patients with locally advanced breast cancer.

There are inherent difficulties in assessing clinical response to induction therapy. At the Milan Cancer Institute, two prospective randomized trials revealed 78% and 74% clinical overall response rates and 21% and 12% complete response rates. Objective response rates as high as 90% are found in the literature, but complete response rates are substantially lower (3,10,12,31,32). However, Jacquillat et al. (10) reported a 100% complete response after induction chemotherapy and irradiation. The overall response rate in the Stanford series is high (92%), but consistent with the literature. Response to induction therapy is important, however, because it is a prognostic indicator of disease-free survival at 5 years of follow-up (33,34). To circumvent the difficulties of clinical assessment of the breast in individuals with LABC, MRI may be a more sensitive method of evaluating residual breast neoplasm than mammography and physical examination. Using MRI, Gilles et al. (35) evaluated the response to induction therapy and identified carcinoma in 17 of 18 patients, whereas mammography showed residual disease in 9 of 14 patients. The extent of residual disease as assessed by MRI correlated well with histologic analysis. MRI may offer a noninvasive way to obtain prognostic information in patients with LABC who have completed induction therapy.

Although a subset of our patients (20) underwent surgical treatment of the breast with either mastectomy or breast-conserving therapy, this study is not an attempt to directly compare this group with those who received radiotherapy alone. It should be noted that those patients who underwent surgery represent a group that either had a partial or complete response (80%) or no response to induction therapy, or chose surgery by per-

sonal preference, whereas the entire group had an overall response rate of 92%. Therefore it may not be surprising that those receiving surgery had a poorer outcome than those who received only radiation following induction chemotherapy. However, the spectrum of clinical disease in those receiving only radiation is similar to that seen in other large series of LABC, and therefore does not account for the good local control rate seen in those receiving only high-dose radiation as their local treatment.

The optimal type and duration of maintenance or adjuvant chemotherapy remain unanswered questions in the treatment of LABC. De Lena et al. (12) randomly assigned patients in clinical CR after four cycles of neoadjuvant chemotherapy and radiotherapy to either receive further chemotherapy or observation. A statistically significant improvement in disease-free survival (DFS) (19 versus 11 months) and a lower rate of local recurrence were seen with the addition of maintenance chemotherapy. However, three additional series fail to show a benefit for either disease-free survival or overall survival with prolonged chemotherapy (7,18,25). In these three studies, the local recurrence rate was high (37–50%). Of the eight patients who recurred locally in our trial, four had concurrent distant metastases and all subsequently developed distant disease. Their primary clinical problem was distant metastases, not the local recurrence. Local recurrence, as a major problem, was the case in only a minority of patients, not justifying surgery for all women with LABC.

Nearly all patients with LABC have distant micrometastases and will subsequently fail in these sites if only treated locally. Thus the most important component of a combined modality approach is systemic treatment. In

the Stanford series, primarily cyclophosphamide, doxorubicin, and 5-FU were used for induction and cyclophosphamide, methotrexate, and 5-FU were used for maintenance therapy. There exist today potent non-cross-resistant agents that have high rates of response in metastatic breast cancer. Paclitaxel, docetaxel, and vinorelbine, for example, have proved activity in advanced breast cancer and warrant investigation in LABC (36–39). In a randomized trial, Moliterni et al. (37) are currently investigating the use of paclitaxel with doxorubicin as a primary therapy in operable breast cancer. The use of high-dose therapy with stem cell support is currently under investigation. A recently published trial of high-dose therapy shows a 64% disease-free survival at 30 months in patients with stage IIIB disease (40). In light of evidence that tamoxifen adds efficacy to chemotherapy in the adjuvant setting for stage I and II patients, one can expect that it could benefit women with LABC. Although many of the patients in this study received tamoxifen, one can draw no clear conclusions about its efficacy.

Local control rates and overall survival have improved with the use of multimodality therapy, but LABC remains a serious problem principally because of distant metastases. This series suggests that surgical removal of the breast or the tumor is not necessary to obtain good rates of local control or overall survival in patients with LABC. It places the focus where it should be in these individuals, on systemic treatment, as radiation at higher dosages is sufficient to produce local control in the majority of patients.

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