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Original Article

Survival after treatment for American Joint Committee on Cancer Stage III breast cancer in Ahmadu Bello University Teaching Hospital Zaria

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Abstract

Background: Breast cancer is the most common malignancy in women worldwide. Patients with American Joint Committee on Cancer Stage III breast cancer have been noted to have good response to neoadjuvant chemotherapy. The aim of this study is to evaluate survival of such patients after treatment at our hospital.

Methods: A 5-year prospective study was conducted between January 2009 and December 2013. Patients had four courses of neoadjuvant chemotherapy (cyclophosphamide, adriamycin, paclitaxel), Auchincloss' modified radical mastectomy, two courses of adjuvant chemotherapy and adjuvant tamoxifen (premenopausal) or letrozole (post-menopausal) for ER-positive tumours. All patients had radiotherapy. Follow-up was on outpatient basis and through phone calls. Statistical analysis was done using SPSS version 21.0, survival analyses with Kaplan–Meier method, multivariate analyses done with $P \leq 0.05$ regarded as statistically significant.

Results: Data from 303 patients (291 females and 12 males) were analysed. One-year, 2-year, 3-year, 4-year and 5-year disease-free survival (DFS) was 79.80%, 56.57%, 51.51%, 47.47% and 47.47%, respectively. One-year, 2-year, 3-year, 4-year and 5-year overall survival (OS) was 80.80%, 61.61%, 55.56%, 51.51% and 51.50%, respectively. Initial tumour size, response to neoadjuvant chemotherapy, number of involved nodes, tumour grade and receptor status had statistically significant relationship with DFS and OS. The relationship between the patients' age, gender and both DFS and OS was not statistically significant.

Conclusion: Five-year DFS and OS were 47.47% and 51.50%, respectively. Initial lesion size, response to therapy, involved nodes, tumour grade and receptor status had statistically significant relationship with DFS and OS.

Keywords: Survival, breast cancer, Stage III

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INTRODUCTION

Breast cancer has been recognised as the most common malignant neoplasm in women worldwide.[1-3] The incidence of this condition varies in different regions of the world as does survival of such patients following treatment.[4-10] In the West African sub-region, most patients with breast

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cancer present with either loco-regional or metastatic disease and this has been postulated to influence how long such patients survive after treatment.[11-13] Other factors that have been put forward as possibly influencing survival after treatment include the patient's age at the time of diagnosis, the initial tumour size, number of involved axillary lymph nodes, histological type and grade of the tumour as well as the hormone receptor status.[2,7,14-17]

Patients with American Joint Committee on Cancer (AJCC) Stage III breast cancer have been noted to have good response to neoadjuvant chemotherapy.[7,18,19] These patients may then undergo surgery with adjuvant therapy but may eventually relapse and present with loco-regional recurrence or metastatic disease which would adversely influence their quality of life and may ultimately lead to their demise.[7,19] Outlining the disease-free survival (DFS) and overall survival (OS) of patients with AJCC Stage III breast cancer would be the focus of this study with the aim of evaluating survival of these patients after treatment at our hospital.

METHODS

It was a 5-year prospective observational study of patients with AJCC Stage III breast cancer who were treated in our hospital between January, 2009 and December, 2013. Ethical approval was obtained from the Health and Research Ethical Committee of the hospital before patient recruitment begun.

All patients with AJCC Stage III breast cancer aged 75 years and below were recruited into the study after counseling and informed consent had been obtained. Patients who had concurrent malignancies, bilateral breast cancer, psychiatric disorders, uncontrolled systemic (medical) conditions as well as those who had received part of their cancer treatment before presentation at this hospital and those who died while receiving neoadjuvant chemotherapy (before they could have mastectomy) were excluded from the study.

On presentation, these patients had triple assessment (clinical, radiological and laboratory including histology and immunohistochemistry) to confirm the diagnosis, stage the disease and confirm patients' fitness for therapy. The 2005 version of AJCC staging was used to identify patients with Stage III breast cancer. They then had four courses of cyclical combined neoadjuvant chemotherapy with cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2 and paclitaxel 80 mg/m^2 (for those without cardiac comorbidities) or cyclophosphamide 400 mg/m^2, epirubicin 30 mg/m^2 and paclitaxel 80 mg/m^2 (for those with cardiac comorbidities). Each course was given once in 3 weeks (with an extra week added if the patient failed to recover from the adverse effects of chemotherapy on time). The sizes of the tumours were measured at presentation and at the end of neoadjuvant chemotherapy and clinical tumour response was determined.

The patients then had Auchincloss' modified radical mastectomy (simple mastectomy with clearance of levels I and II axillary nodes) 3–6 weeks after the last course of neoadjuvant chemotherapy before getting two courses of cyclical combined adjuvant chemotherapy with the same regimen as the one used for neoadjuvant chemotherapy. Patients who had oestrogen receptor-positive tumours received hormonal therapy with tamoxifen for premenopausal patients and letrozole (an aromatase inhibitor) for post-menopausal patients after completion of chemotherapy. External beam radiotherapy was also given to the mastectomy field in the post-operative period after completion of adjuvant chemotherapy. Patients with tumours overexpressing HER-2 receptors did not receive targeted therapy (trastuzumab) because none of them could not afford trastuzumab and the drug was not covered by the National Health Insurance Scheme as at the time the study was conducted.

The patients were then followed up on outpatient basis in the surgical outpatient clinic as well as through phone calls for a minimum of 5 years. This involved outpatient visits once every 3 weeks for the first 3 months, once every 3 months for the next 6 months, once every 6 months for the next 2 years and once every year thereafter. During such visits, the patients had clinical evaluation. Also, radiological assessment was done at least once every 6 months or whenever there was an indication for such assessment. The radiological investigations done included chest X-ray, mammography, abdominopelvic ultrasonography, computerised tomography scans or bone scans as indicated. Laboratory investigations (including complete blood count, serum electrolytes, urea and creatinine, liver function tests) were done once every 3 months or whenever there was an indication to do so. Efforts were made to reach patients who defaulted follow-up through phone calls or visits to their place of residence as stated in their folders.

OS was defined as the time from commencement of neoadjuvant chemotherapy to the last time that the patients in this study were still alive. DFS was defined as time from commencement of neoadjuvant chemotherapy to onset of symptoms and signs of loco-regional recurrence or distant metastasis.

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Statistical analysis was done using the Statistical Program for the Social Sciences version 21.0 (IBM 2012, Armonk, New York, USA) with the results presented as simple percentages and charts. Survival analyses were performed with the Kaplan–Meier method with 1-year, 2-year, 3-year, 4-year and 5-year OS and DFS stated. Univariate and multivariate analyses were done to find the relationship between clinical characteristics of the patients and 1-year, 2-year, 3-year, 4-year and 5-year OS and DFS with $P \leq 0.05$ regarded as statistically significant.

RESULTS

Three hundred and thirty-four patients (consisting of 321 females and 13 males) had treatment for AJCC Stage III breast cancer during the study period and were recruited into the study. Twelve of these patients died before completing neoadjuvant chemotherapy while nine of these patients were lost to follow-up; data from these 21 patients were excluded from the study. Data from the remaining 303 patients (consisting of 291 females (96.04%) and 12 males (3.96%) with male:female ratio of 1:25) were analysed. Table 1 shows demographics of the study population.

One hundred and forty-four patients (47.47%) were free of the disease the end of 5 years of follow-up. There were features of disease progression in 159 patients (52.53%) which included metastasis to the liver in 111 patients (36.63%), to the lungs in 40 patients (13.20) and to the spine in 8 patients (2.70%). Table 2 shows DFS amongst patients in the study.

One hundred and fifty-three patients (51.50%) were alive at the end of 5 years of follow-up. Table 3 shows OS amongst patients in the study.

The initial size of the lesion, response to neoadjuvant therapy, number of lymph nodes involved by the tumour, grade of the tumour and receptor status had statistically significant relationship with DFS with $P = 0.041$, 0.012, 0.001, 0.001 and 0.006, respectively, while the relationship between the patients' age, gender and DFS was not statistically significant with $P = 0.531$ and 0.610, respectively. Table 4 shows the number of tumour-involved nodes with corresponding DFS and OS.

The initial size of the lesion, response to neoadjuvant therapy, number of lymph nodes involved by the tumour, grade of the tumour and receptor status had statistically significant relationship with OS with $P = 0.001$, 0.024, 0.001, 0.001 and 0.012, respectively, while the relationship

Table 1: Demographics of the study population

Patients' parameters	Number of patients (%)
Age (years)	
11-20	12 (3.96)
21-30	9 (2.97)
31-40	97 (32.02)
41-50	111 (36.63)
51-60	62 (20.46)
61-70	12 (3.96)
Total	303 (100.00)
Mean age (years)	44.32±3.88
Age range (years)	13-67
Gender	
Males	12 (3.96)
Females	291 (96.04)
Total	303 (100.00)
Male:female ratio	1:25
Laterality of the lesion	
Right	148 (48.84)
Left	155 (51.16)
Total	303 (100.00)
Initial size of the lesion (cm^2)	
<100	97 (32.01)
100-199	106 (34.98)
200-299	97 (32.01)
300-399	3 (1.00)
Total	303 (100.00)
Response to neoadjuvant	
Therapy	103 (44.00)
Partial response	200 (66.00)
Complete response	303 (100.00)
Total	606
Number of tumour-positive lymph nodes	
0	41 (13.53)
1-2	56 (18.48)
3-4	68 (22.44)
>4	138 (45.55)
Total	303 (100.00)
Histology	
Invasive ductal carcinoma	202 (66.67)
Invasive lobular carcinoma	44 (14.52)
Papillary carcinoma	23 (7.59)
Medullary carcinoma	20 (6.60)
Metaplastic carcinoma	14 (4.62)
Total	303 (100.00)
Tumour grade (nottingham system)	
I	59 (19.47)
II	103 (33.99)
III	141 (46.54)
Total	303 (100.00)
Receptor status	
ER/PR positive	167 (55.12)
ER/PR, HER-2 positive	44 (14.52)
HER-2 positive	26 (8.58)
Triple negative	66 (21.78)
Total	303 (100.00)

ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2

Table 2: Disease-free survival amongst patients in this study

Number of years after treatment	Number of patients with DFS	DFS rate (%)
1	242	79.80
2	171	56.57
3	156	51.51
4	144	47.47
5	144	47.47

DFS: Disease-free survival

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between the patients' age, gender and OS was not statistically significant with $P = 0.575$ and 0.820, respectively.

DISCUSSION

Survival after treatment for breast cancer and factors that influence such survival have been the subject of a number of research work worldwide. [2,4,13,15-17] Objective assessment for the effect of suggested influencers of survival would entail elimination of confounding factors and would yield results that may improve management of breast cancer patients.

This study showed that AJCC Stage III breast cancer was most common amongst those aged 41–50 years (36.63%). This finding may be related to the fact that breast cancer commonly occurs in this age group in Nigerians as reported by Agbo *et al*. from a study in Sokoto State, Northwestern Nigeria which noted a modal age range for AJCC Stage III breast cancer of 41–50 years. [20] Kene *et al*. reported that majority (57.40%) of the AJCC Stage III breast cancer patients seen in a study conducted in Northwestern Nigeria were in the 30–49 years old age group. [21] Adetifa *et al*. from a study conducted in Lagos State, Southwestern Nigeria reported that the highest prevalence of AJCC Stage III breast cancer was in those aged 25–45 years[3] which also contains a subset of the age range with the highest prevalence in the index study. Studies by Othieno-Abinya *et al*. in Kenya and Amir *et al*. in Tanzania both in Eastern Africa showed the median and mean age at diagnosis of AJCC Stage III breast cancer to be 44 years and 44.7 years, respectively. [22,23] These findings lend credence to the fact that AJCC Stage III breast cancer tends to occur 10–15 years earlier in Africans than in populations in North America. [24,25]

Table 3: Overall survival amongst patients in this study

Number of years after treatment	Number of patients with OS	OS rate (%)
1	245	80.80
2	187	61.61
3	168	55.56
4	156	51.51
5	153	50.50

OS: Overall survival

More of the patients in this study had left-sided tumours (54.37%). Kene *et al*., Anele *et al*. and Okobia *et al*. noted similar findings in their respective works amongst Nigerian patients. [21,26,27] The reason behind the higher prevalence of breast cancer on the left side amongst Nigerian patients was not apparent in this study neither was it stated in the earlier studies. Balabram *et al*. also noted the same finding from a study amongst Brazilian patients. [2] Further studies may therefore be necessary to elucidate factors that could underlie this finding.

Initial size of the tumour was significantly related to both DFS and OS ($P = 0.041$ and $P = 0.001$, respectively), as those with initial tumour size <100 cm^2 tended to have longer DFS and OS compared to those with initial size of 200–299 cm^2 who had DFS and OS averaging a third of those recorded by the former group. This is similar to what was noted by Balabram *et al*. while working amongst Brazilian patients. [2] The finding in the index study may be explained by the fact that survival (both DFS and OS) declines significantly with increasing tumour size at initial presentation as noted by earlier researchers on this subject. [28-30]

Response to neoadjuvant chemotherapy was significantly related to DFS and OS. DFS and OS were longer in those that had complete response to neoadjuvant chemotherapy than in those who had partial response. This may be related to the larger amount of residual disease in those with partial response to neoadjuvant chemotherapy as noted by a previous study. [31] Takahashi *et al*. and Ionta *et al*. also reported similar findings from their works amongst populations in Japan and Italy, respectively. [19,32]

The number of lymph nodes involved by the tumour also had significant relationship with DFS and OS. Those who had four or more lymph nodes involved by the tumour had lower DFS and OS than those with involvement of lesser number of nodes. This may be related to the fact that tumour deposits in lymph nodes present a ready source of tumour cells responsible for recurrent disease with consequent reduction in DFS and OS in such patients compared to those without lymph node invasion. [30] This has led some researchers to state that lymph node invasion

Table 4: Number of tumour-involved lymph nodes with corresponding disease-free survival and overall survival amongst patients in this study

Number of tumour-involved lymph nodes	1-year DFS rate (%)	5-year DFS rate (%)	1-year OS rate (%)	5-year OS rate (%)
0	40.20	23.74	40.42	25.30
1-2	23.94	14.24	24.30	15.20
3-4	11.97	7.12	12.10	7.58
>4	3.69	2.37	3.98	2.42
Total	79.80	47.47	80.80	50.50

DFS: Disease-free survival, OS: Overall survival

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had the highest impart on survival, followed closely by the size of the tumour. [2,19,33]

There was a significant relationship between DF, OS and tumour grade in this study. Patients who had Nottingham grade III tumours had shorter DFS and OS compared to those who had Nottingham grade I and grade II tumours. This may attributed to the aggressive biologic behavior of higher grade tumours which has been noted to be associated with lower survival. [2]

The receptor status of the tumours also showed significant relationship with survival. The shortest DFS and OS were noted with those who had HER-2-positive tumours followed by those who had triple-negative tumours while those who had ER/PR-positive tumours or triple-positive tumours had the longest DFS and OS. Patients with HER-2-positive tumours have been noted to have up to 50% chance of recurrence when treated with conventional cancer chemotherapeutic agents and this may underlie this finding in the index study while buttressing the need for targeted therapy in such patients as recommended by some researchers and guidelines. [33,34] The longer DFS and OS observed in ER/PR-positive tumours may be related to high levels of FOXA1 expression which is usual with this subset of breast cancer. [35] FOXA1 is a member of the family of transcription factors associated with oestrogen receptors and its positivity in tumours has been noted to be associated with better survival and is also useful for therapeutic decision making. [35]

The 1-year DFS was 79.80% and progressively declined to 47.47% at 5 years post-therapy. These figures are lower than those reported from studies in patients in Brazil (5-year DFS of 62.50%) and Switzerland (5-year DFS of 81.00%) and this difference may be attributed to the influence of ease of access to healthcare services as well as ease of getting quality treatment for their ailments in the general populace in those countries. [36,37]

The 1-year OS was 80.80% and progressively declined to 50.50% at 5 years post-therapy. These figures fall within the range reported for patients in the United States of America (5-year OS of 41.00%-66.7%) but are lower than that reported for patients in Barcelona, Spain (5-year OS of 70.10%).[14,38] The difference between the figure in this study and that from Spain may be related to enhanced treatment of Stage III breast cancer patients in Spain (such as the use of poly ADP ribose polymerase (PARP) inhibitors such as veliparib, talazoparib and olaparib) with subsequent improvements in 5-year OS of such patients. [39]

Limitations of the study

This study was conducted in a single centre. A multi-centre study would have given a much larger study population than the 334 patients recruited in this study and would have also made comparisons of treatment outcomes for the patients between the centres involved possible.

CONCLUSION

The 5-year DFS and OS were 47.47% and 50.50%, respectively. The initial size of the lesion, response to neoadjuvant therapy, number of lymph nodes involved by the tumour, grade of the tumour and receptor status had statistically significant relationship with DFS and OS.

Recommendations

There should be collaboration between the Federal Government of Nigeria, pharmaceutical companies and interested non-governmental organisations to subsidise the price of targeted therapy for breast cancer (trastuzumab) and make it affordable for patients who have tumours that overexpress HER-2 receptors. The use of enhanced treatment (such as PARP inhibitors such as veliparib, talazoparib and olaparib) for patients with Stage III breast cancer may also increase survival in such patients.

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Conflicts of interest

There are no conflicts of interest.

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