Original Research Article

Breast Conserving Surgery Post Neo-Adjuvant Chemotherapy for Locally Advanced Breast Carcinoma in a Developing Country: Is It Safe?

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Abstract

Breast conserving surgery (BCS) is the standard treatment for early breast cancer and has similar survival with mastectomy. The role of BCS in locally advanced breast cancer (LABC), post neoadjuvant chemotherapy (NACT), is controversial. Surgeons, especially in developing countries, fear higher margin involvement and local recurrence (LR) in BCS. The aim of this study was to determine the LR in BCS compared to mastectomy in LABC post NACT and to ascertain the percentage of involved surgical margins following both methods of surgery. This was a retrospective study of breast cancer patients seen in Universiti Kebangsaan Malaysia Medical Centre (UKMMC). All patients had NACT followed by either mastectomy or BCS. The patients with Her2 enriched carcinomas did not have access to targeted therapy (Trastuzumab or Pertuzumab). The patients with ill-defined tumours underwent ultrasound assessment in the surgical clinics. All had post-operative radiotherapy. All with ER or PR positive cancers were given Tamoxifen for a minimum of 5 years. This study demonstrated that BCS post NACT was safe to be performed in selected patients with LABC in a developing country.

Keywords: Breast conserving surgery; locally advanced breast tumor; local recurrence; mastectomy; neoadjuvant chemotherapy; surgical margin

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Introduction

Breast cancer is a major health problem. According to the Malaysia National Cancer Registry report 2012-2016, breast cancer is the commonest cancer in all ethnic groups in Malaysia and accounts for 34.1% of all cancer cases in Malaysian women (1). Among the three main races in multi-ethnic Malaysia, Malay women have been found to often present late with locally advanced breast cancer (LABC) (2). The incidence of breast cancer has been increasing steadily starting from the age of 25 years with a peak age specific incidence rate in the 60 - 64 age group (3). Worldwide, there are over 1 million newly diagnosed cases each year (4). Over the past few decades, surgical management of breast cancer has undergone a significant de-escalation, from radical surgeries to more conservative types.

LABC includes primary breast tumours with diameters greater than 5cm, breast cancers with skin or chest wall involvement, Stage III tumours, excluding cancers that have metastasised (5).

Other concerns of surgery in LABC are fear of inability of closure of surgical wounds in bigger tumours. Hence, one of the initial objectives of neoadjuvant chemotherapy (NACT) is to downsize the

tumours to overcome this problem. Many surgeons have now started embarking on NACT, to obtain better cosmesis as well (6,7).

Advantages of NACT are to determine chemo-sensitivity in vivo, reduce the micro-metastatic disease component, perform breast-conserving surgery (BCS) in patients who would otherwise need a mastectomy, and it may achieve pathological complete remission (pCR) which leads to an excellent oncologic outcome (6).

Several reports concluded that, compared to Mastectomy, patients who had undergone BCS, have better quality of life. This is because they have a higher body image score, feel more secure, are more sexually active and are associated with better physical and social functioning (8,9). BCS is now considered as the standard treatment for those with early breast cancer as it has shown similar survival with mastectomy (10). However, BCS in LABC post NACT is still controversial (11). Many surgeons still resorted to the conventional Modified Radical Mastectomy for fear of local recurrence (LR). Several earlier studies reported high recurrence rates for patients who underwent BCS post NACT (12,13,14).

There are also concerns regarding increased positive margins (PM) post BCS in LABC. This is postulated from theories whereby the primary tumour may not shrink concentrically but instead break into several smaller islands leading to residual tumour cells (14,15).

The aim of this study was to determine the LR in BCS vs mastectomy in LABC post NACT and to ascertain the percentage of involved surgical margins following both methods of surgery. Other associated parameters such as the tumour oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER-2), grade, completion of RT and endocrine therapy were analysed.

The objectives of this study were to determine the percentage of involved surgical margins following BCS in a LABC as well as to compare the LR rates between BCS versus mastectomy in LABC post NACT.

Materials and Methods

Study design

This was a retrospective study on data of breast cancer patients seen in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) from 1st January 2000 until 31st November 2016. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Universiti Kebangsaan Malaysia - UKM (protocol code FF-2017-488), date of approval 21/12/2017.

Sampling population

All patients from UKMMC who had NACT for LABC followed by either mastectomy or BCS from 1st January 2000 till 31st November 2016. In our centre, the standard chemotherapy regimen given was 3 cycles of 5-Fluorouracil, Epirubicin and Cyclophosphamide followed by 3 cycles of Docetaxel (3FEC-3T). Trastuzumab or Pertuzumab were not given to Her2 enriched patients due to financial constraints, as the patients had to purchase these themselves.

The patients were reviewed in the surgical clinic 1-2 weeks after the third cycle of FEC. This was for assessment of the breast lump via clinical examination. If the margins of the lump were not well defined on clinical examination, breast ultrasound was performed by the breast surgeon. Based on the size of the lesion to be excised along with a surrounding margin of 1-1.5cm, a shared surgical decision, whether to undergo a breast conserving surgery or mastectomy, was made between the surgeon and the patient. The patients underwent post-operative (adjuvant) radiotherapy.

All women with ER and or PR positive were given Tamoxifen for a minimum of 5 years. This was because the hospital's policy at the time was to prescribe the more expensive Aromatase Enzyme, only to post-menopausal women who experienced recurrence or metastases while on Tamoxifen.

Sample size calculation

We compared BCS and mastectomy with a ratio 1:1. The BCS group was estimated to have 18% local recurrence rate compared to 4% in the mastectomy group (16,17). With type 1 error of 0.05 and power of 80%, we needed 77 cases in each arm with a total of 154 cases (Fig. 1).

Selection criteria

The inclusion criteria were all patients with locally advance breast cancer, according to TNM classifications ; tumour size more than 5 cm (T3,T4), stage III tumour and all patients post NACT followed by either BCS or mastectomy.

The exclusion criteria were the patients who did not fulfill the above inclusion criteria, post BCS patients

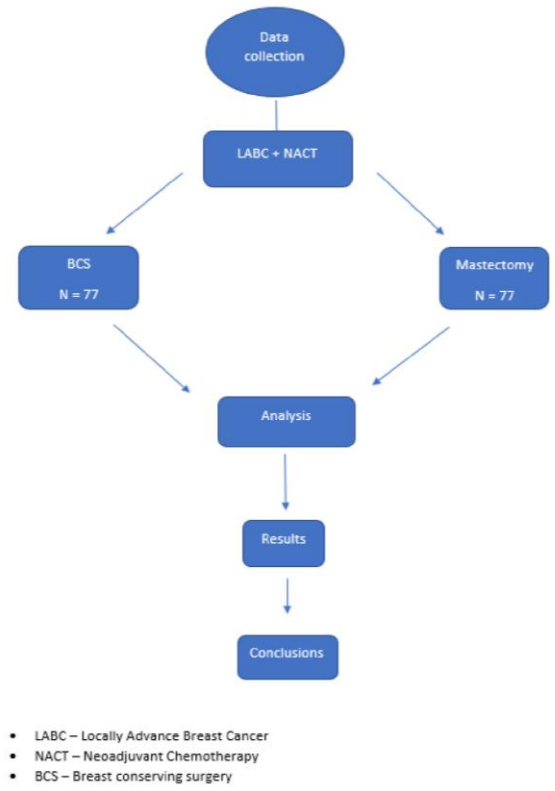

FIGURE 1: Flow Chart of the study design

who did not complete radiotherapy (RT) or did not start RT within 3 months post-surgery, post mastectomy patients with tumour size T3 and above that did not complete RT or did not start RT within 3 months post-surgery and patients who underwent immediate breast reconstruction.

Statistical analysis

The data was entered using SPSS v.19 (SPSS Inc., Chicago Illinois) for statistical analyses and calculations. Depending on their sample size distribution, the difference between two categorical groups were analysed using Chi-square test for large sample size whereas Fisher Exact test for smaller sample size. For scale variables, all the variables underwent the normality test, Kolmogorov Smirnov test to check the normality assumption or equality of continuous probability distribution. Noting with the normality test result, the difference between the two groups with scale variable was analysed using the respective parametric statistical test, Independent Sample T test. All significant analyses were considered 95% confidence level or 5% level statistical significance.

Result

Table 1 showed the data of patients in this study. The mean age of those who underwent BCS was almost similar to the mastectomy group. The ethnic distribution of the group reflected that of the Malaysian population where the majority were Malays 69.6%, Chinese 22.6% and Indians 6.8% (18). The minimum follow up period was 2 years.

Table 2 compared the clinical TNM stage of BCS and mastectomy. The number of patients, who underwent BCS, were almost of those who underwent mastectomy. The mastectomy group had higher clinical T4 and T3 tumours with no T2 tumours. The majority of the BCS group were T3 tumours. The majority of patients in both groups had N1 tumours.

Table 3 showed the surgical margins post BCS and mastectomy. It also showed the local recurrence at 2-year and 5-years post BCS and mastectomy. The BCS group had a better margin clearance (clear margin, 100%) with no tumour involvement at the margins in all patients. The involved margins in the mastectomy group was 11.6% of cases (11 patients) and clear margins in 88.4% of cases (84 patients) with a statistically significant P value of 0.005.

The BCS group also had a lower LR at 2 years. It was 94.5% of cases (52 patients) with no LR compared to 81.1% of cases (77 patients) in the mastectomy group, with a statistically significant P value of 0.027. The BCS group also had a lower LR at 5 years but it was statistically not significant (P=0.567). We felt it was attributed by the small sample size as many patients had defaulted or were lost to follow-up.

The age of the patients were equally distributed in both groups. The mean age of involved surgical margin, local recurrence at 2 and 5 years for BCS was 49.4 years, 29.27 years and 47.13 years compared to the mastectomy group at 48.96 years, 49.86 years and 50.32 years.

Table 4 showed sub-group analysis in changes of ER, PR, Her-2, Grade post NACT between BCS vs mastectomy. ER, PR and HER-2 status are the most commonly used biomarkers in breast cancer for the prediction of patient outcome and the tailoring of adjuvant therapy. It is our hospital policy of not repeating the HR status post NACT due to financial constraint. The discordance in HR status and HG had been reported in the neoadjuvant setting, but these results had not been consistent. In our analysis, 53.66% of cases (22 patients) in the BCS group had changes in the HR status and HG compared to 47.27%

TABLE 1: Data of the patients and study results

	Baseline Characteristics	Count (%)
DEMOGRAPHIC	Age	
	Mean/SD	49.55 (10.88)
	Median/Range	49 (26 - 80)
	Race	
	Malay	100 (66.67%)
	Chinese	40 (26.67%)
	Indian	10 (6.67%)
CLINICAL	TUMOUR_T	
	2	17 (11.30%)
	3	59 (39.30%)
	4	74 (49.30%)
	TUMOUR_N	
	0	27 (18.00%)
	1	93 (62.00%)
	2	22 (14.70%)
	3	8 (5.30%)
	TUMOUR_M	
	0	150 (100.00%)
	1	0 (0%)
HISTO-PATHOLOGY	Infiltrative ductal carcinoma (NST)	139 (92.67%)
	Lobular carcinoma	4 (2.67%)
	Metaplastic carcinoma	3 (2.00%)
	Mucinous carcinoma	4 (2.67%)
	PRE-NACT	
	ER	
	Negative	50 (33.30%)
	Positive	81 (54.00%)
	NA	19 (12.70%)
	PR	
	Negative	68 (45.30%)
	Positive	63 (42.00%)
	NA	19 (12.70%)
	HER-2	
	2+	32 (21.30%)
	3+	31 (20.70%)
	Negative	24(15.90%)
	NA	63 (42.00%)
	GRADE	
	1	27 (18.00%)
	2	59 (39.30%)
	3	33 (22.00%)
	NA	31 (20.70%)
	POST-NACT	
	ER	
	Negative	27 (18.00%)
	Positive	47 (31.30%)
	NA	76 (50.70%)
	PR	
	Negative	39 (52.00%)
	Positive	36 (48.00%)
	NA	75 (50.00%)
	HER-2	
	1+	5 (3.30%)
	2+	20 (13.30%)
	3+	18 (12.00%)
	Negative	30 (20.00%)
	NA	82 (54.70%)
	Grade	
	1	20 (13.30%)
	2	37 (24.70%)
	3	30 (20.00%)
	NA	63 (42.00%)
	Endocrine therapy	
	No	41 (27.30%)
	Yes	75 (50.00%)
	NA	34 (22.70%)
	Lymphovascular invasion	
	No	112 (74.70%)
	Yes	38 (25.30%)
	Margin	
	Clear	139 (92.70%)
	Involved	11 (7.30%)
	Deep	9 (6.00%)
	Superficial + Deep	2 (1.30%)
	Complete response	
	No	135 (90.00%)
	Yes	15 (10.00%)
RECURRENCE	Local recurrence 2 years	
	No	129 (86.00%)
	Yes	21 (14.00%)
	Local recurrence 5 years	
	No	50 (33.30%)
	Yes	4 (2.70%)
	NA	96 (64.00%)
	Group	
	BCS	55 (36.7%)
	Mastectomy	95 (63.3%)

NACT: neoadjuvant chemotherapy; NA: Not available; ER: oestrogen receptor; PR: progesterone receptor; HER: human epidermal growth factor receptor; BCS: breast conserving surgery

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TABLE 2: Comparison of TNM stage

Tests of Normality			
	Kolmogorov-Smirnov*		
	Statistic	df	Sig.
Age	0.053	149	0.200*

	Group		***P*-value**
	BCS	**Mastectomy**	
N	55	95	
Age (Mean/ SD)	49.4 (11.51%)	49.6 (10.55%)	0.898***
Tumour_T			
2	17 (30.91%)	0 (0%)	0.001**
3	26 (47.27%)	31 (33.70%)	
4	12 (21.82%)	61 (66.30%)	
Tumour_N			
0	10 (18.18%)	16 (17.39%)	0.062**
1	39 (70.91%)	52 (56.52%)	
2	6 (10.91%)	16 (17.39%)	
3	0 (0%)	8 (8.69%)	
Tumour_M			
0	55 (100.00%)	95 (100.00%)	--
1	0 (0%)	(0%)	

**Pearson Chi Square*
***Fisher Exacted Test (Corrected Chi Square)*
****Independent Sample T Test*

TABLE 3: Surgical margins post BCS vs Mastectomy and local recurrence at 2 and 5 years

Margin	**BCS**	**Mastectomy**	***P*-value**
Involved	0 (0%)	11 (11.6%)	0.005**
Clear	55 (100.0%)	84 (88.4%)	
Local recurrence 2 at years			
Yes	3 (5.5%)	18 (18.9%)	0.027**
No	52 (94.5%)	77 (81.1%)	
Local recurrence at 5 years	N=15	N=39	
Yes	0 (0%)	4 (10.3%)	0.567**
No	15 (100.0%)	35 (89.7%)	

*** Fisher Exacted Test (Corrected Chi Square)*

TABLE 4: Changes in ER, PR, Her-2, Grade, post NACT between BCS vs Mastectomy

	Group		*P*-value
	BCS N=29	**Mastectomy** N=45	
ER_OUTCOME			
Same	23 (79.31%)	36 (80.00%)	0.943*
Different	6 (20.69%)	9 (20.00%)	
PR_OUTCOME	N=20	N=42	
Same	14 (70.00%)	34 (80.95%)	0.335*
Different	6 (30.00%)	8 (19.05%)	
HER_OUTCOME	N=17	N=26	
Same	14 (82.35%)	21 (80.77%)	0.896**
Different	3 (17.65%)	5 (19.23%)	
GRADE_OUTCOME	N=27	N=40	
Same	15 (55.56%)	29 (72.50%)	0.152*
Different	12 (44.44%)	11 (27.50%)	
Overall_Outcome	N=41	N=55	
Same	19 (46.34%)	29 (52.73%)	0.536*
Different	22 (53.66%)	26 (47.27%)	

**Pearson Chi Square*
***Fisher Exacted Test(corrected Chi Square*

of cases (26 patients) in the mastectomy group, although it was statistically not significant due to the small sample size (Table 4).

The BCS group had a lower LR at 2 years and 5 years in the advance T3-4 stage group and at the endocrine therapy group with a statistically significant value at 2 years (p=0.013). However, the result was statistically not significant at 5 years probably due to the small sample size. Both the sub-analysis on lympho-vascular invasion and pathological complete response group did not have a statistically significant results likely attributed to the small sample size as well. As for the endocrine therapy sub-group, there was no local recurrence at 2 years and at 5 years in the BCS group 100% (27 patients) / 100% (5 patients) compared to 81.3% (39 patients) / 90% (18 patients) in the mastectomy group and 18.7% LR at 2 years and 10% (2 patients) at 5 years with a statistically significant P-value 0.22 at 2 years.

Discussion

Literature review has shown that the use of NACT post BCS in LABC increases the risk of LR (12-14). As margin involvement is an independent risk factor for LR (19), hence attainment of negative margins is of utmost important in performing adequate BCS in LABC.

The use of ultrasound by the surgeon in the outpatient department was very useful. It led to immediate decision making and saved the patients' time as another appointment to see the radiologist was unnecessary. However, breast surgeons should strive to attend some training in ultrasound to achieve reasonable performing standards. We are fortunate that the surgeon in this institution has undergone some formal training. By managing the breast patients adequately, the radiologists were also freed up to perform other more challenging duties (20).

Although there are papers claiming that MRI is the best imaging tool to assess residual disease in post neoadjuvant chemotherapy (21), it is an expensive investigation and is not easily available especially in many smaller hospitals in developing countries. Lee (22) has found that residual disease assessment using ultrasound is as good as MRI.

Generally, patients who underwent BCS had better quality of life, higher body image score, felt more secure, were more sexually active and were associated with better physical and social functioning (8,9). BCS also reduced the number of cases for major reconstructive procedures such as TRAM flap or LD flap, which generally increases the morbidity rate and length of hospital stay. More major reconstructive surgeries also mean longer OT time, longer waiting lists and added cost. Unlike developed countries, the number of surgeons able to do breast reconstructive surgeries in Malaysia, a developing country, is limited and mainly located in the larger cities. Due to this, the majority of women who undergo mastectomy will not have access to breast reconstruction.

We found that a shared decision-making led to a better outcome in terms of patient satisfaction and compliance (23). NACT in BCS can determine chemo-sensitivity in vivo, reduce the micro-metastatic disease component, reduce the mastectomy rate, and it may achieve pathological complete response (pCR) which leads to excellent oncologic outcome (6). The patients with Her2 enriched carcinomas in this study did not have access to targeted therapies such as Trastuzumab or Pertuzumab. This is because they had to purchase it themselves. This situation is different in developed countries like the Netherlands (24) or the United Kingdom where Trastuzumab is given to patients with Her2 enriched carcinomas and this is funded by the government. As expected, the complete pathological response was low; only in 10% of the cases (Table 1). This is because Trastuzumab has been shown to increase the cPR rate when given with chemotherapy (25). Nevertheless, this study showed that despite not having Trastuzumab, the post BCS results were good.

Overall, the age and characteristic of tumours in our study was quite homogenous. However, the tumour size seemed to be larger in the mastectomy group. Our results showed post-operative surgical margins in the BCS group is not inferior to, in fact had better clearance percentage compared to the mastectomy group, which was statistically significant (p=0.05).

The LR at 2 years in BCS also showed a significant lower recurrence percentage 94.5% (52 patients) compared to the mastectomy group 81.1% (77 patients) which was contrary to previous earlier reports. BCS also showed a lower LR at 5 years but it was statistically not significant. This might be due to the small sample size because of patients lost to follow-up. The cases with LR developed lesions at the chest wall, previous surgical wound site, ipsilateral axillary and supraclavicular fossa. Age seemed not to be a factor affecting the involved surgical margin, local recurrence at 2 years and at 5 years between BCS and mastectomy as it did not show a statistically difference.

Prior to starting NACT, it is vital to establish not only the histological diagnosis and pathological grading, but also to assess HR status such as ER, PR and HER-2 as they are important prognostic factors and will guide the treatment strategy. A 2011 meta-analysis revealed that NACT significantly altered both ER and PR status (26). In our analysis, more than half of HR status and HG changed 55.66% (22 patients) in the BCS group and 47.27% (26 patients) in the mastectomy group, although the P-value was statistically not significant (27). The positive results of this will have a large impact on prognostication and influence on the treatment strategies. We recommend future studies with larger sample size to obtain more findings that are significant.

In the sub-group analysis, we looked at various factors that might influence the LR in BCS. In the T3-4 tumour groups, BCS had a lower LR at 2 years and 5 years. This means that even with initially large tumours, post NACT, BCS can be safely performed and will not significantly affect the LR. This is similar with another study, which showed that advanced T stage did not influence the LR post NACT; rather a high Ki-67 expression is associated with high LR (28). We did not look at the Ki-67 expression for this study, perhaps a future study should take this into account.

In the adjuvant endocrine therapy analysis, although the standard treatment is for 5 years, we could already see a significant lower LR at 2 years in both the BCS (no LR, 0%) and mastectomy group 18.7% (9 patients), P-value 0.022. Hence endocrine therapy should be started early in suitable patients.

For both sub-group analysis on complete pathological response and lympho-vascular invasion, we did not get a statistically significant results, which may be due to the small sample size and suggest that this study be continued in the future. Age seemed not to be a factor affecting the involved surgical margin, local recurrence at 2 years and at 5 years between BCS and mastectomy as it did not show any statistical difference.

This study had some limitations. It was a retrospective observational study with a short follow up period at 2 years and small sample size at 5 years. The ratio of T4 tumours was significantly higher in the mastectomy group, which seem to suggest that tumour involvement at the skin and chest wall may influence the LR. We suggest that this study should be continued to obtain a larger sample size.

Conclusion

This study demonstrated that in a developing country, BCS post NACT in LABC can be performed safely. BCS has been shown to be associated with lower post -operative margin involvement and lower local recurrence at 2 years. It was possible even with the limitations of accessibility to breast MRI, trastuzumab and aromatase inhibitors. Changes in the hormonal status and pathological grading should be studied further as it has significant clinical impact on treatment strategies.

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