

RESEARCH COMMUNICATION

Treatment Options for Locally Advanced Breast Cancer - Experience in an Asian Tertiary Hospital

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Abstract

Background: Locally advanced breast cancer (LABC) is characterized by the presence of a large primary tumour (>5cm) associated with or without skin or chest-wall involvement (T4) or with fixed (matted) axillary lymph nodes in the absence of any evidence of distant metastases. These cancers are classified as stage IIIA and IIIB according to the AJCC Staging System. Treatment of choice involves combinations of surgery, chemotherapy, radiotherapy and/or hormonal therapy. Current guidelines recommend primary surgery or neoadjuvant therapy followed by surgery. The primary objective of this study was to compare the outcome of LABC patients subjected to neoadjuvant chemotherapy before surgery and those who underwent surgery as the primary treatment and to determine prognostic predictors. Secondary objectives were to evaluate the response after neoadjuvant therapy and to determine the treatment compliance rate. **Methods:** This retrospective study of Stage III breast cancer patients was conducted over a 5 year period from 1998 to 2002. The survival data were obtained from the National Registry of Births and Deaths with the end-point of the study in April 2006. The Kaplan Meier method was applied for survival analysis. Cox regression analysis by stepwise selection was performed to identify important prognostic factors. **Results:** Out of a 155 evaluable patients, 74 (47.7%) had primary surgery, 62 (40%) had neoadjuvant chemotherapy, 10 patients (6.5%) were given Tamoxifen as the primary treatment, while 9 patients (5.8%) defaulted any form of treatment. After neoadjuvant chemotherapy, 9 patients defaulted further treatment, leaving 53 evaluable patients. Out of these 53 evaluable patients, 5 patients (9.4%) had complete pathological response, 5 (9.4%) a complete clinical response, and 26 (49.1%) had partial response after neoadjuvant chemotherapy. The 5-year survival in the primary surgery group was 56.7% compared to 44.7% in the neoadjuvant chemotherapy group ($p<0.01$). The important prognostic factors were race, size of tumour, nodal status, estrogen receptor status and response to neoadjuvant chemotherapy. **Conclusion:** Patients who had primary surgery had better survival than those who underwent neoadjuvant chemotherapy, which may be due to bias in the selection of patients for neoadjuvant chemotherapy. Out of a total of 155 patients, 25.1% defaulted part of the treatment, or did not receive optimal treatment, emphasizing the importance of psychosocial support and counselling for this group of patients.

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Introduction

Locally advanced breast cancer (LABC) is defined by presence of a large primary tumour (>5cm or T3), associated with or without skin or chest-wall involvement (T4) or with fixed (matted) axillary lymph nodes in the absence of any evidence of distant metastases. (Singletary, and Allred, 2002; Wolff and Davidson 2002) These cancers are classified as stage IIIA and IIIB according to the AJCC Staging System.

Data from Asian countries report a higher incidence of LABC compared to the western developed countries. In India, locally advanced breast cancer are seen in over 50% of women presenting with breast cancer (Agarwal et

al., 2007). In Malaysia, 50 to 60% of women presented with Stage III or IV disease (Hisham and Yip 2003). In Singapore, it was reported that 21.5% of breast cancer patients presented with locally advanced disease (Tan, Wong et al. 2005). Data from the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, indicate that only 7% of patients have Stage 3 disease at presentation (Giordano, 2003).

Compared to patients with early breast cancer, patients with LABC are at a significantly higher risk of local recurrence and distant metastases and have a worse overall survival. According to the SEER data, the 5 year survival rate for women with Stage 3 breast cancer is 55% (Giordano, 2003).

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Women with locally advanced disease require multimodality therapy, and coordinated treatment planning among the medical oncologist, surgical oncologist, and radiation oncologist is necessary to optimize patient care (Giordano, 2003). Current guidelines recommend primary surgery or neoadjuvant therapy followed by surgery. Comparison studies on outcomes in primary therapy for locally advanced breast cancer are scarce. Present data shows that there is no difference in terms of overall survival in those receiving neoadjuvant chemotherapy or primary surgery (Mamounas, 1997; Fisher et al., 1998). The main goal of neoadjuvant therapy is to achieve resectability. Furthermore, the clinical and histological response to neoadjuvant chemotherapy has been shown to be important predictors of recurrence and survival in studies of operable breast cancer.

The objective of this study is to compare overall survival of LABC patients subjected to the treatments above and to determine its predictors of outcome. The secondary objectives are to determine the response to neoadjuvant chemotherapy and to determine the rate of compliance to treatment.

Materials and Methods

This is a retrospective study of patients with Stage III breast cancer presenting to the University Malaya Medical Centre (UMMC) from 1 January 1998 to 31 December 2002. Data were obtained from the Institutional Breast Cancer Registry in UMMC and supplemented by the patients' medical records. An institutional protocol on surgery, adjuvant chemotherapy, neoadjuvant chemotherapy, radiotherapy and hormonal therapy was used. Histopathological variables studied include tumour size, histopathology, Bloom and Richardson grading, oestrogen receptor (ER) status, HER2 status, lymphovascular invasion and surgical margins. Overall survival rate is defined as the percentage of patients who are alive five years after the diagnosis of LABC. The primary end-point of this study is the survival of patients after five years. The survival data were obtained from the National Registry of Births and Deaths with the end-point of the study on April 2006.

The data was entered and analysed using SPSS version 15.0. Descriptive statistics was used to summarize the distribution of the covariates. Cox regression analysis by stepwise selection was done to identify important prognostic factors. The Kaplan-Meier survival estimates were calculated and survival curves compared using the log rank test. All prognostic factors for overall survival (OS) were further investigated using Cox proportional hazards model. Regression estimates are summarised as Hazard Rate Ratio (HRR) with a 95% Confidence Interval. A two-tailed p-value of less than 0.05 was considered to be significant.

Results

Between 1998 and 2002, of a total of 1031 new cases of breast cancer presenting to the University Malaya Medical Centre, 176 patients (17%) presented with LABC.

Twenty-one patients were excluded because of incomplete data and patients had treatment elsewhere after diagnosis. Of the 155 evaluable patients, 74 patients had primary surgery, 62 patients had neoadjuvant chemotherapy, 10 patients had primary hormonal therapy alone as they refused surgery or chemotherapy, and 9 patients defaulted treatment after diagnosis (Figure 1).

The age distribution of the cohort ranged from 28 to 85. The mean age was 51.1 years (SD=11.7) and the median was 50.0 years old. Majority of the patients presented in the 40-59 age-group (66.5%). The majority of the patients were Chinese (53%) followed by Malays (33%), Indians (11%) and others (3%).

The clinicopathological variables (Table 1) showed significant differences between the two groups in terms of clinical stage at presentation, tumour size at operation and number of positive lymph nodes.

Response to neoadjuvant chemotherapy

Of the 62 patients who received neoadjuvant chemotherapy, 59 had the FEC regime (6 cycles of intravenous 5-fluorouracil 500mg/m², Epirubicin 75 mg.m² and cyclophosphamide 500 mg/m² at 3-weekly intervals) while only 3 patients had the TAC regime (6 cycles of intravenous Taxotere 75mg/m², Adriamycin 50 mg/m² and cyclophosphamide 500 mg/m² at 3-weekly intervals). Of these 62 patients, 9 patients refused any further treatment after neoadjuvant chemotherapy leaving 53 patients for analysis.

A partial response (PR) is defined as a reduction of 50% of the initial size of the breast lump, while complete clinical response (cCR) means that there is no more palpable lump felt. A complete pathological response

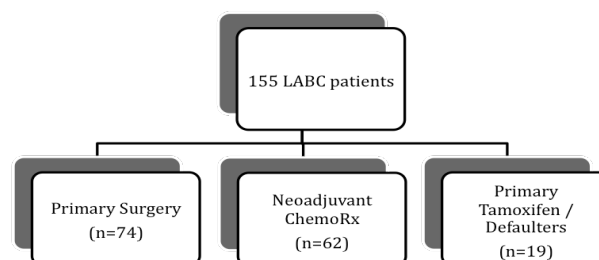


Figure 1. Patients with LABC Presenting to UMMC from 1998 to 2002 According to Treatment Modality

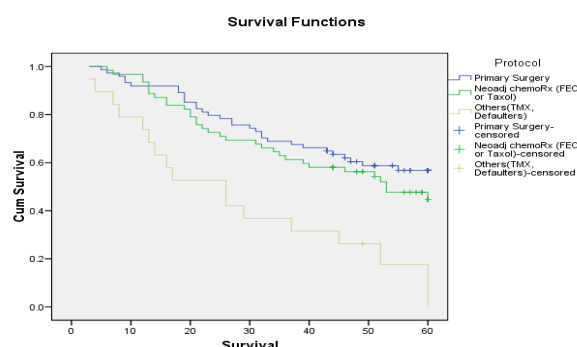


Figure 2. The Kaplan-Meier Survival Curve of Patients with LABC According to Treatment Modalities

Table 1. Clinicopathological Variables of LABC Patients According to Treatment Modality

	Primary surgery n=74 n (%)	Neoadjuvant chemotherapy n=62 n (%)	p value
Stage			
Stage III A	48 (65%)	24 (39%)	0.02
Stage III B	26 (35%)	38 (61%)	
Size of tumour			
Mean (range)	6.7cm (2-15cm)	4.5cm (0-15cm)	<0.001
Grade (B&R)			
1	3 (4%)	2 (3%)	0.729
2	28 (38%)	15 (24%)	
3	35 (47%)	26 (42%)	
N/A	8 (11%)	10 (16%)	
Total no of positive LN's median(range)	4 (0-25)	2 (0-28)	0.04
ER status			
Positive	36 (49%)	26 (42%)	0.977
Negative	37 (50%)	27 (44%)	
N/A	1 (1%)	0	
Cerb2 status			
Positive	24 (32%)	11 (21%)	0.235
Negative	39 (53%)	30 (57%)	
N/A	11 (15%)	12 (22%)	
Lymphovascular invasion			
Yes	24 (32%)	16 (30%)	0.780
No	32 (44%)	24 (45%)	
N/A	18 (24%)	13 (25%)	

Table 2. 5-year Survival Rate and Mean survival Time of Patients with LABC According to Treatment Modalities

	Primary Surgery	Neoadjuvant Chemotherapy	Primary Tamoxifen / Defaulters	Log rank test
5-year survival	56.7%	44.7%	17.5%	p < 0.001
Mean survival time	46 months	43 months	29 months	p < 0.001

Table 3. Negative Survivor Predictors in LABC

	Hazard ratio	95% CI
Stage 3B	1.716	1.098-2.682
Tumour size ≥10cm	2.269	1.044-4.928
No of positive LN's involved 10-19	2.714	1.481-4.974
ER negative	2.146	1.307-3.522
No complete response to chemotherapy	6.480	1.596-26.307
Defaulted chemotherapy	3.611	1.957-6.662
Defaulted radiotherapy	3.663	2.043-6.568
No hormonal therapy	3.651	2.187-6.092

(pCR) is defined as the absence of any malignant cells on histology of the resected tissue or only in-situ disease left. A stable disease or progressive disease (SD, PD) is when response is minimal or the lump increases in size.

In this study, of the 53 evaluable patients, there were 5 pCR (9.4%), 5 cCR (9.4%), 26 PR (49.1 %) while the rest were SD or PD (32.1%).

Compliance rate

In the initial cohort of 155 patients with locally advanced breast cancer, 9 patients (5.8%) defaulted

Table 4. Independent Negative Predictors in LABC Treated by Primary Surgery

	Adjusted Hazard ratio	95% CI
No of positive LN's removed 10-19	4.298	1.829-10.103
Defaulted radiotherapy	8.796	2.529-30.597
No hormonal treatment	5.693	2.357-13.747

Table 5. Independent Negative Predictors in LABC Treated by Neoadjuvant Chemotherapy

	Adjusted hazard ratio	95% CI
No complete response to chemotherapy	4.564	1.061-19.642
No hormonal therapy	2.771	1.157-6.638

before any treatment was initiated. In the neoadjuvant chemotherapy group, 9 out of the total of 62 patients (14.5%) defaulted surgery after receiving neoadjuvant therapy, while in the primary surgery group, out of the 74 patients who were operated on, 11 women (14.9%) defaulted adjuvant chemotherapy after surgery. The compliance rate appear to be similar in the two groups. Of the total of 155 patients, 29 (18.7%) did not complete treatment. When the tamoxifen only group is included as

a non-compliant group, 39 patients (25.1%) did not have optimal treatment.

Overall survival rate and survival analysis in LABC

The 5-year survival rate for patients treated with primary surgery is 56.7% compared to 44.7% in the neoadjuvant group ($p < 0.001$). The mean survival time in the primary surgery group is 46 months compared to 43 months in the neoadjuvant group ($p < 0.001$). Patients who defaulted treatment or treated with tamoxifen alone have the poorest survival with OS of 17.5% in five years and a mean survival time of 29 months (Table 2 and Figure 2).

Univariate analyses identified stage, tumour size, number of positive lymph nodes involved, ER status, complete response to neoadjuvant chemotherapy (either clinical or pathological complete response), chemotherapy, radiotherapy and hormonal treatment as important prognostic factors for LABC (Table 3).

By using the multivariate Cox-regression analysis, the independent predictors of survival for LABC treated by primary surgery are number of positive lymph nodes removed, radiotherapy and hormonal treatment while those treated with neoadjuvant therapy are complete response and hormonal treatment (Tables 4 and 5).

Discussion

In Sabah, Leong et al. (2007) reported that 36% of patients presented with Stage 3 disease while another study documented 60% of new cases in Kelantan to present as Stage 3 and 4 disease (Norsa'adah et al., 2005). The lower percentage of patients with locally advanced breast cancer seen in UMMC at 17% is because this hospital is located in an urban centre and caters to a more middle class group of patients compared to the other two hospitals which cater to a more rural population from a lower socio-economic group.

The majority of our patients presenting with LABC were in the 40 to 59 age group, with a mean age of 51.1 years. Only 14.8% of the patients were less than 40 years old. This is the usual age distribution of breast cancer in Malaysia (Yip et al., 2006) and LABC does not seem to predominate in any single age group.

A population-based mammography screening program has been shown to reduce mortality from breast cancer by earlier diagnosis in the preclinical stage of disease. In the USA 30-40% of breast cancers are detected with screening mammography. Annual mammography is recommended at the age of 40 (Paley, 2001). Unfortunately due to high cost and resources, Malaysia does not have a population-based breast cancer screening program.

The ethnic group distribution in this study is skewed to represent the practice in UMMC, which is mainly urban, and in a predominantly Chinese residential area. Majority of the patients with locally advanced disease were Chinese (53%) and this does not mean that they are more prone to late presentation of disease. The 2nd National Cancer Registry of Malaysia reported that the incidence of breast cancer is higher in Chinese women (Lim and Chye, 2003). In a study looking at patients in Kuala Lumpur Hospital and UMMC, (Hisham and Yip, 2003) it was noted that the Malays tend to present with larger tumors and later

stages compared with the other ethnic groups. Because of this, the Malay women have a poorer survival as seen in a previous study where the 5-year survival of Chinese and Malay breast cancer patients diagnosed between 1993 to 1997 was 63.5% and 47.5% respectively. This may reflect the presentation of the Malay women with later stages of disease. This paper also reported a 5-year survival of 39.8% in women presenting with Stage 3 breast cancer between 1993-1997 (Mohd Taib et al., 2008). This survival is poorer than the 5-year survival of 55% reported by the SEER programme between 1971-1998.

In this study, we found that patients who had undergone primary surgery actually had a significantly better survival compared to those who had neoadjuvant chemotherapy. The 5-year overall survival rate was 56.7% and 44.7% respectively. This is in contrast with the results of most major studies which reported that there is no difference in terms of overall and disease-free survival between the two arms (Mamounas 1997; Fisher et al., 1998; Makris et al., 1998; van der Hage et al., 2001). The reason is that being a retrospective study, there is a selection bias because patients in the primary surgery group were mostly 3A disease (65%) whereas in the neoadjuvant chemotherapy group, most of the patients had stage 3B disease (61%). Therefore, patients in the neoadjuvant chemotherapy group are those in the later stage, hence the worse prognosis.

Both these 5-year survival rates appear to be better than the previous 5-year survival rate of 39.8% reported from women with Stage 3 breast cancer diagnosed in the 1993-1997 era (Mohd Taib, Yip et al., 2008). This improvement in survival reflects the change in practice of breast cancer in UMMC where the Oncology Unit was only started in 1998, and also reflects the change in chemotherapy regimes from the CMF regimes (cyclophosphamide, methotrexate and 5-fluorouracil) to the anthracycline-based regimes.

The prognostic factors for locally advanced breast cancer are similar to the prognostic factors for early breast cancer, with lymph node status and tumour size having the strongest effects on survival. In LABC, the prognosis of patients without lymph node metastases is better than those who had lymph node involvement (Toonkel et al., 1986; Carter et al., 1989). In patients with lymph node involvement, those who have a greater number of lymph nodes involved have a poorer prognosis. In term of size of tumour, patients with larger cancers have poorer survival rates. Valagussa et al. reported the 5-year survival rates for breast tumours measuring < 5 cm, 5-10cm and > 10 cm were 65%, 36% and 16% respectively (Valagussa et al., 1983). In our study on LABC, the most important prognostic factor was complete response to neoadjuvant chemotherapy, followed by compliance to treatment. This has also been shown in the NSABP B-18 study where outcome in women who showed a complete pathological response was better (Fisher et al., 1998). Other poor prognostic factors identified was Stage 3b (as compared to Stage 3a), tumour size more than 10 cm, ER negative tumours, and 10 or more lymph nodes involved. However independent prognostic factor in the neoadjuvant group was complete pathological response,

and no hormonal therapy (which may also be related to ER negativity since tamoxifen would have been given to all ER positive patients). In the group who had surgery first, the independent prognostic factors included non-compliance, no hormonal therapy and involvement of 10 or more lymph nodes. In conclusion Locally advanced breast cancer remains a difficult clinical problem due to a high rate of relapse and low rate of overall survival. Women presenting with LABC require counselling and psychosocial support as compliance is a problem, and as can be seen from this study, non-compliance is an unfavourable prognostic factor for survival.

In this study, although it shows that primary surgery is a better option than neoadjuvant chemotherapy, it must be noted that there is a bias in selection of patients. Majority of the patients receiving neoadjuvant chemotherapy are those with Stage IIIB disease with a poorer prognosis.

Multimodality therapy has now become the standard treatment for locally advanced disease. Clinical judgement is important to decide on whether surgery or chemotherapy should be offered first to patients presenting with locally advanced breast cancer. Most importantly, it is important to include patients in the discussion on treatment options.

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