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CLINICAL INVESTIGATION **Breast**

RETROSPECTIVE ANALYSIS OF LOCALLY ADVANCED NONINFLAMMATORY BREAST CANCER FROM CHENNAI, SOUTH INDIA, 1990–1999

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Purpose: This was a retrospective observational study to elicit the outcome of the therapeutic strategy of concurrent neoadjuvant chemoradiotherapy protocol for locally advanced breast cancer.

Methods and Materials: A large series of 1,117 consecutive cases of locally advanced breast cancer treated at the Cancer Institute (WIA), in Chennai, South India, between 1990 and 1999 and followed through 2004 formed the basis for this study. Disease-free survival was the main outcome, and nodal and tumor downstaging were the intermediate outcome measures studied.

Results: Primary tumor downstaging was observed in 45% and nodal downstaging in 57.5%. The disease-free survival rate of nodal downstaged patients at 5, 10, and 15 years was 75%, 65%, and 58%, respectively. The corresponding rates for pre- and postoperative node-negative patients were 70%, 60%, and 59%. The best survival was seen among those who were tumor and node negative postoperatively. Nodal downstaging halved the risk of disease recurrence and death compared with node positivity, irrespective of tumor sterility.

Conclusions: A randomized trial using cyclophosphamide, methotrexate, and 5-fluorouracil vs. an anthracycline-based regimen in the setting of concurrent chemoradiotherapy appears indicated. Additional preoperative chemotherapy to maximize nodal and tumor downstaging should be investigated. A change in postoperative chemotherapy according to nodal status could also be explored. © 2008 Elsevier Inc.

Locally advanced breast cancer, Concurrent chemoradiotherapy, Neoadjuvant, Nodal downstaging, Disease-free survival.

INTRODUCTION

Female breast cancer was the second most common cancer among women in India, constituting 15% of all female malignancies in 1982. Today, breast cancer constitutes 22% of all female malignancies and occupies the top rank among cancers in women in urban India. The cervix/breast cancer ratio, which was 1:0.53 in 1982, was 1:1.88 in 2002 (1). The age standardized incidence rate of 29.3/100,000 females in Chennai is significantly lower than that in whites (80–110/100,000) (2), but the total burden is high. The annual burden of incident breast cancer in India has increased from 62,000 in 1992 to 80,000 in 2001 and 120,000 in 2005 (1).

Our essential therapeutic problem is advanced disease. Table 1 gives the stage distribution of all treated cases of breast carcinoma in three calendar periods (1960–1979, 1980–1989, and 1990–2000) and reveals that Stage III disease constitutes 43–48% of all cases (3). This study reports on the outcome of a concurrent neoadjuvant chemoradiotherapy protocol for locally advanced breast cancer (LABC) between 1990 and 1999.

Evolution of therapeutic strategy in LABC management at our institute

Our therapeutic policy for LABC between 1960 and 1969, when chemotherapy was still casual, not yet systematized, and had not come into clinical practice, was preoperative radiotherapy (RT), in an attempt to reduce the physical proportions of the tumor and defuse its biologic aggressiveness, followed by appropriate surgery (4). Locoregional tumor regression after RT was more than satisfactory and brought nearly 45% of patients within the scope of surgery, with a disease-free survival (DFS) rate of 45% at 5 years (5). Nevertheless, >50% of cases were still lost to remote disease.

In 1970, chemotherapy was introduced worldwide in an adjuvant setting for operable cancers. Because we had been

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Table 1. Distribution of tumor stage among all treated cases of breast cancer from Hospital Cancer Registry, Cancer Institute (WIA), Chennai, 1960–2000

Tumor stage	1960–1979 (*n*)	1980–1989 (*n*)	1990–2000 (*n*)
I	17 (1.6)	30 (1.4)	56 (1.3)
II	185 (17.0)	447 (21.3)	949 (21.9)
III	523 (48.2)	908 (43.2)	1,897 (43.3)
IV	178 (16.4)	454 (21.6)	669 (15.5)
SNP	182 (16.8)	262 (12.5)	782 (18.0)
Total	1,085 (100.0)	2,101 (100.0)	4,335 (100.0)

Abbreviation: SNP = stage not possible (cases referred after surgery done elsewhere).

Data in parentheses are percentages.

using preoperative RT with acceptable results for LABCs and the major problem was loss to systemic disease, we added preoperative chemotherapy to the RT (concurrent) in what is today referred to as ''neoadjuvant.'' The results clearly demonstrated the value of a multimodality approach in the management of LABC (6).

MATERIAL AND METHODS

Between 1990 and 1999, of 2,700 female breast cancers, 1,833 (69.4) were LABCs, including Stage IIB, IIIA, and IIIB, as defined by the International Union Against Cancer (7). Of these 1,833 patients, 1,778 received preoperative concurrent chemoradiotherapy as described in this report, and 55 were excluded from the present analysis because they had received either adjuvant or another form of chemotherapy.

Of the 1,778 patients who received the protocol treatment, 129 (7.3%) had progressive disease during treatment and 198 (11.1%) were not considered suitable for surgery. Of the 1,451 (81.6%) considered suitable for surgery, 334 declined surgery (18.8%). The present study was a retrospective analysis of 1,117 patients with LABC at presentation, who completed the full treatment protocol, including surgery, between 1990 and 1999 at our institute.

The outcome measures studied included the response of the primary tumor (tumor sterility or no residue pathologically) and nodal disease (nodal downstaging) to preoperative chemoradiotherapy and DFS.

Neoadjuvant treatment protocol

Radiotherapy. Preoperative RT, which consisted of ^{60}C beam therapy to the whole breast at an 80-cm source-skin distance using two tangential medial and lateral fields, 10 × 17 cm^2 was given. The extent of the field covered was superiorly to the inferior border of the clavicle, medially to the midline, laterally to the mid-axillary line, and inferiorly to 2–3 cm below the inframammary fold.

The arm was kept in the abducted position. The medial field was directed 60° and the lateral fields 120° to the vertical line. The angles varied so as not to include more than a 2 cm of the underlying lung as checked on the simulator films. An Aquaplast mold was created for pendulous and large breasts to immobilize the breast in the same position for the daily treatment session. This also acted as bolus when the skin was involved. The tumor dose was calculated on the center of the tumor, computing the dose from the medial and lateral fields. The total tumor dose of 4,000 cGy was delivered in 20 fractions of 5/wk.

For RT to the ipsilateral axilla, the contribution of the dose from the breast fields was measured at the midpoint of the axilla and 3 cm inside the superior edge of the tangential fields. An additional dose was given by the posterior axillary fields of about 8 cm × 10 cm to deliver a total tumor dose of 4,000 cGy in 20 fractions.

For N2 disease and in cases in which the topography of the tumor and patient anatomy required it, a combined field was used for the supraclavicular and axillary regions. A direct anterior field approximately 15 cm × 10 cm was used. A total dose of 200 cGy was calculated at 3 cm for the supraclavicular nodal region. From the same field, the dose at the midpoint of anteroposterior diameter of the axilla was calculated, and an additional dose was delivered from the posterior axillary field of suitable size to reach a daily tumor dose to the axilla of 200 cGy/d. The total tumor dose to the supraclavicular and axillary region was 4,000 cGy in 20 fractions.

Radiotherapy to the breast was delivered using medial and lateral tangential fields, matching with the supraclavicular and axillary fields, using the same technique as above. Field size changes and use of a bolus was decided on an individual basis, as needed.

Postoperative internal mammary RT after mastectomy was given as indicated and consisted of a 6 cm × 15-cm parasternal 9-MeV electron field extending 4 cm ipsilateral and 2 cm across the midline. No bolus was used. The tumor dose was 4,000 cGy at 90% in 20 fractions.

Drug therapy. Regimen 1 consisted of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) as follows: cyclophosphamide 600 mg/M^2 intravenous infusion on Day 1; 5-fluorouracil 600 mg/M^2 intravenous infusion on Day 1; and methotrexate 40 mg/M^2 intravenous bolus on Day 1.

Regimen 2 was an anthracycline-based regimen and consisted of cyclophosphamide, 5-fluorouracil, and adriamycin or epirubicin as follows: cyclophosphamide 600 mg/M^2 intravenous infusion on Day 1; 5-fluorouracil 600 mg/M^2 intravenous infusion on Day 1; and adriamycin 75 mg/M^2 intravenous infusion on Day 1 or epirubicin 90 mg/M^2 intravenous infusion on Day 1.

This was not a randomized study, and the drug regimen used was given on a random basis. Most patients received CMF, because it was more economical in a country with limited resources. Additionally, we were cautious about using anthracyclines in combination with RT.

Chemoradiotherapy schedule. The chemotherapy cycles were given at 3-week intervals. Chemotherapy was administered on Day 1, with RT started the next day. RT was given 5 d/wk (Monday through Friday). The chemotherapy cycles were repeated on Days 21 and 42. Only rarely did any break in RT occur on a chemotherapy day.

At completion of preoperative chemoradiotherapy, the patients were re-evaluated for appropriate surgery (usually Patey's mastectomy). Surgery was generally scheduled for 3 weeks after the end of RT, depending on the patient's skin condition, but not later than 4–6 weeks after RT completion. A fourth chemotherapy cycle was administered approximately 8–12 days postoperatively. Internal mammary and supraclavicular RT given as indicated.

Hormonal therapy. All premenopausal patients underwent bilateral oophorectomy at breast surgery. Very occasionally, these procedures were performed in two stages. All patients received tamoxifen, irrespective of receptor status.

Statistical analysis

Frequency tables describe the factors and outcomes studied. The overall survival time was defined as the elapsed interval between the start of treatment and the date of death, date of loss to follow-up, or December 31, 2004, whichever was earlier. The disease-free survival (DFS) time was defined as ending at the date of disease