Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer

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A patient version of these guidelines appears in Appendix 1.

Abstract

Objective: To define the optimal treatment for women with stage III or locally advanced breast cancer (LABC).

Evidence: Systematic review of English-language literature retrieved from MEDLINE (1984 to June 2002) and CANCERLIT (1983 to June 2002). A nonsystematic review of the literature was continued through December 2003.

Recommendations:

- The management of LABC requires a combined modality treatment approach involving surgery, radiotherapy and systemic therapy.

Systemic therapy: chemotherapy

Operable tumours

- Patients with operable stage IIIA disease should be offered chemotherapy. They should receive adjuvant chemotherapy following surgery, or primary chemotherapy followed by locoregional management.
- Chemotherapy should contain an anthracycline. Acceptable regimens are 6 cycles of FAC, CAF, CEF or FEC. Taxanes are under intense investigation.

Inoperable tumours

- Patients with stage IIIB or IIIC disease, including those with inflammatory breast cancer and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement, should be treated with primary anthracycline-based chemotherapy.
- Acceptable chemotherapy regimens are FAC, CAF, CEF or FEC. Taxanes are under intense investigation.
- Patients with stage IIIB or IIIC disease who respond to primary chemotherapy should be treated until the response plateaus or to a maximum of 6 cycles (minimum 4 cycles). Patients with stage IIIB disease should then undergo definitive surgery and irradiation. The locoregional management of patients with stage IIIC disease who respond to chemotherapy should be individualized. In patients with stage IIIB or IIIC disease who achieve maximum response with fewer than 6 cycles, further adjuvant chemotherapy can be given following surgery and irradiation. Patients whose tumours do not respond to primary chemotherapy can be treated with taxane chemotherapy or can proceed directly to irradiation followed by modified radical mastectomy, if feasible.

Systemic therapy: hormonal therapy

Operable and inoperable tumours

- Tamoxifen for 5 years should be recommended to pre- and postmenopausal women whose tumours are hormone responsive.

Locoregional management

Operable tumours

- Patients with stage IIIA disease should receive both modified radical mastectomy (MRM) and locoregional radiotherapy if feasible. They may be managed with MRM followed by chemotherapy and locoregional radiotherapy, or chemotherapy first followed by MRM and locoregional radiotherapy. Breast-conserving surgery is currently not a standard approach.
- Locoregional radiotherapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The role of internal mammary irradiation is unclear.

Inoperable tumours

- Patients with stage IIIB disease who respond to chemotherapy should receive surgery plus locoregional radiotherapy.
- The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear and should be individualized.
- Patients whose disease remains inoperable following chemotherapy should receive locoregional radiotherapy with subsequent surgery, if feasible.

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Locally advanced breast cancer (LABC) occurs relatively infrequently, but it poses a significant clinical challenge. LABC refers to large breast tumours (> 5 cm in diameter) associated with either skin or chest-wall involvement or with fixed (matted) axillary lymph nodes or with disease spread to the ipsilateral internal mammary or supraclavicular nodes.[1] Inflammatory breast cancer, which manifests as a red swollen breast, is considered a type of LABC. The Tumour–Node–Metastasis (TNM) system is used to classify breast cancer into stages (Table 1).[1] According to this system, LABC is stage III.

During the last 60 years, the management of LABC has evolved considerably. Initially, patients with LABC were treated with radical mastectomy.[2] Based on the disappointing results of surgery and radiotherapy[2–4] in patients with LABC, and the early promising results of adjuvant systemic therapy in women with axillary node-positive breast cancer,[5,6] systemic therapy was subsequently incorporated along with surgery and radiotherapy into the management of patients with LABC, termed "combined modality therapy." Even with such combined modality therapy, the long-term survival rate is approximately 50% among patients with LABC.[7] The focus of this guideline is to determine the optimal therapeutic approach for patients who present with LABC.

Table 1: TNM staging system for breast cancer[1]

Stage	Tumour status*	Node status†	Metastasis status‡
0	Tis	N_0	M_0
I	T_1	N_0	M_0
IIA	T_0	N_1	M_0
	T_1	N_1	M_0
	T_2	N_0	M_0
IIB	T_2	N_1	M_0
	T_3	N_0	M_0
IIIA	T_0	N_2	M_0
	T_1	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1	M_0
	T_3	N_2	M_0
IIIB	T_4	N_0	M_0
	T_4	N_1	M_0
	T_4	N_2	M_0
IIIC	Any T	N_3	M_0
IV	Any T	Any N	M_1

*Tumour status: Tis = carcinoma in situ; T_0 = no evidence of primary tumour; T_1 = tumour ≤ 2 cm in greatest dimension; T_2 = tumour > 2 cm but not > 5 cm in greatest dimension; T_3 = tumour > 5 cm in greatest dimension; T_4 = tumour of any size with chest-wall extension, ulceration, peau d'orange or inflammatory breast cancer.
†Node status: N_0 = no regional lymph-node metastasis; N_1 = metastasis in movable ipsilateral axillary lymph node(s); N_2 = metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph-node metastasis; N_3 = metastasis in ipsilateral internal mammary lymph node(s) or in ipsilateral supraclavicular lymph node(s).
‡Metastasis status: M_0 = no distant metastasis; M_1 = distant metastasis.

Methods

We conducted a systematic review of the English-language literature retrieved from MEDLINE (1984 to June 2002) and CANCERLIT (1983 to June 2002). Search terms used were "breast neoplasms," "locally advanced breast cancer," "stage III breast cancer," "drug therapy," "neo-adjuvant," "primary systemic therapy," "radiotherapy or irradiation," "surgery," "randomized trials" and "high-dose therapy." A nonsystematic review of the literature was continued through December 2003. Additional data were identified by reviewing references in retrieved reports and by monitoring major conferences on breast cancer. The quality of the evidence on which conclusions are based is categorized into 5 levels.[8] The main outcomes considered are locoregional control (defined as freedom from recurrence in the breast, chest wall or regional lymph nodes), disease-free survival (DFS; defined as survival free of breast cancer recurrence) and overall survival (OS).

We were faced with a number of challenges when trying to synthesize the results of the studies from the review of the literature. These included:

- Many studies were case series (levels IV and V evidence).
- The studies included different populations of patients with differing prognoses; for example, some studies included patients with inflammatory breast cancer whereas other studies did not.
- In studies evaluating systemic therapies, local therapy (surgery/radiotherapy) was often not standardized.
- The TNM tumour-staging system changed, in that tumours associated with ipsilateral supraclavicular nodal involvement that were initially considered LABC were considered metastatic breast cancer between 1987 and 2002 and are now considered LABC again.[1]
- The randomized trials that were available were old, had small patient numbers and used systemic therapy combinations that are often not used today.

We developed this guideline using a framework based on the operability of the tumour. The current TNM staging system, which is based on clinical characteristics of the primary tumour and regional lymph nodes, is used to help determine operability (Table 1).[1] Large operable tumours include stage IIB and IIIA disease. Nonoperable tumours include stage IIIB or stage IIIC disease. Patients with ipsilateral supraclavicular lymph-node involvement as their sole site of metastases have in the past been classified as having stage IV breast cancer, but they have a better prognosis than patients with other sites of metastases and are included in the category of inoperable LABC (stage IIIC disease) within this guideline.[1,9,10]

Recommendations (including evidence and rationale)

- **The management of LABC requires a combined modality treatment approach involving surgery, radiotherapy and systemic therapy.**

The clinical management of LABC is complex and should be tailored to the individual patient. Frequently, surgery, radiotherapy and systemic therapy (chemotherapy, hormone therapy) are used. A multidisciplinary approach

to LABC is recommended in which treatment is based on the combined opinions of a surgeon, radiation oncologist and medical oncologist. The initial management of LABC requires histological confirmation (e.g., core biopsy, incisional biopsy or skin biopsy) for diagnosis and for determination of hormone receptor and *HER-2 neu* oncogene status. Cytological evaluation by fine-needle aspiration is insufficient.

Systemic therapy: chemotherapy

Operable tumours

- **Patients with operable stage IIIA disease should be offered chemotherapy. They should receive adjuvant chemotherapy following surgery, or primary chemotherapy followed by locoregional management.**

Patients with stage IIIA breast cancer have potentially operable tumours. There are 2 approaches for treating these patients. The first is modified radical mastectomy (MRM) followed by adjuvant systemic therapy and radiotherapy, and the second is preoperative chemotherapy followed by surgery and radiotherapy.

Surgery followed by adjuvant chemotherapy

There have been only 2 randomized clinical trials of adjuvant chemotherapy exclusively in patients with stage III disease (Table 2).[11,12] One of these studies[11] reported a benefit with chemotherapy (level I evidence). The meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[5,6] included a subset of patients with large operable tumours. Overall, all patients benefited from adjuvant systemic chemotherapy regardless of tumour size (level I evidence). Therefore, it is

Table 2: Summary of studies with surgery followed by adjuvant chemotherapy

Study	Patients	No. of patients	Treatment regimens	Duration of follow-up	Level of evidence	Results/comments
Klefstrom et al, 1987[11]	Stage III breast cancer patients after modified radical mastectomy	120	1. Radiotherapy 2. VAC chemotherapy 3. Both	Minimum 5 yr	I	DFS better with combined treatment than with either radiotherapy alone or VAC alone ($p < 0.001$) (percentages not reported). OS better with combined treatment than with radiotherapy alone ($p < 0.001$) or VAC alone ($p < 0.01$) (percentages not reported)
Derman et al, 1989[12]	Patients with LABC (55% had mastectomy)	231	1. Radiotherapy 2. Radiotherapy + low-dose CMF chemotherapy 3. Radiotherapy + high-dose CMF chemotherapy	Median 56 mo	II	No difference in DFS or OS between the 3 groups (percentages and *p* values not reported)
De Placido et al, 1995[26]	Patients with stage II or III breast cancer after mastectomy (78 patients had stage III disease)	220	1. CMF chemotherapy alternating with EV chemotherapy 2. CMF chemotherapy alone	Median 48 mo	II	No difference in DFS or OS between the 2 groups (percentages and *p* values not reported)
Casper et al, 1987[27]	Patients with LABC treated by modified radical or radical mastectomy	41	1. 6 mo CAF chemotherapy + 6 mo CMFVP chemotherapy 2. 12 mo CMFVP chemotherapy	Median 24 mo	II	Median DFS 23 mo in CAF + CMFVP group, 15 mo in CMFVP group ($p = 0.05$). Median OS 33 mo in CAF + CMFVP group, 18 mo in CMFVP group ($p = 0.26$)
Olson et al (ECOG trial), 1997[59]	Patients with LABC who underwent mastectomy and were then treated with CAFTH chemotherapy	313	1. Radiotherapy 2. Observation + radiotherapy if locoregional failure	Median 9.1 yr	II	DFS not reported. Median survival 8.3 yr in radiotherapy group, 8.1 yr in observation group ($p = 0.94$). Locoregional recurrence 15% in radiotherapy group, 24% in observation group (*p* value not reported). Median time to relapse 4.7 yr in radiotherapy group, 5.2 yr in observation group ($p = 0.68$)

Note: ECOG = Eastern Clinical Oncology Group, LABC = locally advanced breast cancer, DFS = disease-free survival, OS = overall survival, V = vincristine, A = adriamycin, C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, E = epirubicin, P = prednisone, T = tamoxifen, H = fluoxymesterone.

reasonable to extrapolate the overall conclusions of the meta-analysis to patients with operable stage IIIA disease.

Primary chemotherapy followed by surgery

A number of case series have reported on preoperative chemotherapy in patients with operable stage IIIA breast cancer (level IV evidence).[13–16] Table 3 summarizes one retrospective study and the randomized trials that compared preoperative and postoperative chemotherapy.[15–25] The primary purpose of these studies was to determine whether preoperative chemotherapy, compared with postoperative chemotherapy, improved DFS and OS. These studies involved patients mainly with stage I or stage II disease and included a small proportion of women with tumours greater than 5 cm in diameter. No difference in DFS and OS was detected between the pre-

Table 3: Summary of studies with primary chemotherapy followed by surgery

Study	Patients	No. of patients	Treatment regimens	Duration of follow-up	Level of evidence	Results/comments
Hortobagyi et al, 2000[15,16]	Patients with stage IIIA or IIIB breast cancer (28% with stage IIIA disease; 25% with T_3 tumour)	174	All patients received FAC induction chemotherapy then total mastectomy or radiotherapy or both, followed by adjuvant FAC followed by CMF chemotherapy	Median 59 mo	IV	DFS 71% and OS 84% among patients with stage IIIA disease. These rates were superior to those in historical group at the same institution who were treated with local modalities alone (no percentages or *p* values reported). Total clinical response 87.4%; clinical complete response 16.7%
Wolmark et al (NSABP B-18 trial), 2001[19]	Patients with operable, palpable breast cancer (13% had a T_3 tumour)	1523	1. Preoperative AC chemotherapy 2. Postoperative AC chemotherapy	Mean 9.5 yr	I	DFS 55% in preoperative group, 53% in postoperative group (p = 0.50). OS 69% in preoperative group, 70% in postoperative group (p = 0.80). Clinical response 80% in preoperative group; clinical complete response 36%; pathologic complete response 13%
Van der Hage et al (EORTC trial), 2001[20]	Patients with primary operable breast cancer (9% had a T_3 tumour)	698	1. Preoperative FEC chemotherapy 2. Postoperative FEC chemotherapy	Median 56 mo	I	DFS 65% in preoperative group, 70% in postoperative group (p = 0.27). OS 82% in preoperative group, 84% in postoperative group (p = 0.38). Clinical response 49% in preoperative group; clinical complete response 7%; pathologic complete response 2%
Broët et al (Institut Curie), 1999[22]	Premenopausal women with T_2–T_3 breast cancer (27% had a T_3 tumour)	414	1. Preoperative FAC chemotherapy 2. Postoperative FAC chemotherapy	Median 105 mo	II	DFS not reported. OS 65% in preoperative group, 60% in postoperative group (p = 0.36). Clinical response 82% in preoperative group; clinical complete response 30%
Mauriac et al (Institut Bergonie), 1999[23]	Patients with breast carcinoma > 3 cm in diameter (18% had a T_3 tumour)	272	1. 3 cycles of EVM followed by 3 cycles of MiTVd chemotherapy preoperatively 2. 3 cycles of EVM followed by 3 cycles of MiTVd chemotherapy postoperatively	Median 124 mo	II	DFS not reported. No difference in OS (percentages and p value not reported). Clinical complete response 32.8% in preoperative group
Makris et al, 1998[25]	Patients with primary operable breast cancer (5% had a T_3 tumour)	309	1. 8 cycles MiMxM chemotherapy preoperatively 2. 4 cycles MiMxM preoperatively and 4 cycles Mix chemotherapy postoperatively	Median 48 mo	II	No statistically significant difference in DFS or OS (percentages and p values not reported). Clinical response 83% in preoperative group only; clinical complete response 22%

operative and postoperative chemotherapy groups (level II evidence). Preoperative chemotherapy often caused shrinkage of the tumour and permitted the performance of breast-conserving surgery (BCS) when a mastectomy was originally planned.[17–25] However, results from 2 trials suggested that patients whose tumours were down-staged so that BCS could be performed when it was not initially planned were at higher risk of local recurrence[19] and had worse survival.[20]

Choice of chemotherapy

- **Chemotherapy should contain an anthracycline. Acceptable regimens are 6 cycles of FAC, CAF, CEF or FEC (see Box 1). Taxanes are under intense investigation.**

There have been relatively few trials specifically involving women with operable stage IIIA breast cancer that

Table 3 continued

Study	Patients	No. of patients	Treatment regimens	Duration of follow-up	Level of evidence	Results/comments
Therasse et al, 2003[7]	Women with LABC (4% had a T_3 tumour)	448	1. 6 mo CEF chemotherapy 2. 3 mo high-dose EC chemotherapy + GCSF	Median 5.5 yr	II	Progression-free survival 34 mo in CEF group, 33.7 mo in EC+GCSF group ($p = 0.68$). OS 53% in CEF group, 51% in EC+GCSF group ($p = 0.94$). Clinical response 58.9% in CEF group, 60.8% in EC+GCSF group; clinical complete response 31.3 % in CEF group, 26.5 % in EC+GCSF group (p values not reported)
Buzdar et al, 1999[42]	Patients with operable breast cancer (17% had stage IIIA disease)	174	1. 4 cycles of paclitaxel preoperatively 2. 4 cycles of FAC preoperatively	Median 23 mo	II	DFS 94% in paclitaxel group, 89% in FAC group ($p = 0.44$). OS not reported. Clinical response 80% in each group; pathologic complete response 8% in paclitaxel group, 16% in FAC group (p values not reported)
Smith et al, 2002[43]	Patients with LABC or tumour ≥ 3 cm in diameter who had clinical response to CVAP neoadjuvant chemotherapy	102	1. 4 cycles of docetaxel preoperatively 2. 4 additional cycles of the original CVAP chemotherapy preoperatively	Median 3 yr	I	OS improved in docetaxel group (percentages not reported, $p = 0.05$). Clinical response 94% in docetaxel group, 66% in CVAP group ($p = 0.001$). Pathologic complete response 34% in docetaxel group, 16% in CVAP group ($p = 0.04$)
Bear et al (NSABP B-27 trial), 2003[45]	Women with operable primary breast cancer (45% had tumour > 4 cm in diameter)	2400	1. 4 cycles of AC chemotherapy + surgery 2. 4 cycles of AC chemotherapy + 4 cycles of docetaxel + surgery 3. 4 cycles of AC chemotherapy + surgery + 4 cycles of docetaxel	Preliminary results	Preliminary results	DFS and OS not reported. Clinical complete response 40% at time of surgery increased to 64% by addition of docetaxel ($p < 0.001$). Pathologic complete response increased from 13.7% in combined preoperative AC groups to 26.1% when docetaxel added preoperatively ($p < 0.001$)
Papaioannou et al, 1983[61]	Patients with LABC who had 2 cycles of CAVMF chemotherapy preoperatively and 10 cycles postoperatively	205	1. Mastectomy 2. Mastectomy + radiotherapy	Minimum 6 mo	II	DFS not reported. No difference in OS (percentages and p value not reported). Local recurrence 10.5% in mastectomy only group, 8.3% in radiotherapy group (difference not statistically significant, p value not reported). Systemic recurrence 10.5% in mastectomy group, 18.7% in radiotherapy group (difference not statistically significant, p value not reported)

Note: LABC = locally advanced breast cancer, DFS = disease-free survival, OS = overall survival, NSABP = National Surgical Adjuvant Breast and Bowel Project, EORTC = European Organization for Research and Treatment of Cancer, A = adriamycin, C = cyclophosphamide, F = 5-fluorouracil, E = epirubicin, V = vincristine, P = prednisone, M = methotrexate, GCSF = granulocyte colony stimulating factor, Mi = mitomycin C, T = thiotepa, Vd = vindesine, Mx = mitoxantrone.

have addressed the issue of the type of chemotherapy to be used.[11,26,27] The number of patients in these trials was small. Two trials showed improved DFS with anthracycline-based chemotherapy over no chemotherapy (level I evidence)[11] and over a CMF–vincristine–prednisone regimen (level II evidence).[27] A third trial showed no difference in DFS or OS between CMF and a CMF–epirubicin–vincristine regimen (level II evidence) (Table 2).[26] Hence, recommendations concerning the type of chemotherapy regimens to be used in stage IIIA disease are based on extrapolation from trials in women with metastatic breast cancer and node-positive breast cancer.

Results of randomized trials involving women with metastatic breast cancer have shown a superior response rate and prolonged DFS with anthracycline-containing chemotherapy regimens than with CMF.[28,29] Randomized trials have confirmed the superiority of anthracycline-containing regimens such as CEF and CAF over conventional CMF in women with node-negative and node-positive breast cancer.[30–32] In contrast, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 trial, 4 cycles of AC chemotherapy was equivalent to 6 months of CMF.[33] In the most recent EBCTCG overview,[5] there was a statistically significant improvement in survival with anthracycline-based chemotherapy compared with CMF in early stage breast cancer. Although there are limitations to cross-study comparisons, it is reasonable to consider that 4 cycles of AC, although equivalent to 6 months of CMF,[33] is probably inferior to 6 cycles of anthracycline-containing drug regimens such as FAC,[16] CAF,[28,30] CEF[32] and FEC.[34] In women who cannot receive anthracyclines because of underlying cardiac disease, CMF chemotherapy can be considered.

Six cycles of chemotherapy should be administered. This is based on the trials of adjuvant chemotherapy that showed that 6 cycles of CAF or CEF was superior to 6 cycles of CMF[30,32] and that 6 cycles of FEC was superior to 3 cycles of FEC.[35]

In a multicentre trial, 448 women with LABC were randomly allocated to receive either CEF, or EC plus GCSF (Table 3).[7] At a median follow-up of 5.5 years, no difference in survival was detected between the 2 groups (53% and 51% respectively; level II evidence).

Box 1: Chemotherapy regimens

AC	adriamycin, cyclophosphamide
CAF	cyclophosphamide orally for 14 days and both adriamycin and 5-fluorouracil intravenously on days 1 and 8
CEF	cyclophosphamide orally for 14 days and both epirubicin and 5-fluorouracil intravenously on days 1 and 8
CMF	cyclophosphamide, methotrexate, 5-fluorouracil
EC	epirubicin, cyclophosphamide
FAC	5-fluorouracil, adriamycin and cyclophosphamide intravenously every 3 weeks
FEC	5-fluorouracil, epirubicin (100 mg) and cyclophosphamide intravenously every 3 weeks
GCSF	granulocyte colony stimulating factor
TAC	docetaxel, adriamycin, 5-fluorouracil

The role of taxanes in LABC and as preoperative chemotherapy in women with early breast cancer is currently under investigation. Studies involving women with metastatic breast cancer indicate that taxanes can cause significant tumour regression and improvement in symptoms in patients with anthracycline-resistant disease.[36,37] Taxane-containing regimens have been evaluated in randomized trials involving patients with axillary node-positive breast cancer. Compared with AC, AC followed by paclitaxel was associated with improved DFS in 2 trials[38,39] and with improved OS in 1 trial.[38] A recent trial suggested that AC administered every 2 weeks followed by paclitaxel every 2 weeks (dose dense chemotherapy) was associated with improved DFS compared with the usual AC followed by paclitaxel, both administered every 3 weeks.[40] Another recently reported trial involving women with node-positive breast cancer showed that, compared with FAC, the chemotherapy regimen TAC improved DFS and OS.[41]

In a trial of FAC versus paclitaxel, both administered preoperatively, no difference was detected in clinical or pathologic response rate and DFS (Table 3).[42] Results from 2 studies suggested that the addition of a taxane sequentially to an anthracycline-based regimen can improve clinical and pathologic response (Table 3).[43–45]

Currently, there are insufficient data to make definitive recommendations concerning the use of taxane-containing regimens in LABC. However, this is an evolving area of investigation. Management of LABC with systemic therapy remains an area for further research, and randomized studies are needed to identify optimal strategies. Participation in clinical trials is encouraged.

Inoperable tumours

- **Patients with stage IIIB or IIIC disease, including those with inflammatory breast cancer and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement, should be treated with primary anthracycline-based chemotherapy.**
- **Acceptable chemotherapy regimens are FAC, CAF, CEF or FEC. Taxanes are under intense investigation.**

[See the discussion of chemotherapy in the section "operable tumours."] The results of trials of chemotherapy in women with metastatic breast cancer and axillary node-positive breast cancer have demonstrated the superiority of anthracycline-containing combination chemotherapy over CMF.[28–32] On the basis of this evidence, when chemotherapy is used for treating stage IIIB or IIIC breast cancer, an anthracycline-containing regimen should be used if there are no contraindications to its use. A regimen of FAC, CAF, CEF or FEC is preferred.[16,30,32,34] An adequate dose intensity and total dose of anthracycline should be used.[34,46] CMF chemotherapy can be used in women who cannot receive anthracycline-containing chemotherapy because of underlying heart disease. The role of taxanes is currently under investigation, and no recommendations can be made at present for the incorporation of taxanes in primary chemotherapy for inoperable LABC.

There is currently no evidence to support the use of high-dose chemotherapy with stem cell support for this group of patients, as the randomized trials involving women with metastatic breast cancer and breast cancer with extensive nodal involvement have demonstrated no difference in survival between high-dose chemotherapy and standard-dose chemotherapy (level II evidence).[47,48]

- **Patients with stage IIIB or IIIC disease who respond to primary chemotherapy should be treated until the response plateaus or to a maximum of 6 cycles (minimum 4 cycles). Patients with stage IIIB disease should then undergo definitive surgery and irradiation. The locoregional management of patients with stage IIIC disease who respond to chemotherapy should be individualized. In patients with stage IIIB or IIIC disease who achieve maximum response with fewer than 6 cycles, further adjuvant chemotherapy can be given following surgery and irradiation. Patients whose tumours do not respond to primary chemotherapy can be treated with taxane chemotherapy or can proceed directly to irradiation followed by modified radical mastectomy, if feasible.**

Patients with stage III disease who are treated with primary chemotherapy need to be followed carefully for evidence of response. Multivariate analyses in several studies[17–19,49,50] have shown that the primary tumour response is correlated with patient outcome and that patients who have pathological evidence of a complete response following primary therapy have a superior DFS and OS compared with those who do not have such a response (level III evidence). Clinical response is seen in about 80% of patients who receive primary chemotherapy. To ascertain response, at least 2–3 cycles of chemotherapy should be administered.

The treatment of patients with LABC whose tumours do not respond to anthracycline-containing chemotherapy is unclear. It is reasonable to try taxane chemotherapy[42–45] or to proceed directly to locoregional therapy including irradiation and MRM, if possible.

Patients with stage IIIB or IIIC disease who do have a clinical response to primary chemotherapy should receive ongoing treatment until the manifested response clearly plateaus or to a maximum of 6 cycles, whichever comes first. The threshold for anthracycline-associated cardiac toxicity should not be exceeded. The optimal duration of primary chemotherapy is unclear. However, the results of studies involving women with node-positive breast cancer who received adjuvant chemotherapy showed that a regimen of 6 cycles of CMF was superior to that of 3 cycles of CMF[51] and that a regimen of 6 cycles of FEC was superior to that of 3 cycles of FEC.[35]

It is unclear whether additional chemotherapy should be administered following primary chemotherapy and definitive locoregional therapy. This has been examined in several case series (level V evidence).[15,16,49]

Systemic therapy: hormonal therapy

Operable and inoperable tumours

- **Tamoxifen for 5 years should be recommended to pre-and postmenopausal women whose tumours are hormone responsive.**

Following completion of chemotherapy, pre- or postmenopausal patients with LABC and hormone-responsive tumours should receive adjuvant tamoxifen therapy, 20 mg/d, for 5 years (see guideline 8).[5,52] Tamoxifen should be started after completion of chemotherapy.[53] The aromatase inhibitor, anastrozole, has been compared with tamoxifen in postmenopausal women with early breast cancer following surgery.[54] The early results of that study showed that, compared with tamoxifen, anastrozole was associated with improved DFS and had fewer side effects. The role of aromatase inhibitors as adjuvant therapy in breast cancer is evolving.[55] The role of luteinizing hormone-releasing hormone agonists in premenopausal patients is evolving as new data emerge (see guideline 8).

Patients who are not candidates for any chemotherapy can be managed with hormonal treatment and then receive locoregional management as described below.[56–58]

Locoregional management

Operable tumours

- **Patients with stage IIIA disease should receive both modified radical mastectomy (MRM) and locoregional radiotherapy if feasible. They may be managed with MRM followed by chemotherapy and locoregional radiotherapy, or chemotherapy first followed by MRM and locoregional radiotherapy. Breast-conserving surgery is currently not a standard approach.**

MRM (mastectomy plus a level 1 and level 2 axillary dissection) remains the standard surgical treatment for operable locally advanced disease. The role of BCS is unclear and the subject of research. Previous studies demonstrating equivalence of BCS to mastectomy were performed in patients with stage I and II disease (see guideline 3). In the trials that compared preoperative chemotherapy with chemotherapy administered postoperatively, the proportion of women with tumours greater than 5 cm in diameter ranged from 5% to 27%. Patients with operable stage III disease who desire to preserve their breast should be made aware that BCS is currently not a standard approach and is generally not recommended. There is a lack of evidence concerning breast reconstruction surgery in women with LABC. Reconstruction is generally performed after completion of chemotherapy and radiotherapy, because of the concern that postoperative complications could delay chemotherapy and radiotherapy.

In the largest study evaluating locoregional therapy,[59,60] eligible patients with operable LABC had a mastectomy, 6 cycles of anthracycline-based chemotherapy and, if disease-free, were randomly assigned to receive radiotherapy or observation with radiotherapy at isolated sites of locoregional failure (Table 2). Locoregional recurrences were reduced from 24% to 15% with immediate radiotherapy (level I evidence).

Two smaller randomized trials had conflicting results regarding the value of radiotherapy. These trials are summarized in Table 2 (level I evidence)[11] and Table 3 (level II evidence).[61]

There is a large body of level I and level II evidence demonstrating that locoregional radiotherapy following mastectomy in patients with node-positive disease treated with systemic therapy is associated with not only a reduction in locoregional recurrence but also an increase in overall survival (see guideline on postmastectomy radiotherapy). In the 3 largest trials of postmastectomy radiotherapy, 12%–14% of patients had stage IIIA disease.[62–64] A meta-analysis of all trials in which patients were treated with systemic therapy also confirmed the benefit of locoregional radiotherapy in improving disease-free and overall survival.[65]

In summary, the results of 2 randomized trials and data extrapolated from trials involving women with node-positive disease support the use of locoregional radiotherapy in patients with LABC who are treated with mastectomy.

- **Locoregional radiotherapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The role of internal mammary irradiation is unclear.**

When locoregional radiotherapy is delivered following MRM for locally advanced disease, radiation should be de-

Table 4: Summary of studies comparing mastectomy with radiotherapy

Study	Patients	No. of patients	Treatment regimens	Duration of follow-up	Level of evidence	Results/comments
Perloff et al (CALGB study), 1988[67]	Patients with stage III breast cancer who received 3 cycles of CAFVP chemotherapy and whose tumour was deemed operable	87	1. Mastectomy + 2 yr of CAFVP chemotherapy 2. Radiotherapy + 2 yr of CAFVP chemotherapy	Median 37 mo	II	DFS not reported. Median survival 39.3 mo in mastectomy group, 39.0 mo in radiotherapy group (p value not reported). Local recurrence 42% in mastectomy group, 55% in radiotherapy group ($p = 0.43$)
Mourali et al, 1993[68]	Patients with rapidly progressing breast cancer who received 3 cycles of CMF chemotherapy	68	1. Mastectomy + 15 cycles of CMF chemotherapy 2. Radiotherapy + 15 cycles of CMF chemotherapy	Minimum 10 yr	II	DFS and OS not reported. No difference in disease-free interval between treatment groups (percentages and p value not reported)
De Lena et al, 1981[69]	Patients with LABC who received 3 cycles of AV chemotherapy	132	1. Mastectomy + 7 cycles of AV chemotherapy 2. Radiotherapy + 7 cycles of AV chemotherapy	Minimum 6 mo	II	DFS not reported. No difference in OS (percentages and p value not reported). Median duration of remission 15 mo in surgical group, 22 mo in radiotherapy group ($p = 0.58$). Total incidence of locoregional recurrence 29.6% in surgical group, 31.1% in radiotherapy group (no p value reported). Total incidence of treatment failure in distant sites 43% in surgical group, 26.2% in radiotherapy group ($p = 0.25$)

Note: CALGB = Cancer and Leukemia Group B, LABC = locally advanced breast cancer, OS = overall survival, C = cyclophosphamide, A = adriamycin, F = 5-fluorouracil, V = vincristine, P = prednisone, M = methotrexate.

livered to the chest wall and the supraclavicular and axillary nodes. Whether treatment to the internal mammary nodes is required is unclear.[66] In many of the studies reviewed for this guideline, the internal mammary nodes were irradiated. However, there are no studies that examined the impact of such radiotherapy. It is not unreasonable to include radiotherapy to the internal mammary nodal region, provided that this can be done without treating an excessive amount of heart or lung tissue. Locoregional radiotherapy has been associated with a modest increase in late non-breast-cancer deaths of cardiac or vascular origin.[66] The recommended dose of radiation is 50 Gy in 25 fractions or equivalent.

Inoperable tumours

- **Patients with stage IIIB disease who respond to chemotherapy should receive surgery plus locoregional radiotherapy.**
- **The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear and should be individualized.**
- **Patients whose disease remains inoperable following chemotherapy should receive locoregional radiotherapy with subsequent surgery, if feasible.**

Three small trials compared MRM alone with locoregional radiotherapy alone following chemotherapy (Table 4).[67–69] The results of these studies suggest that both treatments are equally effective after primary chemotherapy in inoperable disease (level II evidence).

No randomized trials were found that compared mastectomy plus locoregional radiotherapy with mastectomy alone following chemotherapy, but 2 case series demonstrated that locoregional control was better if both mastectomy and radiotherapy were performed[70,71] (level V evidence).

The results of these studies and data from randomized trials in operable disease support the use of both MRM and locoregional radiotherapy in achieving optimal local control when feasible. It is unknown whether the sequence of surgery and radiotherapy makes a difference. Technical and disease factors will usually influence the order of treatments. For example, patients who have a good response to primary chemotherapy may be best managed by MRM followed by radiotherapy. Patients who remain inoperable after chemotherapy could receive radiotherapy followed by surgery, if feasible. Again, similar to operable disease, the role of BCS in this situation is unclear and is the subject of research.

The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear. In the absence of evidence on this subgroup of patients, it is reasonable that they receive locoregional radiotherapy (including nodal irradiation). The role of completion mastectomy should be individualized and based on such factors as response to chemotherapy and radiotherapy, absence of metastases on re-staging examinations and patient fitness.

Patients who are treated primarily with radiotherapy should be given tumouricidal doses to areas of bulk disease (60–66 Gy in 30 to 33 fractions or equivalent). Higher doses of radiation (70 Gy in 35 fractions by external beam or brachytherapy) to areas of bulk disease may be considered for patients if surgery is felt not to be an option and if tolerance of critical organs permits. Two case series have reported a dose-response relation with higher doses of radiation that resulted in decreased rates of local recurrence (level V evidence).[72,73]

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A guide for patients on the treatment of locally advanced breast cancer appears on page 994.

Appendix 1

Questions and answers on the treatment of locally advanced breast cancer

A guide for women and their physicians

What is locally advanced breast cancer?

Patients with *locally advanced breast cancer* or *LABC* have large breast tumours (more than 5 cm wide) and one or more of the following:

- Tumours that are attached to the chest wall or skin, or skin that is ulcerated or red.
- Lymph nodes (sometimes called *glands*) in the armpit that have become attached to structures in the armpit.
- Lymph nodes above the collarbone (called *supraclavicular nodes*) that contain cancer cells.

These features indicate that the cancer is more extensive than earlier stage breast cancer (see guideline 3) but has not yet spread or *metastasized* to other parts of the body. Inflammatory breast cancer, which makes the breast red and swollen, is a type of LABC.

How is LABC treated?

The treatment of LABC is complex and must be tailored to the individual. Patients will often need a combination of therapies (called *combined modality treatment*), which includes:

- Chemotherapy (treatment with anticancer drugs)
- Radiotherapy (treatment with high-energy x-rays)
- A mastectomy (surgery that removes all breast tissue)
- Hormonal therapy (treatment with the drug tamoxifen)

Usually 3 cancer specialists — a surgeon, a medical oncologist and a radiation oncologist — will work together to choose and schedule the best combined modality treatment for you.

What more can I learn about LABC from this guide?

This guide summarizes a list of recommendations for treating patients with LABC. The recommendations have been written with the use of a treatment framework based on whether or not surgery is possible for the patient with newly diagnosed LABC. In other words, is the tumour *operable* (it can be removed completely in an operation) or is it *inoperable* (it cannot be removed completely)? Inoperable tumours are either:

- attached to the chest wall or skin, or
- inflammatory, or
- have lymph nodes attached to structures in the armpit, or have spread to a lymph node above the collarbone.

I have an operable tumour…

Will I be offered chemotherapy?

Yes, you will probably be offered chemotherapy unless your general health indicates that you would not tolerate it well. In general, the chemotherapy should include anthracyclines (anticancer agents such as doxorubicin and epirubicin). You will most likely have 6 months of chemotherapy (see guideline 8) — scheduled in 1 of 2 ways:

- Anticancer drugs will be given before surgery to shrink the tumour and make surgery easier, or
- Surgery will be done first and then anticancer drugs will be given to try to destroy any remaining cancer cells.

You will need to discuss with your doctor which approach will be used. You will also need to see if your health and level of fitness allow you to have chemotherapy.

Will I be offered radiotherapy?

Yes, you will probably be offered radiotherapy. This is usually scheduled after surgery and chemotherapy. The radiation will be directed at your chest wall and at the lymph nodes in your armpit and above your collarbone.

Will I be offered hormonal therapy?

Yes, if you have a tumour that is identified as one that is likely to respond to hormones. In that case, your doctor will probably recommend that you take tamoxifen (a drug that blocks the effect of estrogens) for 5 years after you finish the chemotherapy and radiotherapy, to decrease the chance of the cancer returning. Women who may not tolerate chemotherapy may be offered tamoxifen instead.

I have an inoperable tumour…

Will I be offered chemotherapy?

Yes, you will probably be offered chemotherapy that includes anthracyclines (anticancer agents such as doxorubicin and epirubicin). If anthracyline-based chemotherapy does not help, you may then be offered taxane-based chemotherapy (anticancer agents such as paclitaxel and docetaxel). If your cancer responds well to a particular kind of chemotherapy, you will have 4 to 6 months of treatment (see guideline 8). The way your cancer responds to the anticancer drugs will determine what treatment you receive next. For example, if the anticancer drugs make the tumour disappear, you may be offered surgery before radiotherapy. If the anticancer drugs have less effect, your physician will probably suggest radiotherapy before considering surgery. Your medical specialists will also need to consider other treatment options if your health and level of fitness do not allow you to have chemotherapy.

Will I be offered radiotherapy?

Yes, you will probably be offered radiotherapy. If your cancer responds to chemotherapy, you may be offered surgery with radiotherapy to follow. If your cancer responds less well to chemotherapy or you are not able to have chemotherapy, you will probably be offered radiotherapy first. At whatever point you receive radiotherapy, the radiation will be directed at your chest wall and at the lymph nodes in your armpit and above your collarbone.

Will I be offered hormonal therapy?

Yes, if you have a tumour that is identified as one that is likely to respond to hormones. In that case, your doctor will probably recommend that you take tamoxifen (a drug that blocks the effect of estrogens) for 5 years after you finish the chemotherapy and radiotherapy, to decrease the chance of the cancer returning. Women who may not tolerate chemotherapy may be offered tamoxifen instead.