Original Article

# STAGE-SPECIFIC FIVE-YEAR SURVIVAL OUTCOMES IN WOMEN TREATED FOR EARLY STAGE BREAST CANCER IN IBADAN, NIGERIA

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## ABSTRACT

**Background:** The disparity between the overall survival of breast cancer between high-income countries (HICs) and low- and middle-income countries (LMICs) has been majorly attributed to the high rate of diagnosis of Early Stage Breast Cancer (ESBC) in HICs, with about three-quarters and one-fifth of the total breast cancer patients diagnosed with ESBC in HICs and LMICs respectively. The median 5-year survival rate of ESBC in HICs is 86% while it is about 72% in Sub-Saharan Africa.
Objectives: To determine stage-specific five-year survival outcomes in women treated for ESBC.
**Methods:** We conducted a longitudinal, cohort study to assess the treatment and outcome of ESBC in a Nigerian tertiary hospital. Patients diagnosed and treated for ESBC over 5 years were recruited and followed up for a minimum of 5 years after treatment. Clinicopathologic parameters, disease progression and known vital status, were retrieved. A 5% level of significance was used.
**Results:** 67(9.6%)patients of 694 new cases of breast cancer seen over the study duration was treated for ESBC, of whichsixty- three (63) were followed up over the specified follow-up period. The mean age was 43(10) years. Based on the American Joint Committee on Cancer staging, 9 patients were stage IA, 16 stage IB, 16 stage IIA and 26 stage IIB respectively. The overall 5-year survival was 77.8%.
**Conclusion:** The survival pattern of our cohort fairly compares with reports in HICs, despite the challenges faced in the multimodal treatment protocol received by our patients.
**Keywords:** early breast cancer,survival, survival analysis, stage-specific

NigerJmed 2020: 152-157


## INTRODUCTION

Breast cancer is the leading cause of cancer and cancer-related deaths in females globally.[1] However, Sub-Saharan Africa accounts for 10% of all breast cancer-related deaths worldwide despite having a lower incidence rate when compared to High-Income Countries (HICs).[2,3] In a multi-continental comparative study, Nigeria had the third highest mortality rate irrespective of the stage at diagnosis and availability of treatment options.[4] HICs such as those in the Asian pacific have a higher overall survival rate of 79% when compared to that of Low and Middle-Income Countries (LMICs) in Sub-Saharan Africa with a 12% survival rate.[5]
The huge difference between the overall survival rates in both regions has been majorly attributed to the high rate of diagnosis of Early Stage Breast Cancer (ESBC) in HICs when compared with that of LMICs, and cutting-edge standard of care. About three-quarters of patients in HICs with breast cancers are diagnosed with ESBC as opposed to one-fifth of the total breast cancer patients diagnosed with ESBC in LMICs.[4] The median 5-year survival rate of ESBC in HICs is 86% while it is about 72% in Sub-Saharan Africa.[6,7]
This difference in survival rates of ESBC is due to a combination of factors such as the age at presentation, tumour biology and availability of treatment options in these countries. Sub-Saharan Africa has a high prevalence of premenopausal patients, a basal-like breast tumour with triple-negative biology which carries a worse prognosis when compared to predominantly postmenopausal patients in HICs.[8,9]
However, early diagnosis may not be the only major factor considered in breast cancer survival since there is evidence of lead-time bias in patients who had no intervention when diagnosed with ESBC (stage 0 and 1), and who experienced a 3 to 10- year lag time before developing late-stage breast cancer.[10] Comparing stage for stage, there was an eighty-four percent 3-year survival rate for ESBC when compared to a 3-year survival rate of 56% for late-stage breast cancer in Africa.[11] In this study, we review the treatment and outcomes of Early Stage Breast Cancer in our hospital over a nine-year follow-up period.

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## METHODOLOGY

Our investigation was a longitudinal, cohort study aiming to assess the treatment and outcome of early-stage breast cancer. It was done in the Department of Surgery, University College Hospital, Ibadan. Ethical approval was obtained from the Oyo State Ministry of Health before the commencement of the study. Patients diagnosed and treated for ESBC over a 5-year period from January 1, 2009, to December 31, 2013, were recruited and followed up till December 31, 2018 (minimum of 5 years after diagnosis and treatment). The age, parity, tumour stage at presentation, tumour biology, disease progression and last known vital status were retrieved.

Patients with complete data set with a clinic opathological diagnosis of ESBC were included in the study. Patients who were neither ESBC at time of presentation or diagnosis or patients whose data were not appropriately stored were excluded. The follow-up protocol was clinical and radiologic (plain chest radiograph, abdominopelvic ultrasound scan along with a bone scan every year for the first 5 years and then every two years after.

Anonymity was ensured by converting the names of patients to coded numbers. Data extraction was done under the supervision of co-investigators by trained residents in the Oncology unit of our centre. Descriptive analysis in terms of frequency, mean, median and mode was generated from the data extracted. It was statistically analyzed using SPSS 20. The analyzed data were interpreted using tables and charts. A 5% level of significance was used for all tests.

## RESULTS

A total of 694 new cases of breast cancer were seen over the study duration, of which 67(9.6%)patients hada diagnosis of ESBC. Sixty- three (63) of the ESBC patients were followed up as stated over the specified follow-up period, with 4 patients lost to follow-up.

The ages of the patients ranged between 21 and 82 years, with a mean of 43(10) years. Forty-six (69%) were postmenopausal, and the majority of them (84%) were multiparous. Based on the American Joint Committee on Cancer (AJCC) staging, nine (9) patients were stage IA, 16 stage IB, 16 stage IIA and 26 stages IIB respectively.

The tumours were graded with the modified Scarff-Bloom-Richardson system into a low, intermediate and high grade (figure 1). Thirty-nine patients (58%) had ER+ cancers, and 19 (28%) had HER2-enriched tumours, of whom 11 patients had immunotherapy with Herceptin®. About a quarter (23%) of the patients referred for radiotherapy received radiation treatment.

**Figure 1.**

**Figure 1:** Clinico-pathologic profile.

| **Characteristics (N - 67)** | **Mean (S.D)** | **n (%)** |
|---|---|---|
| Age at diagnosis | 43 (10) | |
| Age range (21 - 82 years) | | |
| Premenopausal | | 21(31) |
| Postmenopausal | | 46(69) |
| **Parity** | | |
| Nulliparous | | 11(16) |
| Multiparous | | 56(84) |
| **Clinical Stage** | | |
| 0 | | 0 |
| IA | | 9 |
| IB | | 16 |
| IIA | | 16 |
| IIB | | 26 |
| **Tumour grade** | | |
| Low grade | | 21 |
| Intermediate grade | | 19 |
| High grade | | 2 |
| **Immunohistochemistry** | | |
| Estrogen + | | 39 |
| Progesterone + | | 21 |
| HER-2/Neu + | | 19 |
| **Chemotherapy** | | |
| Neo-adjuvant | | 21 |
| Adjuvant | | 56 |
| **Hormonal therapy** | | |
| Yes | | 36 |
| No | | 21 |
| **Immunotherapy** | | |
| Yes | | 11 |
| No | | 8 |
| **Radiotherapy** | | |
| Yes | | 13 |
| No 44 | | |

**Figure 2**: Outcome of patients (n=63)

| Characteristics | Median | n |
|---|---|---|
| Median survival time (months) | 47 (53) | 63 |
| Local Recurrence 0 | | |
| Metastasis | | 13 |
| Visceral (lung, liver, Ovaries, Peritoneum)7 | | |
| Bone | | 13 |
| Brain 3 | | |
| **Vital Status** | | |
| Alive with disease | | 5 |
| Alive without disease 44 | | |
| Dead from disease | | 12 |
| Dead from other causes 2 | | |
| Lost to follow up 4 | | |

**Figure 3:** Kaplan-Meier Survival analysis by AJCC breast cancer stages over the follow up period.

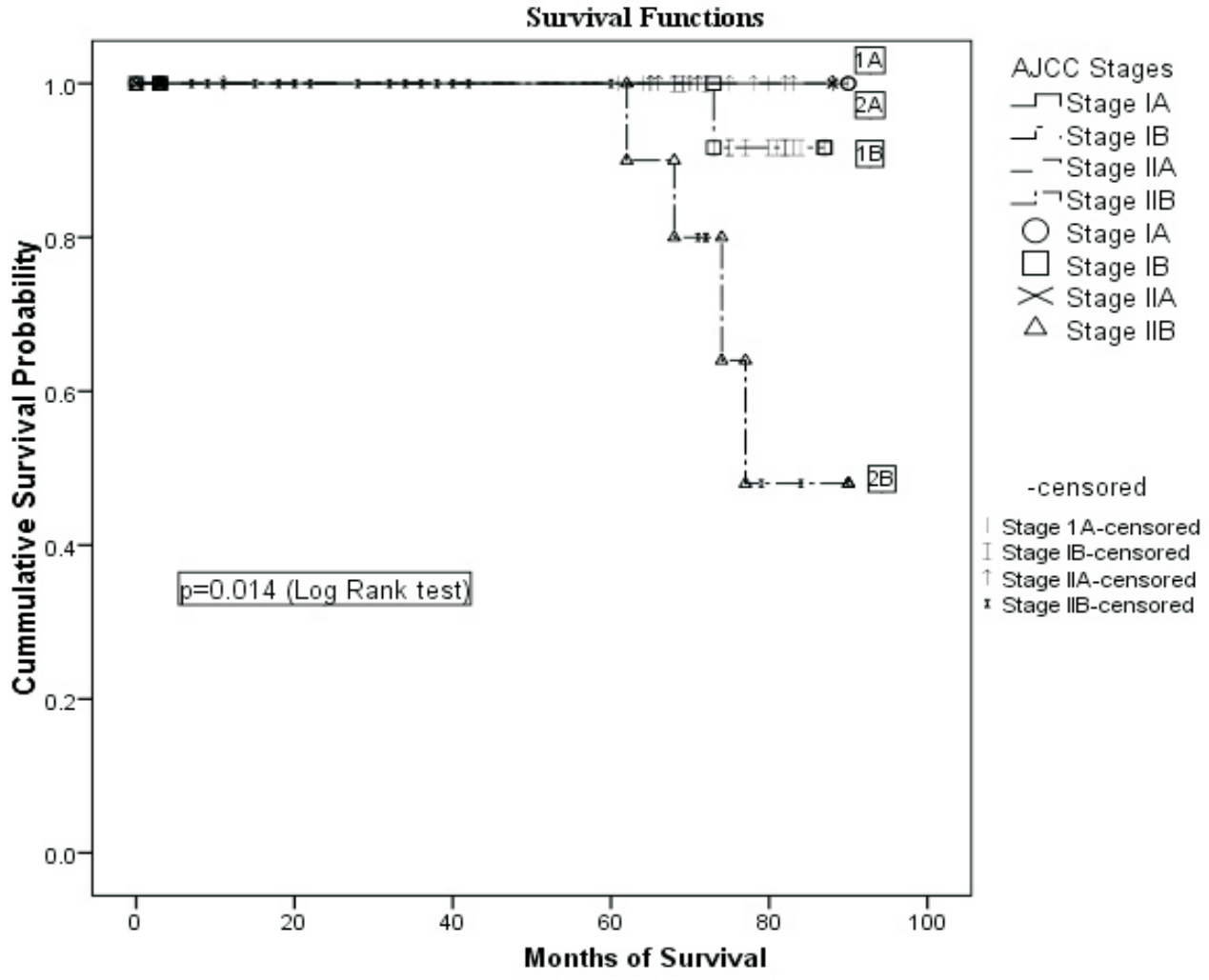

**Figure 2.**
Out of the 63 patients who were followed up for at least 5 years, 49 were alive, 12 died from breast cancer, and 2 patients died from causes other than breast cancer; the overall 5-year survival rate being 77.8%. The median survival time was 47(53) months (figure 2), with survival duration ranging from 3 to 90 months at the end of the follow-up period. All the four patients who were lost to follow-up had Stage IIB disease, defaulted from the out-patient clinic and could no longer be reached within a year after diagnosis (3 – 11 months). All the 12 patients whose deaths were attributable to the disease died within 42 months (11 – 42 months), and all had Stage 2 disease (1 – IIA, 11 – IIB). All seven patients who had surgery alone had clinical and radiological evidence of disease progression within 60 months; while all surviving patients with evidence of disease have histologically high-grade tumours.
None of the patients had local recurrence. Thirteen (13) patients had evidence of metastasis, the commonest site being the bone.
**Figure 3.**

## DISCUSSION

Demographic parameters that are often implicated in the poor outcome of breast cancer in LMICs are well documented, including late presentation,[8,9,12] premenopausal status,[4,8,9,12,15] younger age at diagnosis,[8,9]unfavourabletumour biology[4,8,9,12] as well as poor treatment compliance.[8].
In this study, 69% of the women were postmenopausal. This is in contrast to findings from other local studies conducted about a decade earlier, in which the majority of patients were premenopausal. Huo*et al* reported 43.5%, [13]Adesunkanmi*et al* 33.3% [8] and Ogundiran*et al* 42.4% [12] postmenopausal patients respectively. It should, however, be noted that this study is limited to ESBC,unlike the other reports that recruited all stages of invasive breast cancer. Considering the fact that the mean age at diagnosis is surprisingly higher (49(10)) than previous reports, (46.8(11.3),[13] 48(23-85),[8]47.4(11.4) [12]) and the fact that age at natural menopause in breast cancer patients previously known to be 48.2(5.7);[13] consequently the possibility of a changing pattern in menopausal age should, therefore, be considered, even though our data may be too small and unpowered for such detection. This is important as the age range of our patients (21 – 82 years) is comparable to findings from other studies. In addition, the overwhelming majority of patients in the series reported by Ogundiran*et al.* were Stages I and II breast cancer cases, as they also reviewed only patients who had a mastectomy. One would, therefore, not have expected much disparity in the clinico-epidemiologic parameters, more so, 5-year survival status with respect to menopausal status was statistically significant ($p<0.05$). This trend is akin to the epidemiological picture in the western world – with the outlook that suggests that the epidemiological profile of our elderly breast cancer cohort is starting to mirror the western climes.
Majority of our patients (84%) were multiparous, which is consistent with findings from other local studies, [8, 12] thus supporting the finding that multiparity is protective of breast cancer, regardless of clinical stage. [13] However, considering the complexity of the relationship between parity, fertility and breast cancer, other factors such as the number of full-term pregnancies, breastfeeding, age at first birth and usage of hormonal contraceptives would have to be considered. The Nigerian Breast Cancer Study concluded that multiple live births, late menarche and extended breastfeeding are protective of breast cancer in Nigerian women, even though the overall trend is that of increased breast cancer risk and incidence [16]. The fact that women attain menarche at a younger age, deliberately give birth to fewer children and breastfeed for a shorter duration appears to obviate the positive impacts of the protective factors. In our series, parity had no statistical significance in determining long term survival.
Majority of the patients in this review had intermediate or high-grade tumours, which is in line with findings in the literature.[8,9,14] With tumour grade a known independent predictor of patient outcome in breast cancer regardless of how early diagnosis is made, it is not surprising that all the patients who are still alive with the disease have high-grade tumours ($p>0.05$).
Out of 694 newly-diagnosed breast cancer patients seen in our centre over the 5-year study period, only 67 (9.6%) were ESBC, which is barely half of the figures reported in Nigerian literature, which ranged from 19.4% to 25.2%.[8,17] Considering the fact that our centre serves a predominantly urban population that is expected to be more enlightened than the average Nigerian about common breast cancer screening modalities – self-breast examination, clinical breast examination and mammography.[18]This figure is considered low. This could be because we only reviewed ESBC patients who had prompt treatment of the early disease and subsequent follow-up, not the total number of patients diagnosed with ESBC while the denominator (694) comprises all indexed new cases, regardless of treatment. Ukwenya*et al.* reported a reduction of ESBC from 45.2% at diagnosis to 25.2% at treatment,[16] this attrition being attributable to poor social acceptance of mastectomy and inability to afford orthodox treatment, making the patients seek alternatives, and then later re-present with advanced disease.
None of the patients in our series had AJCC Stage 0 disease, which encompasses a spectrum of conditions – Paget's disease of the breast, ductal carcinoma in-situ and lobular carcinoma in-situ. This could be attributed to the paucity of information about preclinical diagnosis through screening modalities, relative unavailability of mammogram facilities, thelow sensitivity of screening mammogram in younger women as well as high-cost implications of a screening test. Besides, only patients who underwent treatment following diagnosis had their records indexed and entered into the breast cancer database, which probably excluded pre-invasive lesions.
About 58% of the tumours were ER+, which is in keeping with 65% earlier reported.[14] With over 92% of the ER+ patients treated with hormonal therapy as an adjunct, we found a 100% 5-year survival and only 3 patients had evidence of disease progression within 5 years. Our 5-year survival outcomes were better in ER/PR+ tumours compared to triple-negative cancers ($p<0.05$). This further underscores the need for increased advocacy for hormonal manipulation of breast cancer in our population when

indicated by positive immunohistochemistry. Uptake of immunotherapy was, however not as satisfactory, as only 11 out of 19 patients with HER-2 enriched tumours having immunotherapy. Treatment with trastuzumab, even though adjudged cost-effective, is also cost-intensive and many of the patients could not afford it. Only 22.8% of the patients referred to the Radiotherapy department were known to have received EBRT. The recurrent breakdown of the radiotherapy machine in our centre during the time of treatment coupled with consequent unbearable patient load in neighbouring tertiary centres with Radiotherapy units could be responsible for this.

Most of the patients had a multimodal treatment plan, surgery being the mainstay. Breast cancer surgery was combined with one or more of immunotherapy, radiotherapy, chemotherapy and hormonal therapy. All the 7 patients who had surgery alone developed disease progression within 36 to 60 months. This further emphasizes the need for adjunct treatment options in combination with surgery in ESBC treatment.

The overall 5-year survival rate was 77.8% in this study, which is comparable to 86% reported for HICs and 72% for sub-Saharan Africa.[6, 7] This review, being a single tertiary centre-based investigation has a tendency to inflate survival statistics since it was conducted in a leading Oncology centre in the sub-region with facilities and manpower for integrated cancer management, whereas the CONCORD study [6] assessed a much larger dataset extracted from a national cancer registry in Algeria. In addition, the quoted 72% was for 5-year metastasis-free survival of EBSC (in Ethiopia). Nonetheless, the attention of researchers is being drawn to possible changing narratives in some LMICs as the survival of ESBC cases appear to be on the upward trend due to improvement in the standard of diagnostic modalities and cancer care.

The average survival time of patients in our series was 47(53) months, compared to an estimated 9.5 to 30 months' average lifespan of a diagnosed breast cancer patient in Nigeria [17]. The estimate was generated from the dataset that includes all stages of breast cancer, such that early mortality in advanced breast cancer could have swung the average survival towards the unfavourable side.

The survival plots for Stages IA and IIA were similar (figure 3); however, there is a statistically significant difference in the survival outcome of the different group, with Stage IIB disease having the worst proportion of survival ($p<0.05$).

In conclusion, when compared stage-for-stage with breast cancer patients in HICs, the survival outcome of patients treated for ESBC in our cohort is not an abysmal tale of mortality, as our 5-year survival of 77.8% is not far behind 86% reported in HICs. Considering the challenges faced in achieving optimal multimodal treatment protocol received by our patients, including poor uptake of immunotherapy and suboptimal access to radiation therapy, we project that survival pattern in our series could have competed fairly with that of HICs if treatment adjuncts were received as ideal.

Almost all the mortality recorded had stage IIB disease (92%), with the overall survival analysis significantly skewed by the IIB subset. This adds further credence to the growing debate whether IIB disease should be categorized as ESBC at all or if it should be adjudged to have clinical outcomes as stage III, especially since the common denominator is loco-regional disease spread, according to the SEER classification (Surveillance, Epidemiology and End Results), which found the 5-year relative survival of regional breast cancer cases to be 85%.[19] Results of further research in our geographic location will elucidate more on this on a global perspective.

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