

# Management of Locally Advanced Breast Cancer: Challenges and Treatment Outcomes in an Emerging Tertiary Hospital in South-Western Nigeria

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## ABSTRACT

**Introduction:** Patients presenting with advanced breast cancer is a common phenomenon in Nigeria and many developing countries. At this stage, patients' high expectations of survival conflict with the realities of the clinical outcome, thus creating enormous challenges to the attending surgeon practicing in a resource-poor setting.

**Aim:** To evaluate patients who presented with Locally Advanced Breast Cancer (LABC), management challenges and treatment outcomes.

**Materials and Methods:** This was a retrospective study of patients with LABC at Ekiti State University Teaching Hospital (EKSUTH), Ado-Ekiti between January 2016 and December 2018. The variables of interest were patients' demographics, findings of triple assessment, presentation, diagnosis, treatment intervals, the treatment received and follow-up outcomes. Results were presented using descriptive statistics mean±SD, median and Interquartile Range (IQR).

**Results:** Seventy-eight patients had LABC in the study period. ages ranged from 24-94 years (mean 50.1±14.0). Total 77 (98.7%) were females and patients had breast lump ranging in size from 3-22 cm (mean 8.7±3.3, median 8, IQR 6-10). A vast majority of

patients (84.6%) had tumour >5 cm in size. More than two-thirds (69.2%) were clinical stage IIIB. The duration of symptoms was 2-42 months (mean 10.1±7.8). The duration between presentation and cancer confirmation ranged from 7-140 days (mean 40.1±32.1, median 28.5, IQR 16.5-60.0). There was no facility to determine the receptor status of the tumours. Forty-six (59.0%) patients were routinely placed on tamoxifen (hormone therapy). Fifty-six (71.8%) patients had Modified Radical Mastectomy (MRM). Only 30 (38.5%) completed the chemotherapy schedules while the rest had them haphazardly, mainly due to financial reasons. Five out of 22 (22.7%) referred for radiotherapy received it after an average of 5.2 months. Postmastectomy, 7 had loco-regional recurrence at one year and 15 within three years. Overall, 40 were alive, 16 were dead while 22 were lost to follow-up at three years. There was significant difference in 3-year survival among those who had chemotherapy and mastectomy compared to those who had just one of the two (Fisher's-exact p=0.002).

**Conclusion:** Delayed presentation, diagnostic and treatment inadequacies are the common challenges of management of LABC. Early diagnosis, adequate provision of diagnostic facilities and subsidisation of all aspects of care will be a reasonable panacea to some of the challenges.

**Keywords:** Semi-urban hospital, Treatment challenges, Tumour

## INTRODUCTION

Breast cancer is a global disease with an increasing incidence among women. The American Joint Committee on Cancer (AJCC) aids to unify description of the disease, using the prognosis to classify it as early (stage 0-II b), locally advanced (stage III) and systemic or metastatic disease (stage IV) [1]. In countries with robust health care systems, high public health awareness and sound screening programs, the majority of breast cancer is early disease, and treatment outcomes are remarkable. In contrast, late-stage disease predominates and treatment outcomes are dismal in Low and Middle-Income Countries (LMICs) [2-6] that have weak health systems and low public health awareness.

Clinically, LABC describes breast cancer in which the primary tumour is >5 cm in diameter with regional lymphadenopathy (N1-3) or tumour of any size with skin and/or chest wall infiltration regardless of regional lymphadenopathy or presence of fixed or matted ipsilateral axillary node, internal mammary, infraclavicular or supraclavicular nodes in the absence of systemic disease [7]. These clinical features correspond to AJCC version 7, 2010: stage IIIA (T3, N1 or any N2), IIIB (any T4, N0-N2) and IIIC (any T + N3) disease [1]. This definition also includes the clinically aggressive entity referred to as inflammatory breast cancer which has a distinct clinicopathologic characteristics such as extensive erythema, oedema and warmth of the breast.

The standard management of breast cancer is an individualised approach by a dedicated Multi-Disciplinary Team (MDT) adopting a multi-modal protocol comprising of surgery, chemotherapy, hormonal therapy, targeted/biological therapy and radiotherapy. The standard management targets the locoregional control to alleviate the physical local and regional burden of the disease and the control of any systemic disease. In High-Income-Countries (HICs), the well-developed health system facilitates early detection, more precise diagnosis and staging of disease and the standard management protocols are implemented, translating into a better outcome stage-for-stage of breast cancer care when compared with resource-challenged environments [2,3,8,9]. Thus, despite the highest incidences of breast cancer in developed countries, LMICs still record a higher proportion of breast cancer related-deaths due to the dearth of facilities [10].

This study was carried out to review patients that presented with LABC in a relatively young center in Nigeria, highlighting the management challenges and the outcomes.

## MATERIALS AND METHODS

The study center was established in March 1971 as a General Hospital but was upgraded and renamed Ekiti State University

Teaching Hospital (EKSUTH), Ado-Ekiti, in 2008. It is a 350-bedded hospital receiving patients from the primary and secondary health facilities in Ekiti State, South-west Nigeria and other neighbouring states in South-west, North-central and South-east Nigeria. The hospital has a dedicated breast clinic that is run on a weekly basis by the general surgery division of the Department of Surgery.

This was a retrospective study of patients diagnosed with locally advanced BC (AJCC stage III) and managed at EKSUTH, Ado-Ekiti over a three year period from January 2016 to December 2018. The Ethics and Research Committee of EKSUTH approved this study before data collection (EKSUTH/A67/2018/07/008). Only the patients with histologically confirmed breast cancer and those that received at least one form of treatment were included. The records of surgical outpatient clinic, Emergency Department and Operating Theatre were reviewed to extract the names and hospital numbers of patients managed for breast cancer during the period. The list obtained was used to retrieve patients' case notes at the medical records department. Patients with early breast cancer, metastatic and recurrent disease were excluded. The variables of interest were patients' demographics, findings of triple assessment, presentation, diagnosis, treatment intervals, the treatment received (chemotherapy, surgery and radiotherapy) and follow-up outcomes (complications of surgery, recurrence and status at the end of study). Data were collected with the aid of a specially designed proforma.

## STATISTICAL ANALYSIS

The data generated were analysed for frequencies and simple percentages using the Statistical Package for Social Sciences (SPSS) version 21.0. Results were presented using descriptive statistics: mean $\pm$ SD, median and IQR and 95% Confidence Intervals (95% CI). To highlight the challenges of treatment, the duration of presentation was compared with historical value of 90 days and the proportion of patients getting definitive treatment was described. Comparison of the three years treatment outcome was made using Fisher's-exact test and p-value <0.05 was considered statistically significant.

## RESULTS

A total of 98 breast cancer patients were newly diagnosed during the study period, 78 (79.6%) with LABC (AJCC stage III) were eligible. The age range was 24 to 94 years (mean 50.1 $\pm$ 14.0 years, median 50.0 years, IQR 39.0-58.0). The socio-demographic profile of the patients is shown in [Table/Fig-1]. The modal age bracket was 51-60 years, the majority (42, 53.9%) were 50 years or below. Seventy-seven (98.7%) were females while only one (1.3%, 95% CI 0-6.9) was a male. Forty-six (59%, 95% CI 47-70) of the women were pre-menopausal.

The chief complaint was a lump in all patients with size ranging from 3-22 cm (mean 8.7 $\pm$ 3.3, median 8, IQR 6-10). The vast majority of patients, 66 (84.6%) had tumour >5 cm in size. The duration of symptoms was 2-42 months (mean 10.1 $\pm$ 7.8 months, median 8 months, IQR 5.8-12.0) and the tumour laterality was right in slightly more than half (51.3%) of patients. According to AJCC Staging, more than two-thirds (69.2%) were clinical stage IIIB. The mean duration of patient delay (time from the discovery of the first symptom to the first visit to a health care provider) was significantly longer than 90 days {213 days compared to the historical 90 days (95% CI 160-266)}. The duration between presentation and histopathology confirmation ranged from 7-140 days (mean 40.1 $\pm$ 32.1, median 28.5, IQR 16.5-60.0) and the duration between disease confirmation and initiation of treatment was 4-660 days (mean 45.9 $\pm$ 88.3, median 23, IQR 12-42.8). Patients who had Fine Needle Aspiration Cytology (FNAC) got their reports earlier than those who had tissue biopsy.

A total of 70 (89.7%) initiated the anthracycline-based chemotherapy regimen while fewer patients 8 (10.3%) initiated Taxane based regimen. Only 30 (38.5%, 95% CI 28-50) completed the Neoadjuvant Chemotherapy (NAC) and adjuvant regimen as prescribed,

Socio-demographics	Frequency	Percentage
<b>Age group (year)</b>		
21-30	7	9.0
31-40	18	23.1
41-50	17	21.7
51-60	20	25.6
61-70	8	10.3
>70	8	10.3
<b>Sex</b>		
Female	77	98.7
Male	1	1.3
<b>Educational status</b>		
None	17	21.8
Primary	7	9.0
Secondary	19	24.3
Tertiary	35	44.9
<b>Marital status</b>		
Single	3	3.9
Married	59	75.6
Divorced/separated	5	6.4
Widowed	11	14.1
<b>Parity</b>		
0-1	14	17.9
2-4	40	51.3
>4	24	30.8
<b>Menopausal status</b>		
Pre-menopausal	46	59.0
Post-menopausal	31	39.7
Not applicable	1	1.3
<b>Religion</b>		
Christianity	76	97.4
Islam	2	2.6
<b>Occupation</b>		
Civil servants	15	19.2
Trading	18	23.1
Farming	5	6.4
Artisan	4	5.1
Teaching	21	26.9
Others	6	7.6
Unemployed	9	11.5

[Table/Fig-1]: Socio-demographic data of patients.

48 (61.5%, 95% CI 50-72) either could not complete NAC or received haphazard doses. A total 46 of 78 (59%, 95% CI 47-70) were routinely placed on hormonal therapy without immunohistochemistry report. No patient received targeted therapy.

A total of 56 (71.8%, 95% CI 60.5-81.4) patients received MRM while the remaining 22 (28.2%, 95% CI 18.6-39.5) did not have mastectomy. The most common complication of mastectomy was numbness at the operation site in 10 (17.9%) patients. Five (8.9%) patients developed wound infection while 2 (3.6%) had flap necrosis and they were all managed with daily dressing and antibiotics. Two (3.6%) patients had seroma collection which resolved after needle aspirations.

Using tumour size of >5 cm as indication for radiotherapy, 66 (84.6%) patients required adjuvant radiotherapy but only 22 (33%, 95% CI 22-46) were referred due to economic constraints. In the end, only 5 (7.6%, 95% CI 2.5-17) of the total 66 patients who needed radiotherapy and 5 (22.7%, 95% CI 7.8-45.4) of the 22 referred were able to receive radiotherapy. The probability of completing

chemotherapy was eight times higher compared to completion of radiotherapy {RR 8.3 (95% CI 3.5-20)}.

The follow-up period was 5 to 36 months (mean 26.3±11.3 months, median 36 months, IQR 15-36). Among the 56 patients who had MRM, 7 (12.5%) had loco-regional recurrence at one year, 12 (21%) at two years and 15 (26.8%) at three years. Overall, 40 (51%) were alive, 16 (21%) were dead and 22 (28%) were lost to follow-up after three years [Table/Fig-2].

Outcome	1 <sup>st</sup> year (N,%,CI)	2 <sup>nd</sup> year (N,%,CI)	3 <sup>rd</sup> year (N,%,CI)
Alive	64 82% (72-90)	47 60% (49-71)	40 51% (40-63)
Dead	7 9% (4-18)	4 14% (7-24)	5 21% (12-31)
Lost to follow-up	7 9% (4-18)	13 26% (16-37)	2 28% (19-40)

**[Table/Fig-2]:** Outcome of treatment.  
N: Number of patients; CI: Confidence interval

The comparison of three years treatment outcome is shown in [Table/Fig-3]. There was no difference in the proportion of patients alive after three years among those that completed chemotherapy and those that started but did not complete chemotherapy (fisher's-exact p=0.83). There was a significant difference in the proportion alive after three years among those who had MRM compared to those who did not (fisher's-exact p=0.002) and there was also a significant difference in three year survival among those who had chemotherapy and MRM compared to those who had just one of the two (fisher's-exact p=0.002).

Outcome after 3 years	Alive (n=40)	Dead (n=16)	p-value
Completed chemotherapy	17	3	0.83
Not completed chemotherapy	23	13	
MRM*	37	9	0.002
No MRM	3	7	
Chemotherapy + MRM (combined)	16	0	0.002
Chemotherapy or MRM	24	16	

**[Table/Fig-3]:** Comparison of 3 years treatment outcome.  
\*MRM: Modified radical mastectomy; p-value <0.05 statistically significant

## DISCUSSION

The burden of management of advanced breast cancer to both the patient and the managing surgeon is quite enormous. Irrespective of the stage at presentation, patients still hold high expectation of long term survival when presenting for hospital care. The patients' high expectations conflict with the realities of the clinical outcome, thus creating enormous challenges to the attending surgeon practicing in a resource-poor setting where diagnostic armamentarium and treatment facilities are severely deficient. Approximately, 80% of the patients had LABC during the study period, this was slightly higher than 72% reported by Anyanwu SNC [2] for stages III and IV breast cancer. However, this is a sharp contrast to 11.3% and 18.9% incidence of stage III and IV among American Whites and African-Americans respectively [11]. Most studies in Nigeria and other developing countries showed that the majority of patients presented in stages III and IV [2,3,12,13]. There is an urgent need to change this ugly trend for improved prognosis.

The average duration of symptoms was 10 months in this study. A time gap >3 months between symptom detection and first medical consultation was regarded as patient delay [14]. The delay in this study was significantly longer than 90 days, this is associated with presentation with more advanced disease and necessitating chemotherapy, radiotherapy and more aggressive surgical therapy. Delayed presentation and advanced stage of breast cancer which are common in LMICs have been adduced to many factors such as ignorance of breast cancer symptoms, fear of mastectomy, lack of awareness due to poor

health programs, inadequate funding of health sector and lack of screening programs [15-17]. Screening facilitates early detection and prompt treatment with good outcome. However, the high cost of screening mammography makes it infeasible in LMICs and the fact that younger population of women aged 40-49 are affected puts to question the benefits of mammography [18,19]. Therefore, emphasis should be placed on awareness campaigns, self-breast examination and clinical breast examination that can lead to increased early breast cancer detection rates and potential downstaging [20-22]. Efforts should also be made to reduce the turnaround time of histopathology specimen to shorten the time to treatment.

Immunohistochemistry for biomarkers diagnosis was not available in the study center thus tailored therapy could not be offered. The problem of inadequate diagnosis still persists in most developing countries [23]. The routine use of hormonal therapy in the absence of oestrogen- and/or progesterone-receptor status in patients with breast cancer is not in accordance with the international best practices. Despite this diagnostic deficiency, many surgeons routinely put patients on this therapy perhaps because it is available and not as costly as other therapies [24-26]. Just a minority of hormone receptor negative patients will benefit from this therapy, the others might be harmed. It is unclear whether this kind of treatment should continue in this era of evidenced-based medicine where there are diagnostic limitations. The challenge of out-of-pocket payment for health care is a major factor confronting breast cancer patients across Nigeria and other developing nations of the world. Only 30 (38.5%) patients did not default from the chemotherapy schedules during their treatment but the rest (61.5%) of them could either not complete chemotherapy or had their medications haphazardly. The National Health Insurance Scheme (NHIS) established in 1999 to achieve a universal health coverage for the citizens at an affordable cost could have mitigated this problem but still has less than 5% coverage in the entire country even after twenty years of its establishment. The prohibitive cost of chemotherapy will continue to militate against adequate and successful treatment of cancer in Nigeria until the cost of medications and treatment are highly subsidised by the government.

Surgery is an integral part of breast cancer management and MRM is the mainstay of surgical treatment in LABC [27,28]. In advanced presentation with no evidence of distant metastasis, a radical and "mutilating" procedure is inevitable as the surgeon still aims at complete loco-regional disease control but local recurrence is a major problem affecting up to half of patients [28]. Of the 56 patients who had mastectomy in the hospital, 15 (26.8%) developed locoregional recurrence within three years. This high recurrence rate is connected with extensive skin and chest wall involvement coupled with the inability to receive adjuvant radiotherapy following surgery. Although, local recurrence might also be a manifestation of a more aggressive tumour biology or suboptimal surgical technique. An assessment of the quality of mastectomies still needs to be done in LMIC in order to identify areas for improvement [29]. Radiotherapy plays an important role in the management of LABC. It can be used preoperatively to downstage an unresectable tumour or postoperatively to improve the locoregional control and increase disease free and overall survival [30]. But-Hadžić J et al., suggested that radiation therapy should always be considered regardless of the response to initial chemotherapy for noninflammatory LABC [31]. Radiotherapy services are grossly inadequate in Nigeria and other LMICs in Africa; in the present study, the majority of patients requiring radiotherapy did not receive it and the probability of completing chemotherapy was eight times higher compared to radiotherapy. A systematic review revealed that 29 of African countries lack any radiotherapy



capacity [32]. In 2010, there were only eight radiotherapy centers in Nigeria [33]. Presently, there are 11 radiotherapy machines in Nigeria, out of which only 4 are functional at a particular time and there is none in the state where this study center is located. With the Nigeria population of over 180 million and an increase in the incidence of breast cancer, these centers are grossly inadequate to meet the needs of patients. Other barriers to radiotherapy access include power outages, incessant health workers' strikes, frequent machine breakdown and financial difficulty [33,34]. These factors contribute to postponement of appointments and irregularity of services.

Only five (22.7%) out of 22 patients referred for radiotherapy were able to access the treatment. Apart from travelling a long distance to the few centers where the facility is available, the appointment at these centres ranges from two to six months making patients to be highly discouraged and reluctant when the need for this treatment arises. Considering the fact that LABC accounts for the majority of breast cancer cases in LMICs and radiation treatment is a paramount aspect of care, the gross insufficiency of radiotherapy capacity is a concern and will definitely increase the avoidable mortality [35]. Forty (51.3%) of the patients were alive at three years. Mensah AC et al., in Ghana reported 33.95% for clinical stage III breast cancer at five years of follow-up while Kene TS et al., in Northwestern Nigeria reported 70.4% survival rate at 3 years but only 46.6% of their patients were stage III in the study [36,37]. Although, the survival rate in this study is lower than 69.0-83.0% estimated 3-year survival rate for stage III breast cancer in HICs such as Canada, Sweden, Norway, Denmark and the United Kingdom [8], improvement on the diagnostic and treatment barriers will positively impact the outcome. In this study, mastectomy alone or mastectomy in combination with chemotherapy significantly improved the patients' survival at three years whereas there was no significant difference in the proportion of patients alive among those that completed chemotherapy and those that started but did not complete chemotherapy.

### Limitation(s)

Being a retrospective study, the findings are still limited by the large number of patients lost to follow-up which could hamper accurate data collection on outcomes. Perhaps, the mortality rate of about 21% recorded at three years could have been more as some of those lost to follow-up could have possibly succumbed to their disease.

### CONCLUSION(S)

The vast majority of breast cancer patients still present with locally advanced disease in the setting and MRM are the major treatment offered. There are inconsistencies in the chemotherapy, hormonal and radiotherapy treatments as a result of financial and facility challenges with attendant poor outcome in terms of survival. Government efforts at increasing awareness campaigns for early diagnosis and prompt treatment, improvement of hospital facilities and subsidisation of all aspects of care will be a reasonable panacea to the numerous challenges of care.

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