LOCALLY ADVANCED BREAST CANCER: AN EXPERIENCE IN MASHHAD, NORTH-EAST OF IRAN, 1995 – 1999

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Background: Locally advanced breast cancer (LABC) remains a clinical challenge as the majority of patients with this diagnosis develop distant metastases despite appropriate therapy.

Objective: To evaluate the treatment results of patients with locally advanced breast carcinoma who attended our hospital in Mashhad, North-East of Iran. Some presumed prognostic factors were also assessed.

Methods: We retrospectively reviewed the medical records of 133 patients with LABC who were treated in Omid Hospital, affiliated to Mashhad University of Medical Sciences, between April 1995 and April 1999. One hundred and five patients with available follow-up information were selected for statistical analysis. Ninety-seven of 105 patients had undergone mastectomy prior to referral. Eight cases had received neoadjuvant chemotherapy. All patients were treated with adjuvant radiotherapy with 95 receiving adjuvant or neoadjuvant chemotherapy (40 CMF, 50 CAF, and 5 cases CAF sequential to CMF). We used the Kaplan-Meier survival analysis for evaluation of survival rates and the log-rank test to compare the survival profile between groups.

Results: During a median follow-up period of 32 (range: 5 – 96) months, 47 (45%) of 105 patients experienced recurrence. The mean ± SEM 2- and 5-year overall survival rates were 80.4 ± 5% and 47.7 ± 9%, respectively. The mean ± SEM 2- and 5-year disease-free survival rates were 69.3 ± 6% and 42.6 ± 8%, respectively. Advanced nodal disease (N2, N3 vs. N0, N1: \( P = 0.031 \)), more advanced tumor stage (T4 vs. T3: \( P = 0.025 \)), and younger ages (≤ 35 vs. > 35: \( P = 0.0001 \)) had significant adverse effects on survival rates. There was not a significant difference in survival rates between the chemotherapy regimens of CMF and CAF (\( P = 0.9 \)).

Conclusion: A high recurrence rate in our patients underlines the need for general public education and the design of a program for the early diagnosis of breast cancer in Iran. We should also seek more effective systemic regimens for LABC.

Keywords: Breast carcinoma • chemotherapy • locally advanced disease • prognosis • radiotherapy

Introduction

Breast cancer has a major impact on the health of women. In developing countries, up to 50% of patients with breast cancer present as locally advanced breast carcinoma (LABC) while in developed countries, this figure is 5% – 20% with 15% for the United Kingdom, as an example.\(^1,2\) This difference may be due to differences in socioeconomic status, availability of medical facilities such as mammography screening, or even variations in tumor behavioral characteristics among different countries and ethnic groups.

According to the 1992 American Joint Committee (AJC) TNM classification, LABC is defined as a tumor larger than five cm with positive axillary lymph node(s), tumor invasion to the ribs and intercostal muscles, invasion to the skin, inflammatory carcinoma, fixed axillary lymph node(s), involvement of internal mammary node(s), and invasion to the ipsilateral supraclavicular lymph node.\(^3\)
In LABC, the goals of treatment are: 1) local control and 2) eradication of micrometastases, which are highly common at presentation and that make the prognosis worse.4

In the present study conducted in Omid Hospital, affiliated to Mashhad University of Medical Sciences, North-East of Iran, we presented our experience with patients with LABC. In addition, we evaluated some presumed prognostic factors such as age, stage, and chemotherapy regimen.

**Patients and Methods**

Between April 1995 and April 1999, a total of 460 new cases of breast cancer were referred to the Oncology Department of Omid Hospital of whom, 133 (29%) patients had LABC. All patients were staged according to American Joint Committee (AJC) TNM classification.

Staging work-up consisted of a complete blood count (CBC), blood chemistry, chest X-ray, ultrasonography of the liver, and bone scan.

Of the 133 patients with LABC, 28 who were followed less than five months were excluded from statistical analyses.

Ninety-seven patients had undergone surgery prior to the referral (80 had modified radical and 17 had simple mastectomy). Only eight patients underwent neoadjuvant chemotherapy and mastectomy, thereafter. Ninety-five patients were treated with at least six courses of adjuvant or neoadjuvant chemotherapy, which consisted of standard cyclophosphamide, methotrexate (MTX), and 5-fluourouracil (5FU) (CMF) in 40 patients; cyclophosphamide, adriamycin, and 5FU (CAF) in 50; or sequential courses of CAF and CMF in five patients. All patients underwent external radiotherapy to the chest wall and regional lymph nodes with a total dose of 5000 cGy in 25 fractions. A cobalt-60 unit was used for radiotherapy.

Hormone therapy with tamoxifen (20 mg/day for five years) was a component of treatment in all patients with estrogen receptor positive status as well as in those with unknown receptor status.

The patients were visited every three to four months for five years and every six months, thereafter.

Actuarial disease-free survival (DFS) and overall survival (OS) were plotted using the Kaplan-Meier survival method. The log-rank test was used for univariate analysis of different prognostic factors such as age, stage, and chemotherapy regimens.

**Results**

The median age of patients was 48 (range: 22 – 90) years. The median follow-up was 32 (range: 5 – 96) months. During follow-up, 47 (45%) of 105 eligible patients had recurrence. Metastases were found in 44 patients of whom 12 had concurrent local recurrences. Four patients had only local recurrences. The median time-to-progression was 24.5 months. The most common sites for metastases were bone, lung, brain, pleura, liver, and skin. The mean ± SEM two- and five-year overall survival rates (OS) were 80.4 ± 5% and 47.7 ± 9%, respectively. The mean ± SEM two- and five-year disease-free survival rates (DFS) were 69.3 ± 6% and 42.6 ± 8%, respectively.

| Table 1. Univariate analysis of presumptive prognostic factors to predict survival. |
|------------------------------------------|---------|-------|---------|------------------|
| Variable                              | Median OS (MO) | SEM | 95% CI   | Log-rank P Value |
| Node status                           | Early node (N0 or N1) | 57   | 4       | 48 – 66          |
| Age                                    | Advanced (N2)   | 15   | 8       | 12 – 44          |
| ≤ 45                                   | 40               | 7    | 43 – 69  |
| > 45                                   | 56               | 4    | 45 – 61  |
| Chemotherapy regimen                   | CMF             | 40   | 11      | 30 – 76          |
|                                      | CAF or (CAF + CMF)| 55  | 8       | 30 – 62          |
| Tumor                                  | T3              | 56   | 5       | 58 – 78          |
|                                        | T4              | 39   | 5       | 35 – 55          |

OS = overall survival; SEM = standard error of mean; CI = confidence interval; CMF = cyclophosphamide + MTX + 5FU; CAF = cyclophosphamide + adriamycin + 5FU; MO = month.
Univariate analyses were done to evaluate presumptive prognostic factors to predict overall survival (Table 1). Overall survival rate was significantly \( (P = 0.0001) \) worse for those younger than 35 years as compared to older patients.

In terms of nodestage, patients were divided into two groups including early (N0, N1) and advanced node stages (N2, N3). As shown in Figure 1, patients with early node-stage disease had a significantly \( (P = 0.031) \) better overall survival rates as compared to those with advanced node-stage disease.

In comparison with patients with T3 tumor stage, the overall survival rate was significantly \( (P = 0.025) \) worse for those with T4 tumor stage. There was no significant correlation between overall survival rates and the primary chemotherapy regimen administered \( (P = 0.09) \).

**Discussion**

We analyzed the treatment results of 105 eligible patients with LABC who were referred to Omid Hospital during a five-year period (April 1995 - April 1999). We used a triple-modality approach (surgery, radiotherapy, and chemotherapy) to treat our patients. We found that node stage, tumor stage, and age had a significant impact on overall survival rates (Table 1).

Several trials have studied the efficacy of adjuvant therapy in LABC. Local recurrence is seen in 11% – 44% of high-risk patients with tumors resected, and in 80% of those with distant metastases who received no adjuvant therapy.\(^5\)

Most investigators believe that combination therapy using the triple-modalities of chemotherapy, surgery, and radiotherapy is superior to bimodal therapy, in terms of controlling the local recurrence and metastasis in LABC. In a retrospective study by Perez et al, 398 women with LABC were assessed. The median follow-up period was 5.8 years. Treatment methods used for these patients included radiotherapy alone for 34 patients; radiotherapy combined with adjuvant chemotherapy for 31 patients, mastectomy and radiotherapy for 84 patients, and mastectomy, radiotherapy plus chemotherapy (triple-modality) for 214 patients. The locoregional tumor failure rates at five years were 69%, 46%, 18%, and 7% in the four groups, respectively. The triple-modality group had better locoregional control \( (P < 0.01) \) and cause-specific survival \( (P = 0.01) \) as compared to the single or bimodality treatment groups. The two- and five-year cause-specific survival rates in the triple-modality group were 90% and 60%, respectively.\(^6\) Ogston et al\(^7\) reported that a consecutive series of 176 patients with large tumors (\( \geq 4 \) cm) and LABC were treated with...
multimodality therapy. The overall five-year and disease-free survival rates were 71% and 60%, respectively.

Shen et al 8 assessed 33 patients with stage T4 LABC who completed treatment consisting of four cycles of neoadjuvant chemotherapy, lumpectomy, radiation therapy, and consolidate chemotherapy. The five-year DFS and OS rates were 70% and 78%, respectively.

In our study, only eight out of 105 patients underwent neoadjuvant chemotherapy. To date, although there is no evidence that neoadjuvant chemotherapy improves overall survival as compared to postoperative treatment, this approach has been successful in down-staging tumors. Therefore, a higher proportion of women may be candidates for breast conservation surgery.9 – 14 The five-year overall survival rates in our study were somewhat lower than reported in the aforementioned studies. This difference might be in part due to lower median follow-up duration secondary to socioeconomic problems of our patients.

The most established prognostic factor in breast cancer is nodal status. The prognosis of patients without lymph node involvement is better than those with lymph node involvement.15 For patients with lymph node metastases, a greater number of lymph nodes involved and a higher nodal stage predicts poorer survival.16 The size of the primary tumor is also associated with survival; patients with larger tumors have poorer survival rates. Valagussa et al found that five-year survival rates were 65%, 36%, and 16% for breast tumors measuring <5 cm, 5 – 10, and >10 cm, respectively.17 As shown in Table 1, nodal status and T stage were also important prognostic factors in our study. It was shown that young age is an adverse prognostic factor. This observation, however, has not been reported by all investigators.18 In our study, most patients below 45 years were in peri- or pre-menopausal states. We found a relatively better prognosis for patients below 45 years, but it was not statistically significant. However, patients below 35 years have a significantly worse prognosis than older patients.

In our study, chemotherapy regimens containing adriamycin had no advantage over CMF regimen in terms of overall survival (Table 1). The use of regimens containing adriamycin has still not been proven superior to other regimens for neoadjuvant therapy. On the other hand, in most studies, the use of regimens containing anthraclycines is recommended for adjuvant therapy in high-risk patients. In patients with Her-2-positive tumors, chemotherapy with anthraclycines is preferred.1 Twenty-eight (51%) out of 55 patients in the adriamycin-containing group and 11 (27%) of 40 patients in CMF group had T4 tumors ($P = 0.09$). A prospective randomized trial is needed for proper evaluation of the various chemotherapy regimens.

We concluded that for better management of patients with LABC, the following is recommended:

- Early diagnosis of breast cancer is vital for better results of treatment. General education about early symptoms of the disease and access to medical facilities are important in diminishing breast cancer mortality in our country.
- Cellular biological markers such as Her-2, P53, etc. should be evaluated as prognostic factors in prospective randomized studies.
- Randomized trials are recommended for comparing new adjuvant regimens containing taxans with CAF or CMF in Iran.

References


