

PREDICTORS AND CHARACTERISTICS OF PATIENTS LOST TO BREAST CANCER FOLLOW-UP CARE IN SOUTHWESTERN NIGERIA

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ABSTRACT

Background: Breast cancer is the commonest cancer in Nigeria and a significant proportion of patients discontinue follow-up care after treatment. The aim of this study is to describe the characteristics and predictors of loss to follow-up among breast cancer patients on follow-up care at Radiotherapy Department, University College Hospital (UCH), Ibadan.

Methodology: This is a retrospective study of patients with histological diagnosis of breast cancer post-radiotherapy and/or chemotherapy with or without surgery between 1st January, 2005 to 31st December, 2014. Data extraction form was used to obtain information on socio-demographic and disease related variables and time to loss to follow-up.

Loss to follow-up rates and its predictors were estimated using Kaplan Meier, Log rank test and Cox's regression methods of analyses.

Results: Five hundred and four breast cancer patients were studied. Their mean age was 47.7 (± 10.6) years, 58.2% presented late with advanced stage disease, 40% and 39% had metastasis and anaemia respectively. The 5 year and 10 year loss to follow-up rates were 69.8% and 92.6% respectively. The median loss to follow-up time was 44 months. Patients loss to follow-up were more likely to be older than 45 years [HR=1.415; 95% CI, 1.044-1.917], have metastasis [HR=1.793; 95% CI, 1.3962.302], be anaemic [HR=1.404; 95% CI, 1.1201.760] and have late stage disease [HR=1.310; 95% CI, 1.047-1.639].

Conclusion: Breast cancer patients studied have high loss to follow-up rates due to late presentation and high disease burden related factors.

Keywords: Breast cancer, Loss to Follow-up, Characteristics, Predictors

INTRODUCTION

Breast cancer is the leading female malignancy in the world and the most common cancer in Nigeria¹. The peak incidence of the disease in Nigeria is at least a decade earlier compared to the Caucasians.² The incidence of breast cancer in Nigeria is on the increase from 13.8 to 15.3 per 100,000 population in 1992 to 116 per 100,000 in 2001 in Ibadan.³ The major constraint in the management of breast cancer patients in Nigeria is the limitation of resources. Our patients bear the burden of out of pocket payment for cancer treatment in a low resource country. Having a population of over 150million and a Gross Domestic Product of about 2000US Dollar per capita annually, Nigeria ranks among the poorest nations in the world⁴ (World Economic Outlook Database, 2012), with a Health Insurance Scheme that is still in its formative stage, paying for cancer treatment is an uphill task for the majority of

patients, as such significant proportion of patients may not present for treatment or complete the prescribed courses of treatment due to deficiencies in treatment availability, accessibility and affordability in many developing countries.⁵

Once the patients are treated for breast cancer, post therapy surveillance, that is, follow-up is required to diagnose and treat early recurrence of the disease, treatment of therapy related side effects, psychosocial aspects of support and counselling, encouragement and support for physical exercise and weight reduction to improve quality of life, re-evaluation of current adjuvant therapy and monitoring of compliance with endocrine therapies. These benefits are however, missed by patients loss to follow-up. Recent study in Ibadan reported that majority of breast cancer recurrences were detected within 2 years of primary treatment,⁶ this situation supports the fact that follow-up evaluations

should be closely monitored.

There are nine functional radiotherapy centres in Nigeria today with a population of over 150 million. This comes to one radiotherapy centre to about 20 million persons, as against the WHO recommendation of 1: 250,000 persons,⁷ this means that patients will have to travel long distances for radiotherapy. Longer distances means more financial loss as patient's family members may have to take more time off from work, leading to loss of pay, the costs of feeding, travelling and hotel after arriving at UCH, Ibadan can be very high to discourage the patient from seeking routine follow-up.

The aim of this study was to define the characteristics and identify predictors of loss to follow-up among breast cancer patients. It is essential to target this group of patients and understand the socio-demographic and disease related barriers to post therapy follow-up care in order to provide strategic interventions to prevent them.

METHODOLOGY

Data of five hundred and four patients diagnosed with breast cancer and registered in the Radiotherapy Clinic Cancer registry of the University College Hospital, Ibadan from 1st January, 2005 to 31st December, 2014 (10 years) were retrospectively collected for the study. The department is equipped with a Telecobalt and HDR Co60 brachytherapy machines with modern treatment planning system. Patients included in the study were breast cancer cases referred for adjuvant chemotherapy and/or radiotherapy to the breast or chest wall. Hospital case files with follow-up records and radiotherapy treatment cards of breast cancer patients attended to was retrieved and the data was collected using a data extraction form, the data includes age at diagnosis, sex, educational status, marital status, menopausal status, parity, stage of breast cancer at diagnosis, grade of differentiation, histology of breast cancer, lymph node status, development of metastasis, duration of symptoms before diagnosis, distance of home town to Ibadan (in Kilometres), and baseline packed cell volume (PCV). The status of patient on follow-up was defined as either loss to follow-up or censored (censored means death or survival beyond end of study) and time to event is defined as time to lost to follow-up or to censoring in months.

The data was analysed using SPSS version 16.0, frequency, percentage, mean, median, range and standard deviation were used to summarise the sociodemographic, clinical and treatment variables of the patients and presented using tables. Loss to follow-up rates were calculated using Kaplan-Meier method and compared using Log rank test. Log rank test was used to test for an association between dependent variable lost to

follow-up and independent variables such as age, educational level, marital status, menopausal status, duration of symptom before diagnosis, distance of home/town to Ibadan, stage of disease at presentation, lymph node status, histological grade, metastasis and anaemia. The analysis was considered to show significant association when the P-value was = 0.05. The clinical features were recoded (regrouped) into two groups for ease of comparison between the clinical subgroups. The variables recoded were age; grouped into younger patients (= 45 years) and older patients (above 45 years), educational status; low educational level (primary school and below) and high level (secondary school and above), marital status; into married and not married (single, divorced, widow, separated), menopausal status; premenopausal and postmenopausal, duration of breast cancer symptoms before diagnosis; into less than or equals to 12 months and above 12 months, distance of home town to Ibadan; into less than or equal to 50 KM that is for patients coming from (Ibadan and surrounding villages) and beyond 50 KM (Far from Ibadan), Manchester stage; into early stage (stage I&II) and late or advanced stage (stage III & IV), axillary node status; into negative axillary nodes and positive axillary nodes, histological grade; into well differentiation and moderate/poor differentiation, development metastasis; into presence of metastasis and absence of metastasis and PCV status; into Low PCV (<30% i.e., anaemia) and Normal PCV (=30% i.e., no anaemia). Multivariate analysis was carried out using Cox-proportional hazard models to determine the predictors of loss to follow-up. This was done using covariates that showed statistically significant association with loss to follow-up at p= 0.1 (covariates with significance at p= 0.1 instead of p= 0.05 was chosen in order to bring-in more variables to enrich the multivariate analysis) on bivariate analysis (Log-rank test). In analysis of loss to follow-up using Kaplan-Meier, time of origin was the time of breast cancer diagnosis. The patient status as at 31st Dec, 2014 was categorized as alive, dead or lost to follow-up. The endpoint of patients was loss to follow-up, patients that died before or found alive at end of December 2014 were censored. Ethical clearance to conduct the study was sought from the University of Ibadan / University College Hospital, Ibadan Joint Ethical Review Committee.

RESULTS:

CHARACTERISTICS OF BREAST CANCER PATIENTS STUDIED.

A total of 504 (Females: n=500, Males: n=4) patients

satisfied the inclusion criteria. The mean age of patients with breast cancer studied was 47.7 ± 10.3 years, most of the patients are between the ages of 41-50 years (34.1%), closely followed by 31-40 years (26.6%) and 51-60 (24.1%). The mean age for males and females were 61.3 and 47.6 respectively. Married patients 412 (81.7%) constituted the majority while 44 (8.7%), 23 (4.6%), 17 (3.4%), 7 (1.4), and 1 (0.2%) were widows, single, unknown, divorced and separated respectively. Patients without any form of formal education accounted for 182 (36.1%) followed by those with tertiary education 156 (31.0%) while patients with secondary, primary and below primary school educations accounted for 117 (23.2%), 41 (8.1%) and 8 (1.6%) respectively. Majority of women with breast cancer were postmenopausal 272 (54.0%) while 216 (42.9%) were pre-menopausal and 16 (3.1%) had unknown menopausal status. Thirty three (6.5%) of patients were nulliparous, 230 (45.6%) were multiparous, 231 (45.8%) were grand-multiparous while parity was unknown in 10 (2.1%) of patients. Mean duration of symptoms before diagnosis was 11.6 months, most patients 370 (73.4%) spent less than or equals 12 months with symptoms of breast cancer before diagnosis while 134 (26.6%) had symptoms for more than 12 months, 74 (14.7%) of patients came from within and around Ibadan (within 50KM distance) and 430 (85.3%) beyond 50KM. The commonest site of breast cancer was in the left breast 244 (48.5%) while the right breast accounts for about 227 (45.0%) and 33 (6.5%) of breast cancer was seen in bilateral breasts during the study. Stage I, II, III and IV accounted for 29 (5.8%), 177 (35.1%), 138 (27.4%) and 155 (30.8%) respectively. However, early stage breast cancer (stage I&II) accounted for 40.9% while late stage breast cancer (stage III & IV) constituted the majority 58.1%. Sixty two (12.3%) of patients had no axillary nodes detected while the majority of patients 418 (83%) had positive axillary nodes. Status of axillary nodes cannot be obtained in 24 (4.7%) of patients.

Invasive ductal carcinoma accounted for the commonest histological type of breast cancer seen 443 (87.9%) while invasive lobular carcinoma and inflammatory breast cancer accounted for 23 (4.6%) and 10 (2.0%) respectively. Grade I breast cancer accounted for 89 (17.7%), while grade II and grade III accounted for 303 (60.1%) and 84 (16.7%) respectively, the grade of 28(5.6%) patients was unknown. Two hundred and two (40.1%) of the patients presented with distant metastasis, however among the different sites of metastasis, bone was the commonest site 116 (23.0%) while lungs, liver and brain accounted for 104 (20.6%), 40 (7.9%) and 26 (5.2%) respectively.

Three hundred and ten (61.5%) had a normal PCV (PCV = 30%) at baseline before treatment, while

194 (38.5%) had low PCV (PCV < 30%). Most women patients had radical breast surgery 413 (81.9%) while 57 (11.3%) and 34 (6.8%) had breast conservative and no surgery respectively.

Table 1: Kaplan Meier Estimates of Loss To Follow-Up Of Breast Cancer Patients By Clinical Features.

Variable	MLT (months)	SE[s(t)]	95%CI	Log rank Chi-square	P-value
Age					
Younger patients = 45 yrs	44.0	2.965	38.18-49.81	3.498	0.061
Older patients > 45 years	44.0	2.325	39.44-48.56		
Educational level				1.053	0.305
Primary school and below	41.0	2.195	36.70-45.30		
Secondary school and above	47.0	2.265	42.60-51.40		
Marital status				8.289	0.004
Not married	39.0	2.315	34.50-43.50		
Married	45.0	1.954	41.20-48.80		
Menopausal status				2.965	0.085
Premenopausal	44.0	3.356	39.40-52.60		
Postmenopausal	45.0	1.876	41.30-48.70		
Distance of home/town to Ibadan				2.731	0.098
= 50 KM	53.0	3.982	45.20-60.80		
> 50KM	42.0	1.954	38.17-45.83		
Duration of symptoms before diagnosis				4.868	0.027
Up to 12 months	47.0	2.233	42.60-51.40		
Above 12 months	37.0	1.914	33.20-40.80		
Stage of disease				19.500	<0.001
Early stage (I&II)	51.0	2.416	46.30-55.70		
Late stage (III&IV)	37.0	1.542	34.00-40.00		
Axillary node status				1.600	0.198
No axillary nodes	51.0	6.717	38.00-64.00		
Presence of axillary nodes	44.0	2.023	40.00-48.00		
Grade of differentiation				1.360	0.244
Well differentiated	41.0	2.729	35.70-46-30		
Moderate/poor differentiated	45.0	2.334	40.40-49.60		
Metastasis				49.761	<0.001
Presence of metastasis	31.0	2.233	26.60-35.40		
No metastasis	51.0	2.213	46.70-55.30		
Baseline packed cell volume (PCV)				18.775	<0.001
Low PCV < 30%	38.0	2.147	33.80-42.20		
Normal PCV = 30%	47.0	2.183	42.70-51.30		

MDT=Median Loss To Follow-Up Time; CI=Confidence Interval; SE=Standard Error.

LOST TO FOLLOW-UP RATES OF BREAST CANCER PATIENTS STUDIED.

Breast cancer patients treated and followed-up had a 44 months mean time to loss to follow-up. The 1 year and 2 years lost to follow-up rates were 15.3% and 24.1% while 5 year and 10 year loss to follow-up rates were 69.8% and 92.6% respectively.

MEAN ESTIMATES OF LOST TO FOLLOW-UP OF BREAST CANCER PATIENTS BY CLINICAL FEATURES.

Table 1 above shows a Kaplan Meier log-rank test mean estimates of loss to follow-up durations by clinical features. Marital status, duration of symptoms before diagnosis, stage of disease, presence of metastasis and baseline PCV were found to be statistically significant at $P=0.5$ while covariates such as Age, educational level, menopausal status, distance of home to Ibadan, axillary node status and grade of differentiation were not statistically significant at $P=0.5$.

PREDICTORS OF LOSS TO FOLLOW-UP IN BREAST CANCER CARE.

The Multivariate analysis was done using Cox proportional Hazard model with covariates that showed statistically significant association with lost to follow-up at $P<0.1$ (instead of $P<0.05$) from Kaplan Meier Log rank test (see table 1). Table 2 below showed the results of the Cox proportional hazard model on variables associated with loss to follow-up. Patients with metastasis [HR=1.793; 95% CI, 1.396-2.302], anaemia [HR=1.404; 95% CI, 1.120-1.760], Advanced/late stage disease [HR=1.310; 95%CI, 1.047-1.639] and older age [HR=1.415; 95%CI, 1.044-1.917] are more likely to discontinue follow-up early.

Table 2: Cox Regression Analysis Of Hazard Ratios Of Predictors Of Loss To Follow-Up According To Clinical Features Of Breast Cancer Patients.

Variable	B	SE	HR	95%CI	P-value
Development of metastasis					
There is metastasis	0.584	0.128	1.793	1.396-2.302	<0.001*
No metastasis			1.00		
Baseline packed cell volume (PCV)					
Low (anaemia)	0.339	0.115	1.404	1.120-1.760	0.003*
Normal (no anaemia)			1.00		

Stage at presentation (Manchester stage)					
Late stage (Stage III&IV)	0.270	0.114	1.310	1.047-1.639	0.018*
Early stage (Stage I&II)			1.00		
Distance of home/town to Ibadan					
= 50 KM	-0.244	0.156	0.784	0.577-1.064	0.118
> 50KM			1.00		
Duration of symptoms before diagnosis					
= 12 months	-0.189	0.121	0.827	0.653-1.048	0.116
> 12 months			1.00		
Menopausal status					
Premenopausal patients	0.103	0.154	1.108	0.820-1.498	0.504
Postmenopausal patients			1.00		
Age					
Older patients	0.347	0.155	1.415	1.044-1.917	0.025*
Younger patients			1.00		
Marital status					
Not Married	0.208	0.136	1.231	0.943-1.606	0.126
Married			1.00		

$\hat{\alpha}$ = vector coefficient for predictor variable, SE=Standard Error, CI=Confidence Interval,

HR=Hazard Ratio, 1.00=Reference category,

* Statistically significant at 5% level.

DISCUSSION

The incidence and mortality of breast cancer is falling in developed world due to early detection and improved treatment methods, while in developing countries like Nigeria the reverse is the case. This study revealed a mean age of patients with breast cancer studied to be 47.7 ± 10.26 years and the peak age of occurrence at 40-49 years, from Ile Ife a similar finding was reported among breast cancer patients with a mean age 48 ± 12.3 years and peak age of 40-49 years.³ The result is also consistent with findings from Niger Delta, Nigeria,⁸ Kenya,⁹ and Beirut, Lebanon.¹⁰ However, a mean age of 58.0 years from the US reiterates the fact that breast cancer patients in this environment are a decade younger than those in Caucasians. Male breast cancer accounted for 0.8% of cases of breast cancer studied, this does not compare with previous studies done in Ibadan¹² and¹³ from Maiduguri, North Eastern Nigeria where they reported 2.9% and 3.7% respectively. The figure is also

consistent with figures among the Caucasians, where less than 1% were quoted.^{14,15,16} Our study showed that 6.5% are nulliparous while the majority 91.4% are either multiparous or grand-multiparous, these wouldn't have been the case since the higher the number of full term pregnancies, the greater the protection from breast cancer and that there is a reduction in risk of breast cancer by 7% for each birth after the first, in the absence of breast feeding and women who breast feed reduce their risk compared to those who do not.¹⁷

It is emphasized that prognosis is heavily dependent on stage of disease at presentation.¹⁸ Late presentation with advanced stage disease (stage III& IV) was seen in 58.2% of the patients studied, unfortunately when compared to earlier studies from Nigeria and sub-Saharan Africa the outlook remained poor and the same.^{3,6,19,20,21} The factors responsible for late presentation with advanced disease in this study are low and poor level of education, as 69% of the patients were not educated beyond secondary, almost half of the patients came from far places in Nigeria outside South Western states, mean duration of symptoms before diagnosis was 11.6 months, duration of 11.2 months was reported in Ife³ about 83% of these patients have detectable axillary nodes limited to or beyond the ipsilateral axilla. The low education level may lead to poor understanding of symptoms and compliance with measures for early detection and presentation. These patients are more likely to be of low socioeconomic class. About 40% of patients in this study had metastasis, this can be explained by the fact that large number of these patients presented late with advanced disease, had palpable axillary nodes within and beyond the axilla,²² a higher figure of 52% with metastasis was reported from Ile Ife while a lower figure of 26% was reported from the US.¹⁸ Racial differences in the tumour biology of breast cancer seen in Nigeria and African Americans compared to Caucasians point to possible differences in the aetiology or in the genetic make-up. Tumours in blacks tend to be more aggressive because most tumours diagnosed among blacks are Oestrogen receptor negative (ER Negative) and ER negative tumours tend to be poorly differentiated with shorter doubling time.^{23,24} ER receptor status could not be determined because is not routinely tested for in UCH, Ibadan due to limited resources. A significant proportion of these patients (38.5%) presented with anaemia. This is probably due to the large number of patients with advanced disease in this study. These patients have bulky disease and high tumour burden, thereby resulting in recurrent bleeding,

excessive metabolic demands and poor intake.

This study found that the predictors of loss to follow-up among breast cancer patients on follow-up care and therapy are advanced stage disease with distant organ metastasis and anaemia. Similar report was seen²⁵ from India and²⁶ South Bronx, the poorest district of the US demonstrating significant association of higher and poor disease burden with lost to follow-up. In the present analysis, patients with metastasis and anaemia were more likely to be lost to follow-up, as the disease progresses, the patient becomes more dependent and more support is needed to keep up with follow-up care. These trends were observed among patients with advanced stage cervical cancer in India.^{25,27} Thus patients without metastasis and anaemia and with better performance status were more likely and more capable to keep to their follow-up. This study also found that older patients are more likely to discontinue follow-up care early. This is because older patients may be more dependent on others, they are less likely to speak up as death is inevitable at such a fragile age and would like to avoid further painful treatment. However, younger patients may be more capable and can attend some of the visits on their own without depending on other family members. Older age as a predictor of discontinuation among breast cancer patients on follow-up therapy was also identified by.^{28,29,30}

Overall, loss to follow-up among breast cancer patients that are older and anaemic with advanced stage disease and metastasis might be explained by death. These patients have high disease burden that may result into gradual organs and systems failure and ultimately death.

CONCLUSION

The rates of loss to follow-up in breast cancer patients is very high in our environment. It is more common in the presence of late stage disease, metastasis and older aged non married patients.

RECOMMENDATIONS

- * Attention to non-compliance with follow-up should be addressed.
- * Supportive care should be given to non-married women particularly those with advanced stage disease and metastasis, in order to improve breast cancer outcomes in these patients.

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