Management of Locally Advanced Breast Cancer

Review Article [1] | September 01, 1997
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Multimodality therapy—ie, surgical excision followed by appropriate systemic therapy and radiotherapy—has an established role in managing patients with locally advanced breast cancer.

Introduction

In 1962, Bloom and colleagues described the natural history of locally advanced breast cancer.[1] (For the purposes of this manuscript, we will define locally advanced breast cancer as tumors that measure more than 5 cm, tumors that extend to the chest wall or skin, and tumors with fixed ipsilateral nodes or ipsilateral internal mammary nodes. These characteristics therefore correspond to operable disease stage IIIA (T3, N1 or any N2) and to initially inoperable stage IIIB (any N3 or any T4) disease.[2]) Bloom et al retrospectively analyzed data from 250 untreated patients with locally advanced breast cancer (97.6% of whom had T3 or T4 disease) who were hospitalized in the Middlesex Hospital in London between 1805 and 1933. The patients, who were in the hospital for at least 6 months, died in the hospital and were autopsied. Mean survival time was 2.7 years (range, 3 months to 18 years).

Today, with the use of a consistent multimodality approach including surgical excision followed by appropriate systemic adjuvant therapy and radiotherapy, 3-year survival rates for women with locally advanced breast cancer range from 50% to 80%. However, 10-year survival rates are between 30% and 40%.

Surgical therapy has traditionally involved modified radical mastectomy, but by downstaging the primary tumor with induction chemotherapy, breast-conserving surgery becomes an option for some patients. The extent and dose of radiotherapy depends on the size of the cancer, adequacy of axillary dissection, number of axillary nodes involved, and type of primary surgery performed. The major obstacle to long-term survival for patients with locally advanced breast cancer is the development of distant metastases. Therefore, the development of more effective systemic therapies is required.

Systemic therapy has traditionally involved chemotherapy followed by hormonal agents. Recently developed cytotoxic agents (the taxanes in particular) are starting to be incorporated in clinical studies targeted to patients with locally advanced breast cancer. High-dose chemotherapy requiring stem-cell rescue is also being studied as is the use of monoclonal antibodies against breast cancer-related antigens (either individually or as vehicles to deliver chemotherapy, radioisotopes, or natural toxins). Determination of the ultimate impact of these newer agents on overall and long-term disease-free survival, local control, and quality of life will require further investigation.

In this article, we will discuss several issues relating to the optimal management of patients with locally advanced breast cancer, including the roles of combined-modality therapy; new chemotherapy agents, such as the taxanes; and high-dose chemotherapy with stem-cell transplantation. We also will describe the tools currently available to assess response to induction chemotherapy, as well as biologic correlates to predict response to treatment.

Combined-Modality Therapy

Surgery

The surgical options for patients with locally advanced breast cancer include radical mastectomy, modified radical mastectomy, and breast-conserving surgery. Studies have demonstrated that radical or modified radical mastectomy as a single treatment modality leads to local relapse rates ranging from 20% to 50%, with a 5-year overall survival of only 30% to 40% and a 10-year overall survival of approximately 20% to 30%.[3-5] Locoregional control has traditionally been achieved using mastectomy and postoperative radiotherapy. Historically, breast conservation has not been a treatment option for women with stage III disease. Recently, however, the use of induction chemotherapy has allowed increasing...
numbers of patients to undergo breast-conserving surgery.

**Breast Conserving Surgery** Numerous investigators, including Winchester and Cox,[6] have discussed the standards for breast-conserving surgery. The absolute and relative contraindications to breast-conserving surgery are:

- First- or second-trimester pregnancy;
- More than one malignancy in separate quadrants of the breast or diffuse malignant or indeterminate microcalcifications;
- History of prior therapeutic radiation to the involved breast;
- Large tumor in a breast in which adequate resection would cause significant cosmetic deformity; and
- Subareolar location, which may result in suboptimal cosmesis due to the removal of the nipple-areolar complex.

Clinically suspicious mobile axillary lymph nodes or microscopically involved axillary nodes are not considered contraindications to breast-conserving surgery. Beside the usual radiotherapeutic contraindications, additional surgical concerns must be considered when a patient is evaluated for breast-conserving surgery.

The surgeon should not cut the surgical specimen before the pathologist has examined it and should orient the specimen for the pathologist. Both the pathologist and surgeon should examine the specimen for adequate margins. Despite the widespread use of breast-conserving surgery for patients with breast cancer, the optimal resection margin is still not well defined. Moreover, examination of breast specimens is far from uniform.

Pathologists need to reach a better consensus about the definition of a positive margin,[7] since positive or uncertain margins of excision are associated with a significantly greater incidence of residual tumor on reexcision[8-10] and a higher risk of local recurrence after radiation therapy.[11]

Despite the precautions taken at initial biopsy, reexcision of a previous biopsy site may be necessary to ensure negative margins. Proper orientation of the original biopsy specimen will help avoid reexcision of already clear margins, and thus the unnecessary removal of normal breast tissue.

When the site of the positive margin is unknown, a rim of tissue around the entire biopsy cavity will need to be removed. Placing clips to outline the breast cavity may aid in marking the tumor bed and in planning radiation therapy.[12]

**Axillary Dissection** The prognosis of patients with locally advanced breast cancer is related to nodal status, size of the primary lesion, and estrogen/progesterone receptor status. Axillary node status, the single most important prognostic indicator, still requires axillary dissection with histologic examination for definitive diagnosis. With breast-conserving surgery, axillary dissection is generally done through a separate axillary incision for better cosmesis.

The extent of the axillary dissection depends on the extent of disease. A level I and II dissection is appropriate for most invasive tumors, with a minimum of six lymph nodes required to adequately sample the axilla. Levels I, II, and III lymph nodes that contain obvious disease are removed. The long thoracic, thoracodorsal, and medial pectoral nerves are preserved routinely.

Axillary dissection has the potential morbidity of arm edema (reported incidence, 2% to 22%), upper extremity cellulitis (which often aggravates arm edema), and sensory disturbance in the distribution of the intercostal brachial nerve.

The length of hospitalization necessary following these surgical procedures—ie, mastectomy, breast-conserving surgery, and axillary dissection—has decreased significantly over the last few years, with outpatient surgery being technically possible for an increasing number of patients.[13,14]

**Surgery Following Induction Chemotherapy** The role of surgery following induction chemotherapy has been debated recently.[15-17] Investigators from British Columbia evaluated the impact of mastectomy in patients with locally advanced breast cancer who received induction chemotherapy (three cycles of doxorubicin [Adriamycin] and cyclophosphamide [Cytoxan] on day 1 and methotrexate and 5-fluorouracil [5-FU] on day 14) followed by radiotherapy between 1979 and 1983.[Joseph Ragaz, md, personal communication, December, 1996] If patients were deemed to have operable disease, the physician could recommend mastectomy or continued observation. Ten-year results document a statistically significant improvement in overall survival for the mastectomy group compared with the observation group. However, when a subset of patients who achieved either a complete or partial response to induction chemotherapy was analyzed, no
statistical difference in overall survival emerged. The role of breast-conserving surgery (lumpectomy) for patients who have undergone induction chemotherapy for locally advanced breast cancer has also been evaluated recently.[18-20] Touboul and co-workers examined three different locoregional approaches based on response to induction chemotherapy.[20] Patients who had residual tumors > 3 cm or multifocal tumors underwent a mastectomy; patients deemed to have no residual disease received radiation therapy alone; and patients who had small tumors (defined as ≤ 3 cm) after induction chemotherapy underwent wide excision and radiation therapy. Between 1982 and 1990, 97 patients were enrolled. At a median follow-up of about 8 years, the 5-year locoregional relapse rate was 16% in patients treated with radiation alone, 16% in those given radiation plus wide excision, and 5.4% in those who had mastectomy (P = .04 for mastectomy vs radiation alone or with wide excision). However, the 5-year breast-conservation rate was 52%, and the 5-year overall and disease-free survival rates were identical for all three arms with 5- and 10-year overall survival rates of 80% and 69%, respectively. (Five-year and 10-year survival rates after conservative local treatment were 85.5% and 67.8%, respectively, vs 75.7% and 71.9% after nonconservative treatment, P = .9). The study concluded that local treatment does not influence 5- and 10-year overall survival and that preoperative chemotherapy and radiation therapy do allow conservative surgery to be used more often. Radiation therapy as a single modality in managing patients with locally advanced breast cancer (standard dose, approximately 60 Gy) leads to a local relapse rate ranging from 25% to 70%, with a 5-year overall survival of only 10% to 40%. Higher radiation doses (above 70 Gy) increase local control but also increase local toxicity.[21-24] Although data comparing the combination of surgery and radiation with surgery alone in patients with locally advanced breast cancer are limited, they support the conclusion that local control is improved when surgery is combined with radiation therapy. Despite this improvement in the rate of locoregional relapse, however, the rate of distant failure continues to be significant.[25-29]

Radiation vs Surgery After Primary Chemotherapy
Two randomized studies that compared surgery with radiation therapy alone after primary chemotherapy found no differences in survival. The Cancer and Leukemia Group B (CALGB) analyzed 113 patients with stage III breast cancer who were treated with three cycles of induction CAFVP (cyclophosphamide, Adriamycin, 5-FU, vincristine [Oncovin], and prednisone) chemotherapy.[30] Of the 113 patients, 91 (81%) were judged to have operable disease and randomized to either surgery or radiotherapy after chemotherapy. Four patients refused randomization, leaving 43 patients randomized to surgery and 44 to radiation therapy. Of the initial disease relapses in each treatment arm, approximately half were local (27% in the radiotherapy arm and 19% in the surgery arm). Distant failure occurred in approximately 25% of patients in both treatment groups, and no major survival difference emerged between the groups (overall median follow-up, 37 months).

DeLena et al[26] randomized 132 women with locally advanced breast cancer to radiotherapy or mastectomy following three cycles of doxorubicin and vincristine chemotherapy. A higher proportion of women achieved complete remission after mastectomy than after radiotherapy (100% vs 60%), but response rates at the end of combined-modality treatment were identical (75%). In addition, no significant differences were evident between the two treatment groups in terms of failure patterns, median response durations, or total survival.

Long-term complications associated with radiation therapy for locally advanced breast cancer are believed to be low, but may include a 0% to 12% risk of radiation pneumonitis,[16,25,29-31] a 0% to 16% risk of rib fracture,[16,31] an 8% risk of matchline fibrosis,[31] and a 0% to 2% risk of radiation pericarditis.[16,30] Two studies found no risk of brachial plexopathy.[16,29] The risk of secondary malignancy following radiotherapy administered after mastectomy or breast-conserving surgery is low and is associated with prolonged latency periods (15 to 20 years). The risk is poorly defined but includes a possible increased risk of developing lung cancer.[32-35] There have been case reports of the development of angiosarcoma[36] and pleural mesothelioma[37] following radiation therapy for breast cancer. The extent of the increased risk of second malignancy attributable to radiotherapy is difficult to ascertain as there may be other confounding factors, eg, chronic lymphedema (associated with angiosarcoma) and smoking (a risk factor for lung cancer). The absolute risks of lung cancer associated with current radiotherapy practices for breast cancer are probably small.[32] In 1985, Harvey and Brinton estimated that for 10-year survivors of breast cancer in Connecticut, adjuvant radiotherapy might cause an extra seven to eight cases of lung cancer per year among 10,000 irradiated women.[35]
For most women with breast cancer, especially for those with locally advanced breast cancer, the risk of a secondary malignancy from radiotherapy is relatively insignificant compared with the risk of death from metastatic breast cancer.

Systemic Therapy
Retrospective data demonstrate improved disease-free and overall survival for patients with stage IIIA or IIIB disease who received chemotherapy, surgery, and radiation therapy, as compared with those treated with surgery and radiation therapy alone.[38] Although standard practice for managing patients with locally advanced breast cancer has been the use of local therapy combined with systemic treatment in the form of chemotherapy plus hormonal therapy, numerous trials have attempted to determine appropriate sequencing of these modalities and optimal specific therapies to employ in combined-modality regimens.[29,31,38-40]

Hormonal manipulation has a response rate of approximately 30% to 40%.[41,42] Chemotherapy can be administered as induction (preoperative or neoadjuvant) therapy, concurrent with radiotherapy, or as adjuvant therapy. The overall response rate to systemic chemotherapy is approximately 50% to 90%, with an overall survival of about 50% to 80% at 3 years and 30% to 50% at 5 years; median survival is approximately 3 to 4 years.

Preoperative Chemotherapy
Preoperative chemotherapy has been used often over the last few years, even for patients with resectable disease, but its effect on median and overall survival has not been evaluated thoroughly in a randomized fashion. Justification for this approach comes from retrospectively analyzed data and from multiple phase II studies that demonstrated the feasibility of this approach; long-term data from large prospective comparative trials are not yet available. The administration of preoperative chemotherapy after a diagnosis of breast cancer has several theoretical advantages and disadvantages. The long-term effects of this approach on locoregional control and overall survival have yet to be defined. Preoperative chemotherapy has been used extensively in operable and inoperable locally advanced breast cancer with the goals of reducing tumor and facilitating local treatment via breast-conserving surgery or mastectomy and radiation therapy. Several of these studies demonstrate partial responses in 60% to 90% of tumors, including a study from Milan in which breast preservation was possible in approximately 70% of patients with tumors > 5 cm and in 91% of the total group of women with tumors > 3 cm.[19]

**Table 1** summarizes recent studies that have analyzed combined-modality therapy with breast-conserving surgery in locally advanced breast cancer.[19,20,25,26,29,31,39,41-46] Local control rates in these studies ranged from 50% to 90%. Although based on indirect comparisons, the highest local control rates seem to be achieved with triple-modality therapy consisting of chemotherapy, local excision, and radiotherapy.

Two Prospective Trials
Preliminary data are now available from two prospective trials of preoperative chemotherapy.[44] In a French study, 390 premenopausal women with tumors > 3 cm were randomized to either neoadjuvant chemotherapy (four cycles of cyclophosphamide, doxorubicin, and 5-FU) and radiotherapy followed by surgery or to neoadjuvant radiotherapy followed by surgery and postoperative chemotherapy. With a median follow-up of 54 months, a statistically significant survival difference favored the neoadjuvant chemotherapy group over the neoadjuvant radiotherapy group (5-year survival, 90% vs 80%; \( P = .039 \)). Breast-conservation rates at the end of primary treatment were statistically similar in the two groups (82% and 77%, respectively). No difference in disease-free interval or the rate of local recurrence emerged between the two groups.

The other trial is the National Surgical Adjuvant Breast and Bowel Project B-18 study, in which more than 1,300 patients were randomized to four cycles of either preoperative or postoperative AC (Adriamycin and cyclophosphamide) chemotherapy. The response rate to preoperative AC was 80%, including 37% complete responses, with a complete response rate of 18% in patients with tumors > 4 cm. Breast-conserving surgery was possible in 65% of patients who received chemotherapy before surgery, as compared with 57% of those given chemotherapy postoperatively.

Perhaps most interesting was the fact that 59% of the preoperative chemotherapy group vs 42% of the surgery-first group were found to have negative lymph nodes. However, 4-year follow-up data show equivalent disease-free and overall survival rates in the two treatment groups.[Eleftherios P. Mamounas, MD, personal communication, December 1996]

**New Approaches to Systemic Chemotherapy**
As distant metastasis remains the major determinant of survival for patients with locally advanced breast cancer, new management approaches include the incorporation of novel chemotherapeutic
agents, such as the taxanes, into combined-modality therapy and the use of dose-intensive chemotherapy

**Incorporating New Agents**

The proven activity of the taxanes docetaxel\[47,48\] (Taxotere) and paclitaxel\[49,50\] (Taxol) in patients with advanced breast cancer, including women who have not responded to prior anthracycline therapy, has prompted various groups to investigate the potential role of taxanes administered either before or after surgery to patients with locally advanced breast cancer. The National Surgical Adjuvant Breast and Bowel Project is performing a study to evaluate whether patients with operable breast cancer who have received AC induction chemotherapy benefit from the addition of docetaxel before or after surgery. Other studies incorporating docetaxel as induction chemotherapy are now being designed.

The efficacy of paclitaxel, either singly or combined with doxorubicin, in the management of metastatic breast cancer prompted the incorporation of the doublet into new trials for patients with locally advanced disease.[51,52] In a study by Gianni and co-workers, of the 49 patients with metastatic breast cancer and good performance status who received paclitaxel (200 mg/m² over 3 hours) and doxorubicin (60 mg/m² as an intravenous bolus) with granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) support, 94% responded, with 40% achieving a complete response.[52] At a median of 16 months' follow-up, overall survival was 85%, the 2-year projected probability of survival was 58%, and the projected median survival was 31 months.

Reducing the total doxorubicin dose to 360 mg/m² in this regimen appears to decrease cardiotoxicity; of the 49 patients enrolled, 25 received a cumulative doxorubicin dose of 480 mg/m² while 24 received a 360-mg/m² cumulative dose. The incidences of reversible congestive heart failure with the two cumulative doses were 24% and 4%, respectively. Therefore, this combination chemotherapy regimen appears to be very active, with high rates of overall response and clinical complete responses, making it a very reasonable choice of agents for managing patients with locally advanced breast cancer.

The same Italian investigators have already reported preliminary data from a pilot study of doxorubicin/paclitaxel as induction chemotherapy in patients with locally advanced breast cancer that demonstrates the feasibility of this approach. Initial results are promising.[53]

A randomized European study is currently assessing doxorubicin/paclitaxel as primary chemotherapy in earlier-stage operable disease, under the direction of Gianni and colleagues.[personal communication, Luca Gianni, MD, December 1996] The organizational pattern of the trial is shown in Figure 1. The study is evaluating the role of four cycles of doxorubicin/paclitaxel as either neoadjuvant or adjuvant therapy in patients who have operable breast cancer and who will also receive four cycles of cyclophosphamide/methotrexate/5-FU. A control group is scheduled to receive adjuvant doxorubicin instead of the two-drug combination.

A feasibility study is also being conducted in the United States. It includes the incorporation of paclitaxel along with radiotherapy, then surgery, in patients with locally advanced breast cancer.

**High-Dose Chemotherapy**

The role of high-dose chemotherapy with peripheral or bone marrow stem-cell infusion in patients with locally advanced breast cancer has generated significant interest, but most available data are derived from phase II studies.[54,55] Preliminary data from a randomized phase II study evaluating standard- vs high-dose therapy with stem-cell transplantation in patients with locally advanced breast cancer have recently become available.[56] In this Dutch study, 95 patients younger than 60 years with untreated stage II or III breast cancer who had positive apical axillary nodes[52,57-59] received three cycles of FEC (5-FU, epirubicin, and cyclophosphamide) chemotherapy. The patients then underwent definitive surgery and were randomly assigned to receive either one more cycle of FEC or FEC with stem-cell harvesting followed by cyclophosphamide (6 g/m²), thiopeta (Thioplex; 480 mg/m²), and carboplatin (Paraplatin; 1,600 mg/m²).

With a follow-up of 31 months, no differences in disease-free or overall survival have emerged between the two groups (overall and disease-free survival rates of 80% and 75%, respectively, for both treatments). The authors conclude that the data do not predict a major survival advantage for high-dose therapy in patients with high-risk breast cancer defined by a tumor-positive apical axillary lymph node at infraclavicular biopsy.

**Analysis of Response to Induction Chemotherapy**

Since decisions about which type of surgery to perform are often based on the response to chemotherapy, the best way to assess this response is being investigated. The options include physical examination, mammography, MRI, and radioimmunoguided surgery, among others.[60-63]

A study by Pierce and co-workers evaluated response to chemotherapy by physical examination and...
mammography in patients with stage III breast cancer who received combined-modality therapy.\[61\] The positive predictive value of the mammogram was 79%, but its negative predictive value was only 56%, and the negative predictive value of physical examination was only 36%. The investigators concluded that more sensitive modalities are needed to assess response to induction chemotherapy in patients with locally advanced breast cancer.

A study by Abraham and colleagues assessed response to induction chemotherapy by RODEO MRI (a tridimensional way of performing MRI) in 39 patients with stage II to IV breast cancer.\[62\] The investigators confirmed the results of physical examination, mammography, or MRI with pathologic assessment of residual disease.

The study showed that the clinical assessment of response agreed with MRI findings in only 52% to 55% of cases, but that MRI predicted pathologic determination of residual disease in 97% of cases. The authors concluded that RODEO MRI is a better method of assessing response to preoperative chemotherapy than is physical examination in patients with locally advanced breast cancer who receive induction therapy.

The use of monoclonal antibodies to measure response to therapy and the presence of persistent tumor is being evaluated. Percivale and colleagues assessed radioimmunoguided surgery using a gamma detection probe in 21 patients with locally advanced breast cancer.\[63\] After three courses of induction chemotherapy, patients were injected with either iodine-125-B72-3 (anti-TAG72) or F023CS (antarcinoembryonic antigen) monoclonal antibodies, with a gamma detection probe used to locate the tumor and the presence of ipsilateral axillary metastases at the time of surgery.

The data comparing the results of the gamma detection probe with those of the pathologic findings at surgery demonstrated no false-positives, but the gamma camera identified only 40% of the patients with axillary node-positive disease. The authors concluded that monoclonal antibodies are not adequately sensitive for clinical use and that further studies were needed.

**Biologic Predictors of Response to Induction Chemotherapy**

There are many biologic opportunities to be explored in patients with locally advanced breast cancer, including the evaluation of genes and protein expression as predictors of response and/or resistance, as well as the evaluation of molecular changes with therapy. Predictors of response to chemotherapy include P53, S-phase, ras, and various growth factor receptors, including Her2-neu and epidermal growth factor. The role for these laboratory predictors in tailoring chemotherapy is still being investigated.\[64-67\]

**Conclusions**

Historically, the outcome of patients with locally advanced breast cancer treated with surgery and/or radiation therapy was uniformly poor, with 5-year survival rates of 30% to 40%. The addition of systemic chemotherapy has improved results, both in terms of locoregional control and survival, when compared with locoregional treatment alone. Five-year survival rates with triple-modality therapy are approximately 50% to 60%.

The optimal timing and sequencing of a combined-modality approach including chemotherapy, surgery, and radiation therapy have not been determined. No one approach currently produces significantly better results than any other.

Until the results of new trials become available, a reasonable approach in patients with locally advanced breast cancer is to use induction chemotherapy and assess response via physical examination and mammography. Lack of response or disease progression should prompt consideration of mastectomy if the tumor is operable, followed by radiation therapy and then second-line chemotherapy. If mastectomy is not possible, radiation should be considered to reduce the tumor burden followed by mastectomy and second-line chemotherapy.

If the patient is judged to have had a complete or partial response to induction chemotherapy, performing either mastectomy or lumpectomy is reasonable, depending on the patient's preference and the size of the tumor. Adjuvant chemotherapy and radiation therapy can then follow this initial surgery.

The impact of newer chemotherapeutic agents (eg, the taxanes), high-dose chemotherapy with stem-cell transplantation, and hormonal and immunologic therapies on disease-free and overall survival has yet to be defined. Although prolonged control of stage III breast cancer can be achieved with combined-modality treatment in which cytotoxic chemotherapy precedes and follows locoregional treatment, a significant number of patients with locally advanced breast cancer still succumb to metastatic disease. Therefore, new approaches and regimens must continue to be evaluated so that increased cure rates and decreased morbidity can be achieved.
References:


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Management of Locally Advanced Breast Cancer
Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

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