Original Article

EXPERIENCE WITH ADJUVANT THERAPY IN 117 PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

Shapour Omidvari, MD; Niloofar Ahmadloo, MD; and Ahmad Mosalaei,* MD

Department of Radiation Oncology, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

BACKGROUND–*Loco-regional recurrence and distant metastases are frequently disturbing events in patients with locally advanced breast cancer. This study was carried out to evaluate the role of postmastectomy conventional adjuvant treatment in such patients.*

MATERIALS AND METHODS–*During the last five years, a total of 117 patients with locally advanced breast cancer (T3-T4 and/or more than four involved lymph nodes and/or fixed lymph nodes) were treated with postoperative chemotherapy and radiotherapy. Departmental records of these patients including stage, histology, sex, age, and therapeutic modalities were reviewed to assess the result of treatment. The cases with proven metastasis or T1-T2N0 lesions were excluded. The patients were divided into three groups. Arm I included T3-4N0, Arm II as a large primary tumor (T3-4) with 1 to 4 positive axillary nodes, and patients with more than 4 involved or fixed axillary lymph nodes, were considered as Arm III. We compared the result of adjuvant treatment in these groups.*

RESULTS–*After a 7-year follow-up, loco-regional recurrence was seen in 13 (11.1%) patients and distant metastasis in 67 (57.2%) patients. The median event-free survival was 28 months in all patients. The median event-free survival was 78 months in patients with negative axillary nodes, 28 months in patients with one to four positive nodes, and 20 months in those with more than four positive or fixed axillary nodes. The difference in event-free survival between 3 groups was statistically significant (p = 0.026).*

CONCULSION–*With conventional, local, and systemic treatment, a marked difference in local and distant failure exists between breast cancer patients with a T3-T4 N0 tumor and patients with positive axillary nodes.*

Keywords: ***breast cancer; locally advanced; radiotherapy; chemotherapy; mastectomy.***

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*Corresponding author:
Ahmad Mosalaei, MD
Department of Radiotherapy, Nemazee Hospital
Shiraz University of Medical Sciences, Shiraz, 71935, Iran.
Fax: +98-711-626013
E-mail: mosalaa@sums.ac.ir.

INTRODUCTION

Breast cancer accounts for about 17% of female noncutaneous malignancies.[1] Locally advanced breast cancer includes a heterogeneous group with one or more of the following characteristics:

- Tumor > 5 cm measured by ultrasound or mammography.
- Proven skin involvement.
- Chest wall muscle or skeletal involvement.
- Fixed or more than four involved axillary lymph nodes.
- Clinical sign of mastitis carcinomatosa.
- Tumor positive apical (infraclavicular) node.[2]

These so-called advanced diseases need multimodality treatment: systemic therapy (hormonal and chemotherapy)[3, 4] due to high probability of blood-borne metastases (about 80%), surgery, and radiotherapy for local-regional control. When local recurrence manifests, it can be controlled in approximately 50% of the patients and there is a small number of patients with metastatic disease who will receive a course of chemotherapy to remain relapse free.[1, 5, 6] Postoperative radiotherapy seems to be useful for locoregional control in high-risk patients and chemotherapy is beneficial to reduce distant metastases.[7 – 9] The aim of this descriptive study was to evaluate the effect of conventional adjuvant therapy on local control and survival of high risk patients managed in a 5-year period.

MATERIALS AND METHODS

A total of 117 patients with locally advanced breast cancer were referred to the radiation oncology department of Nemazee Hospital within the last five years, for adjuvant treatment. We reviewed the departmental records of all patients for sex, age,

histology of the primary tumor, tumor size, pathologic axillary node status, surgical procedure, TNM AJCC stage, adjuvant chemotherapy, and radiotherapy. Time of local or distant failure and overall survival were recorded. Of 114 female patients, 61 were postmenopousal and 53 cases were premenopousal. Tumor was detected in left breast in 63 patients and in right breast in 54 cases. Fifty-two masses were located in the medial or central portion and 65 in the lateral portion.

Our study included the patients with T3 or T4 primary tumor and/or more than four axillary lymph node involvement. The patients with proven metastatic lesion or T1-2 primary tumor with less than four positive lymph nodes, and those who refused adjuvant treatment or just didn't return for follow-up, were excluded from the study.

All of the patients underwent operation after histologic confirmation via open biopsy. Two weeks after surgery the patients got 3 – 4 courses of chemotherapy, each one three weeks apart. Then they were irradiated and chemotherapy was again continued up to 6 – 8 cycles. Hormonal therapy was the unit policy for all patients at the time these cases were treated, irrespective of hormone status.

Surgical procedures were: modified radical mastectomy in 112 (95.7%) patients, radical mastectomy in 3 (2.6%), patients, and simple mastectomy in 2 (1.7%) patients. All of the patients had negative resection margins on histologic examination. Axillary node dissection of the level I-II in most cases or I-III level in some cases was performed and a median of 14 nodes (range, 0 – 35) was found in axillary dissection. Except for three patients, all got 6 – 8 cycles of chemotherapy. Three patients received CAF (cyclophosphamide, 700 mg/m^2-adriamycin, 50 mg/m^2-5-FU 600/m^2), 111 patients received CMF (cyclophosphamide, 700 mg/m^2-MTX, 50 mg/m^2-5-FU, 600 mg/m^2) as I.V. boluses. When I.V. cyclophosphamide was not available we used oral cytoxan, 100 mg/m^2 for 14 days. Maximum dose of adriamycin was 500 mg/m^2.

Dose modification was allowed according to blood counts and symptomatic toxicity. Three patients refused chemotherapy. Complete blood count was performed before each course of chemotherapy and drugs were administered if Hgb was more than 10 gm/dL, platelet >100,000/µL, and WBC > 3,000/µL. Tamxifen (20 mg/day for five years) was a component of care in all patients as endocrine therapy.

All patients got external radiation to the chest wall and regional lymphatic area after 3 – 4 courses of chemotherapy. The chest wall was treated using conventional two opposing tangential fields. The retrosternal nodes were irradiated by one anterior field and dose was calculated at a depth of 3 cm. An anterior field treating the supraclavicular fossa and axillary apex, targeted a reference depth of 2 cm. A small posterior field was applied to effectuate an adequate midline dose in the axilla. We used cobalt-60 machine in all cases. The fields were treated every day. Irradiation dose rates used were 2 Gy/day (200 rad/day), and 10 Gy/week (1000 rad/week) and the total (accumulated) dose ranged 45 – 50 Gy (4,500 – 5,000 rads). We categorized the patients into three groups of large primary tumor with negative axillary nodes, (T3-T4 N0M0), large primary with one to four axillary nodes involvement (T3-T4 N1M0), and a group with more than 4 positive or fixed lymph nodes.

Overall survival was calculated in months from date of histologic diagnosis to death or to the date of last follow-up, for the living patients. Event-free survival was defined as the length of time from operation to any evidence of recurrence. Locoregional recurrence was described as failure in chest wall or regional lymph nodes (axillary, internal mammary, infraclavicular and supraclavicular), and distant metastasis as failure in sites other than those mentioned above. Radiation side effects were recorded as the early complications, if they appeared during radiotherapy or up to 4 weeks post irradiation, early-delayed, if they were present between 4 weeks and 4 months after irradiation. They were considered as the late effects of irradiation, if appeared later.

The patients were visited every three months for two years and every six months for another three years and then annually. History, physical examination and routine laboratory tests (complete blood count and liver enzymes) were examined in each visit. Chest X-ray (CXR) and mammography were taken annually. Every relapsed patient was treated with systemic adriamycin based chemotherapy if she was adriamycin naive. Radiotherapy was used as palliative therapy when needed. The records of patients were analyzed with permission of research council of the department and the names and addresses of the patients remained confidential. Data entry, coding and then analysis were done by SPSS software version 9.

Kaplan-Meier survival curves were used to calculate disease-free and overall survival. Differences in these outcomes among different patient subsets were tested using the log-rank test. To compare the mean age in 3 groups we used the ANOVA test.

RESULTS

Out of 117 patients, 3 (2.6%) were male and 114 (97.4%) were female. The patients had an age range of 23 – 66 years and a mean, 44.5 years. Among this group there were twenty patients with a T3-T4 N0M0 tumors (group 1), twenty-one patients with a T3-T4 primary tumor and one to four positive axillary nodes (group 2), and 76 patients with more than four positive or fixed axillary nodes (group 3).

Table 1 shows the characteristics of the patients. The histology of primary tumor was infiltrating ductal carcinoma in 101 patients (86.4%), invasive lobular carcinoma in 6 patients (5.1%), medullary carcinoma in 8 patients (6.8%) and papillary carcinoma in 2 patients (1.7%). All patients had been diagnosed with breast cancer by physical examination, mammography and tissue biopsy. Preoperative investigations to rule out distant metastases were performed including complete blood count, liver and renal function tests, urine analysis, CXR, abdominopelvic sonography, and bone scan.

Patients in these 3 groups had mean ages of 45.45, 47.44, and 43.24 years. The differences between mean ages showed no statistical significance using the ANOVA test (p = 0.16). There was loco-regional recurrence in 13 patients (11.1%): ten in chest wall, two in axillary lymph nodes and one in both sites. Distant metastases were observed in 67 patients (57.2%) and the most common site was bone, followed by liver, lung, brain, and distant lymph nodes.

Table 2 shows complications caused by irradiation. The median event-free survival in all patients was 28 months (95%, CI = 17.55 – 38.45 months). The median event-free survival was 78 months in group one (95%, CI = 21.07 – 134.93), 28 months in group two (95%, CI = 0 – 59.74), and 20 months in group three (95%, CI = 15.38 – 24.62). The difference in event-free survival between the three groups reached statistical significance using the log-rank test (p = 0.026). The clear difference in event-free survival is shown in Figure 1.

Table 1. Distribution of analyzed patients according to sex-stage of the disease and histopathology.

Characteristics	No. (%)
Sex	
Male	3 (2.6)
Female	114 (97.4)
Stage	
I	—
II	42 (36)
III	75 (64)
IV	—
Histopathology	
Infiltratingductal carcinoma	101 (86.4)
Invasive lobular carcinoma	6 (5.1)
Medullary carcinoma	8 (6.8)
Papillary carcinoma	2 (1.7)

Table 2. Radiation-induced complications according to time of presentation.

Side effect	No. (%)
Early complications*	
Wet desquamation of chest wall skin	34 (29)
Nausea	31(26.5)
Esophagitis	63 (53.8)
Early delayed complications**	
Symptomatic radiation pneumonitis	23 (19.7)
Late complications***	
Arm edema	92 (76.7)
Decreased arm mobility	21 (17.9)
Apical lung fibrosis	40 (34.2)

*Side effects during or in 4 weeks after radiotherapy,** Complication presenting between 4 weeks and 4 months after radiation, *** Side effects after 4 months.

DISCUSSION

Disease-free survival is an important goal in treatment of breast cancer. Local recurrence is seen in 11 – 44% of high-risk resected breast cancer patients, and distant metastases in 80% without adjuvant treatment.[10-13] Keeping in mind that these figures challenge important goal of treatment, several trials have studied the efficacy of adjuvant therapy in locally advanced breast cancer. Polyzos[14] reported 20 patients with locally advanced breast cancer who received neoadjuvant chemotherapy followed by surgery and radiotherapy. In that study most of the recurrences were distant, and the local failure occurred only in 4 patients, as in our study. Longer median disease free survival (36 months) in that report may be attributed to more aggressive chemotherapy.

In another retrospective analysis, Favret[15] studied 64 cases with locally advanced breast cancer. The patients were treated with preoperative chemotherapy (CAF for 3 – 6 cycles), irradiation (50 Gy), then surgery, and postoperative consolidative chemotherapy (CMF for 4 – 8 courses). Five years local recurrence rate of 20%, distant metastasis rate of 35% and disease-free survival rate of 58% were reported.

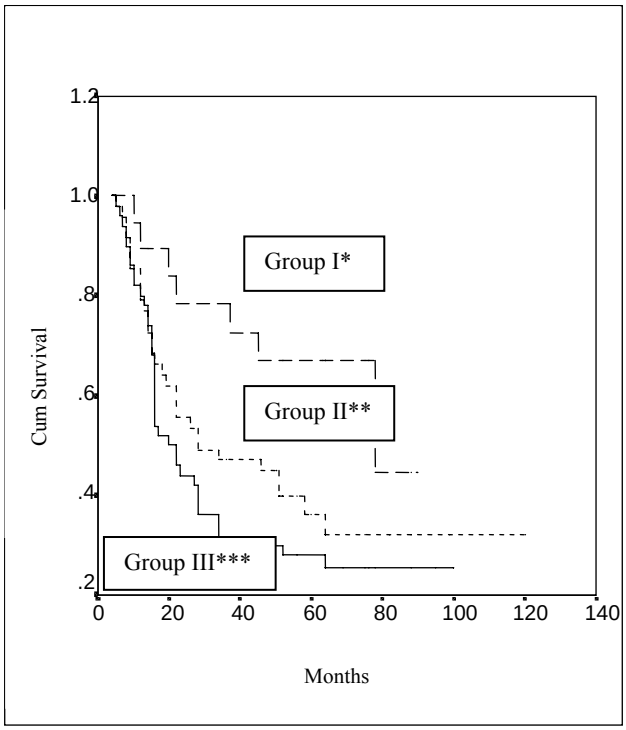

Figure 1. Disease-free survival after surgery. (*Group 1 = T3 T4 N0 + M0 **Group 2 = T3 T4 1 – 4 LN+ M0 *** Group 3 = T any > 4LN+ M0).

We had lower local recurrence rate, however more distant metastasis; this again may be due to the more aggressive chemotherapy in the aforementioned study. The patients in our study had a seven-year local recurrence rate of 11.1% which is somewhat low compared to other studies, for instance: Cheng[16] showed that a 4-year local recurrence in his study was around 16.1%. Moreover, the patients in his study were in a lower stage as far as the primary tumor and axillary nodes were concerned. This improvement may be attributed to postoperative irradiation in our patients. Helinto[17] and coworker in a series with 38 T3N0M0 breast cancer patients also used postoperative irradiation and systemic therapy (CMF or tamoxifen). They reported 56 months median disease-free survival.

We had 78 months median disease-free survival in first arm that included T3-4 N0M0 patients. Helinto used tamoxifen in postmenopausal and CMF in premenopausal cases, while we treated all patients with both chemotherapy and tamoxifen. In Abdol-Wahab's[18] study, 55 patients with locally advanced breast cancer were treated with chemotherapy (MVAC) and radiation. They reported the 50 months as the mean of overall survival.

Willsher[19] used preoperative chemotherapy (MMM), mastectomy, irradiation and hormonal therapy for 55 patients with locally advanced breast cancer and reported 43 months as the median survival time. McIntosh[20] and coworker also treated 173 women with locally advanced breast cancer defined as T2 > 4 cm, T3, T4, N0, N1, and M0 tumors with multimodality therapeutic agents. All patients received 4 – 6 courses of chemotherapy (cyclophosphamide, adriamycin, vincristin, prednisolon), then surgery, and radiation therapy (45 – 50 Gy). They gave tamoxifen for 5 years to all of the patients. The reported median for overall survival was 62 months in all of the patients. We had almost similar patients and therapeutic protocol with aforementioned studies. Our result (55 months mean survival in all patients) was also the same.

At the time of treatment of our patients, immunohistochemical study was not available in order to check estrogen-progesterone receptor so we had to offer tamoxifen to all cases and consequently some of the patients received unnecessary hormonal therapy. Taxane and more effective systemic treatment like hormonal therapies, other than tamoxifen, were not available. Some of the patients, who refused adjuvant treatment or didn't refer for follow-up, were excluded from the study. Although the benefit of adjuvant treatment in patients with locally advanced primary tumor (but with negative axillary nodes) is not debatable, dismal outcome in patients with involved axillary nodes, warrants postmastectomy adjuvant treatment further consideration.

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