

DETERMINANTS OF SURVIVAL OF CERVICAL CANCER PATIENTS IN A LOW-RESOURCE SETTING: A SINGLE INSTITUTION STUDY

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ABSTRACT

Introduction: Cervical cancer is the second commonest cancer, and foremost cause of death from cancer in Sub-Saharan Africa accounting for 117,944 new cases and 76,140 deaths in 2022. In Nigeria, Cervical cancer is the third commonest malignancy and third commonest cause of death from cancer patients. In low-resource countries, over 80% of cervical cancer cases are very advanced at presentation and poor access to treatment, and many socio-demographic and cultural barriers; ultimately cumulating into poor clinical outcomes. **Objective:** The objective of the study was to determine the 2-year and 5-year survival of cervical cancer patients and factors that determine them. **Methodology:** This was a retrospective cross-sectional study. Patients' data which include socio-demographic characteristics, clinic-pathological variables and treatments received, were obtained from the clinical and treatment notes from the health information unit as well as the radiotherapy treatment room. Patients who were treated in the Department of Radiotherapy and Oncology, Ahmadu Bello University Teaching Hospital Zaria, Kaduna state, Nigeria from January 2008 to December 2012 were considered for the study. Survival analysis was done using the Kaplan-Meier method and Cox regression. **Result:** A total of 243 patients were included in the study. Their age ranged between 25.0-80.0 years with the mean age been 50.7 ± 11.1 years. Most of the patients 225(92.6%) presented with locally advanced disease (FIGO stage IIB- IVA). Only 19(8%) of patients received concurrent chemoradiation, while 159 (65.4%) received external beam radiotherapy to total dose of 50Gy. A total of 113 (46%), 121(50%), and 9(4%) of patients had complete, partial and no response following treatment, respectively. The 2-year and 5-year overall survival were 85.2% and 31.7% respectively. Following adjustment for independent variables using Cox regression, age of patient, clinical stage at diagnosis and response following treatment were significantly associated with survival. **Conclusion:** Survival of cervical cancer in this study was low and similar to survival studies in Nigeria and other Sub-Saharan African countries; when compared to survival of the same disease for high income countries. Factors that are associated with survival include age and stage of disease at diagnosis, and clinical response following treatment. Multi-facet efforts need to be put in place towards designing and implementing strategies that will help address the problems of cervical cancer care in low-resource settings, which will ultimately improve its overall survival.

Keywords: Cervical cancer, survival, FIGO stage, response, age

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INTRODUCTION

Cancer of the cervix is a major health problem world globally with estimated 662,301 new cases and 348,874, making it the 8th commonest cancer, and 9th commonest cause of death from cancer in 2022.¹ The large majority of global burden of cervical cancer occurs in the less developed regions like Africa, Southeast Asia and Latin America which accounts for about 85% of the global burden of cervical cancer.^{1,2} For instance, cervical cancer is the second commonest cancer, and foremost cause of death from cancer in Sub-Saharan Africa accounting for 117,944 new cases and 76,140 deaths in 2022.³ In Nigeria, Cervical cancer is the third commonest malignancy and third commonest cause of death from cancer patients.⁴

The morbidity and mortality from cervical cancer in Nigeria and other Sub-Saharan Africa countries reflect the absence of effective national cancer control programs, including vaccination, screening, early detection and financial access to radiotherapy and other treatments.⁵ In low-resource countries, over 80% of cervical cancer cases are very advanced at presentation and poor access to treatment, and many socio-demographic and cultural barriers; ultimately cumulating into poor clinical outcomes.⁶ To put it clearly, the mortality-incidence ratio for cervical cancer is currently 0.65 for Sub-Saharan Africa.³

The management of cervical cancer usually involved the use of multiple modalities which include surgery, radiotherapy, chemotherapy and other supportive care.⁷ It is an established fact that increased survival is associated with treatment using radiation therapy and concomitant chemotherapy, compared to use of surgery or radiotherapy alone. Many randomized studies have laid credence to this fact.^{9,10} Other tumour factors like stage, histological type, duration of illness with cancer, presence of

comorbid conditions affect clinical outcome of cervical cancer independent of treatment received.^{10,11}

Overall, the 5-year survival rate for cervical cancer varies widely with stage at diagnosis, with values of about 91%, 60% and 19% for early, locally advanced and metastatic diseases respectively.¹¹ On the average, 5-year survival for cervical cancer in sub-Saharan Africa is 33%,¹²⁻¹⁴ which is in sharp contrast with values of 90%¹⁵ and 67%¹⁶ for the United States and United Kingdom which are high-income countries. There are very few studies that accessed survival rates of cervical cancer in Nigeria. This research is a single-institution-based study that aim to assess the survival of cervical cancer patients and factors associated with their survival.

MATERIAL AND METHODS

Study Area

The study was conducted in Ahmadu Bello University Teaching Hospital Zaria (ABUTH), which is a tertiary healthcare facility and a Centre of excellence for cervical cancer care in Northern Nigeria. Nigeria in the period from January 2008 to December 2012.

Study Design

It was a retrospective cross- sectional study.

Study Population

The study population comprised of all histologically confirmed locally advanced cervical cancer (FIGO StagesIIa-IVa) cancer patients who were treated in ABUTH within the period from January 2008 to December 2012 that received at least 3 cycles of chemotherapy, external beam radiotherapy to the primary site, and had at least 1 follow up visit following treatment. Patients with missing or incomplete information about treatment received were excluded from the study.

Data Collection Tool

Data was collected from patients' clinical case notes and treatment records in the radiotherapy and brachytherapy treatment rooms. These were recorded using a semi-structured questionnaire.

Measurement of study variables

The categorical variables were recorded using frequencies and percentage, while the numerical variables will be presented using mean and standard deviation, for normally distributed data; and median and interquartile range for skewed data.

Statistical analysis

Data was saved using Microsoft Excel application and then transferred into the Statistical Packages for Social Sciences (SPSS) version 20.0 manufactured by the International Business Machines Corporation (IBM), California. The variables were analysed and summarized using tables and charts. Sociodemographic, clinical and treatment variables of patients were presented in tables, graphs, histogram and charts using frequency and percentages. The survival probabilities were computed using Kaplan-Meier method of estimating the survival times for patients. Log-rank test was used to identify predictors of survival. The P value of, 0.05 was considered statistically significant

Ethical consideration

Ethical approval was obtained from Ahmadu Bello University Teaching Hospital Health Research and Ethics Committee, and was given identity number ABUTHZ/HREC/D31/2018. The data obtained were de-identified to avoid tracing information obtained to any of the cancer patients of the study whether they are dead or alive.

RESULTS

A total of 626 patients were seen during the study period, out of which 243 patient files who met the selection criteria were recruited in the study. The age of cervical cancer patients ranged between 25.0-80.0 years with the mean age been 50.7 ± 11.1 years, the median and modal age was 50.0 years (Table 1)

Majority of the patients 139(57.2%) had given birth to five or more children. About a third 80 (32.9%) had sexual debut at age of 17 or less, while about half 120 (49%) had sexual debut between 18 to 20 years. Only 19 (7.8%) of patients were retroviral positive at the time of diagnosis; while about one-fifth 50(20.6%) of the patients had at least one pap smear done prior to diagnosis of cervical cancer (Table 1).

Out of all the enrolled patients, Only 18 (7.4%) presented with early disease (FIGO stage IIA), most 225 (92.6%) had locally advanced disease at diagnosis (FIGO stage IIB – IVA) (Table 1). Most of the patients 223 (91.8%) received platinum-based chemotherapy while 20 (8.2%) received other forms of chemotherapy. Most of the patients 172 (70.8%) received induction (neoadjuvant) chemotherapy, while 52 (21.4%) and 19 (7.8%) of patients received adjuvant and concurrent chemoradiation respectively.

The majority of patients 171 (70.4%) had EBRT as adjuvant treatment, while 53 (21.8%) and 19(7.8%) received it as primary treatment and concurrent chemoradiotherapy respectively.

Only 25 (10.3%) of patients received low-dose brachytherapy following external beam radiotherapy to a total dose of 75 Gy or above; while majority 159 (64.5%) received 50 Gy of external beam radiotherapy, and 59 (24.3%) received external beam radiotherapy of 54 Gy.

Table 1: Sociodemographic and clinic-pathological characteristics of respondents (n= 243)

Variable	Frequency (%)
Age (years)	
< 40	35 (14.4)
40- 49	69 (28.4)
50- 59	83 (34.2)
≥ 60	56 (23.0)
Marital status	
Married	231 (95.0)
Single	6 (2.5)
Widowed	6 (2.5)
Age at sexual debut (years)	
≤ 17	80 (32.9)
18- 20	120 (49.4)
≥ 21	43 (17.7)
Parity	
Nulliparity	12 (4.9)
1 - 4	92 (37.9)
≥5	139 (57.2)
Education	
Non- formal	148 (60.9)
Formal	95 (39.1)
Occupation	
Civil servant	5 (2.1)
Farming	15 (6.2)
Trading	13 (5.3)
Others	44 (18.1)
Not employed	166 (68.3)
Retroviral status	
Positive	19 (7.8)
Negative	224 (92.2)
Pap smear prior to diagnosis	
Yes	50 (20.6)
No	193 (79.4)
FIGO STAGE	
IIA	18 (7.4)
IIB	106 (43.6)
IIIA	39 (16.1)
IIIB	70 (28.8)
IVA	10 (4.1)
Histology type	
Squamous cell carcinoma (SCC)	66 (27.2)
Large Cell non-Keratinising SCC	81 (33.3)
Large Cell Keratinising SCC	66 (27.2)
Adenocarcinoma	11 (4.5)
Others	19 (7.8)
Histology grade	
Well differentiated	12 (4.9)
Moderately differentiated	7 (2.9)
Poorly differentiated	31 (12.8)
Undocumented	193 (79.4)
Width of tumour at diagnosis	
≤ 4 cm	60 (24.7)
> 4cm	183 (75.3)

Response to treatment: A total of 113 (46.5%) of patients had complete response following treatment while 121(49.8%) had partial response and 9(3.9%) had no response to treatment.

Survival Rates: the 2-year survival among cervical cancer patients in this study was 85.2%, with 12.8% dead and 2.1% lost to follow-up. Conversely, the 5-year survival among cervical cancer patients had only 31.7% being alive, while 65.0% were dead and 3.3% lost to follow-up. The 2-year and 5-year survival rates were disaggregated based on age, source of referral, stage and grade of disease at presentation; retroviral

status of patient and illness duration and presented in Table 2.

Cox Regression Model for Independent Variables

The median survival time is 46.0 months (CI:40.6-51.4). Only 3.3% of the study population died as a result of other causes. Unadjusted and adjusted hazards ratios on variables are presented in Table 3. Variables with significant unadjusted ratios hazard ratios include age (<40 and 40-49 years), length of tumor (≤ 4 , 4.1-5.0 and 5.1-6.0 cm), width of tumor (≤ 4 , 4.1-5.0 and 6.1-7.0 cm), stage at presentation(stage 2a, 2b, 3a and 3b), total doses of radiotherapy (50 and 54) and response to treatment (Table 3)

Table 2. Distribution of the 2-year and 5-year survival rates of cervical cancer patients by selected variables

Variable	2-year survival rate (%)	5 years survival rate (%)
Age (years)		
<40	88.6	57.1
40-49	95.7	34.8
50-59	79.5	28.9
60+	78.6	16.1
Source of referral		
Secondary	79.7	23.7
Tertiary	87.0	34.2
Stage of presentation		
Stage 2a	94.4	44.4
Stage 2b	94.3	40.6
Stage 3a	79.5	25.6
Stage 3b	72.9	21.4
Stage 4a	80.0	10.0
Grade at presentation		
Well differentiated	100	58.3
Moderately differentiated	71.4	42.9
Poorly differentiated	74.2	29.0
Undocumented	86.5	30.1
Retroviral status		
Positive	89.5	26.3
Negative	84.8	32.1
Duration of illness prior to presentation		
<6 months	84.4	32.2
6-12 months	87.8	31.3
>12 months	78.9	31.6

Table 3. Cox Regression Model for Independent Variables

Variable	Unadjusted		Adjusted	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (years)				
<40	0.261 (0.125-0.546)	<0.001	0.162 (0.070-0.375)	<0.001
40-49	0.307 (0.176-0.538)	<0.001	0.340 (0.189-0.610)	<0.001
50-59	0.531 (0.330-0.855)	0.531	0.548 (0.323-0.926)	0.026
60+ (ref)				
Ethnic group				
Hausa	1.257 (0.822-1.921)	0.291	1.171 (0.749-1.831)	0.489
Yoruba	1.297 (0.614-2.741)	0.496	0.848 (0.366-1.968)	0.702
Igbo	0.698 (0.169-2.880)	0.619	0.534 (0.121-2.347)	0.406
Others (ref)				
Length of tumour (cm)				
≤ 4				
4.1-5.0	0.453 (0.236-0.876)	0.017	0.295 (0.090-0.965)	0.043
5.1-6.0	0.509 (0.290-0.893)	0.018	0.758 (0.300-1.913)	0.557
6.1-7.0	0.496 (0.274-0.897)	0.020	0.472 (0.209-1.066)	0.071
>7.0 (ref)	0.618 (0.327-1.167)	0.138	0.593 (0.274-1.281)	0.183
Width of tumour (cm)				
≤ 4	0.727 (0.257-0.867)	0.016	2.435 (0.751-7.897)	0.138
4.1-5.0	0.311 (0.160-0.606)	0.001	1.111 (0.394-3.197)	0.842
5.1-6.0	0.676 (0.366-1.250)	0.212	2.025 (0.843-4.864)	0.114
6.1-7.0	0.504 (0.262-0.970)	0.040	0.665 (0.295-1.498)	0.325
>7.0 (ref)				
Stage of disease at presentation				
Stage 2a				
Stage 2b	0.195 (0.065-0.584)	0.003	0.326 (0.090-1.182)	0.088
Stage 3a	0.190 (0.090-0.404)	<0.001	0.243 (0.095-0.623)	0.003
Stage 3b	0.431 (0.196-0.949)	0.037	0.484 (0.191-1.229)	0.127
Stage 4a (ref)	0.477 (0.229-0.996)	0.049	0.512 (0.213-1.230)	0.134
Total doses radiotherapy				
50				
54	3.865 (1.405-10.636)	0.009	2.009 (0.668-6.047)	0.214
75 (ref)	4.616 (1.611-13.230)	0.004	2.748 (0.901-8.376)	0.075
Response				
Complete	0.120 (0.049-0.293)	<0.001	0.080 (0.026-0.241)	<0.001
Partial	0.291 (0.124-0.682)	0.004	0.172 (0.061-0.483)	0.001
No response (ref)				

However, after adjusting for variables, patients aged < 40 years (HR=0.162, 95% CI=0.070-0.375), 40-49 years (HR=0.340; 95%CI=0.189-0.610) and 50-59 years (HR=0.548; 95%CI=0.323-0.926) were about four, three and two times less likely to die from cervical cancer compared to those aged 60 years and above respectively (Table 3, Figure 1).

Patients who presented at stageIIa and stageIIb (HR=0.243; 95% CI=0.095-0.623) were about four times less likely to die from cervical cancer compared to those who

present at stage 4 a respectively (Table 3, Figure 2).

There was no significant difference in survival based on tumour length, tumour width and total dose of radiation received (Table 3).

However, patients who had complete and partial responses to treatment were about twelve times (HR=0.080; 95%CI=0.026-0.241) and six times (HR=0.172; 95% CI=0.061-0.483) less likely to die from cervical cancer compared to those who had no response. These were statistically significant at $p<0.05$ (Table 3).

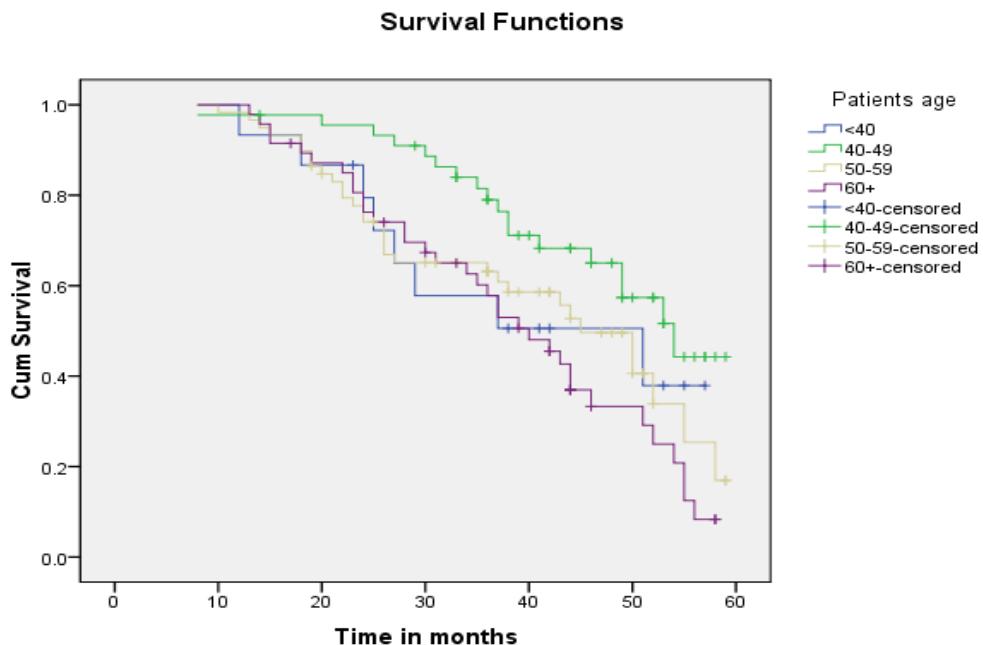


Figure 1. Survival segregated by age category of cervical cancer patients

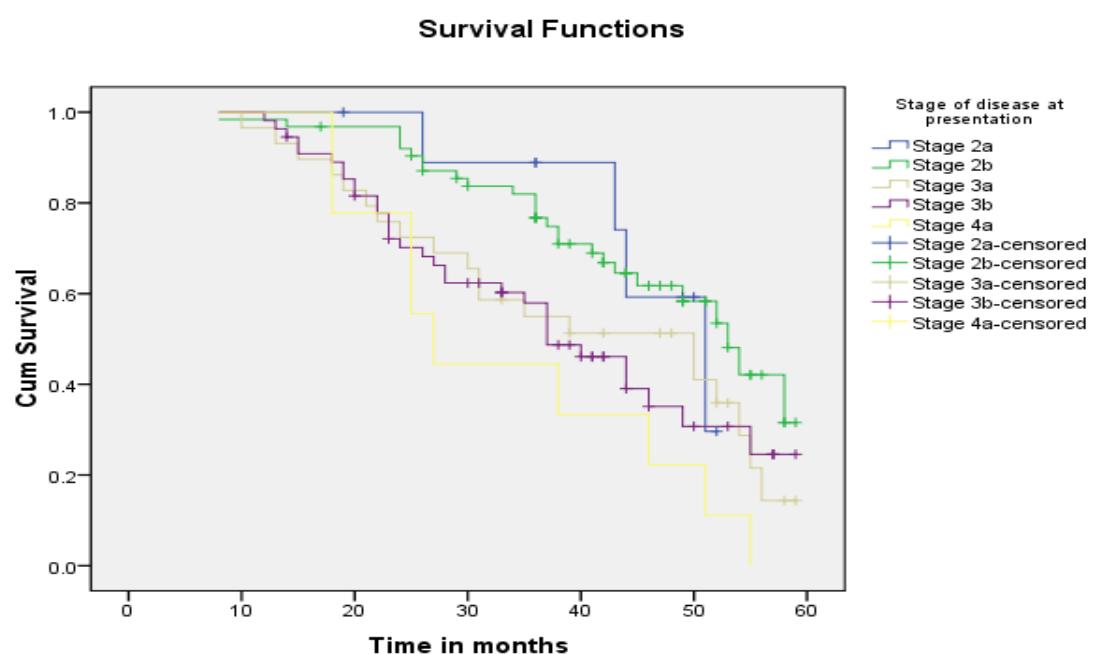


Figure 2. Survival segregated by stage at diagnosis of cervical cancer patients

DISCUSSION

From the study, the overall 2-year and 5-year survival survival rate for cervical cancer patients were 85.2%, and 31.7% respectively. A similar study conducted in an apex tertiary hospital in Southwestern Nigeria, had the 2-year and 5-year survival for cervical cancer as 69.6% and 45.8%

respectively.¹⁷ The findings were equivocal when compared to the index study as the 2-year survival was higher, while the 5-year survival was lower in value to the index study. However, the findings of this study remained consistent with findings of other studies from Sub-saharan African region. For instance, a study conducted in Ghana

showed 3-year and 5-year survival of 39% and 30% respectively.¹⁸ Furthermore, another study from Ghana found 3-year and 5-year survival at 51.5% and 32.4% respectively.¹⁹ The above studies, along with other studies have consistently demonstrated the relatively low survival as a result of poor clinical outcome for cervical cancer patients in low-resource settings as a result of combination of many factors.^{20, 21}

This study demonstrated a wide disparity in survival between patients with FIGO stage IIA/IIB when compared to FIGO stage IVA as the later are four times likely to die compared to the former. This is consistent with other studies from low-resource setting which found those with lower stage at diagnosis having significant higher chance of survival.¹⁷⁻²⁰

In this study, patients aged below 40 years, 40- 49 years and those 50-59 years were about four, three and two times less likely to die from cervical cancer compared to those aged 60 years and above respectively, due to more advanced stage at presentation, suboptimal treatments and associated comorbidities. This finding is consistent with a study in California, which found that 5- year survival of cervical cancer patients was significantly lower in women above 65 years compared to those 65 years or below.²² Furthermore, a systematic review and meta-analysis of East African studies on cervical cancer found age to be significantly associated with survival with younger age having better prognosis.²³ Other studies from Sub- Saharan Africa and Middle East have arrived at similar conclusions of age being significantly associated with survival in cervical cancer patients.^{13, 24} However, another study in Jeddah Saudi Arabia, found no significant difference in survival across the age groups.²⁵

The study also found that cervical cancer patients with complete response were twelve times more likely to survive than those with no response, while those with partial response were six times more likely to survive compared to those with no

response following treatment. This finding was supported by a study in Botswana which clearly demonstrated that response to treatment affected the overall survival of cervical cancer patients.²⁶

Overall, the findings from this study demonstrated that effective cervical cancer control in low-resource setting requires a multi-facet approach that involves raising awareness and knowledge on cervical cancer in the community and effective community-based screening. These measures will drastically reduce late presentation with advanced disease, and improve survival significantly as patients diagnosed at earlier stage disease have more likelihood of survival.^{20, 28} In addition, more efforts will be required to ensure geographic and financial access to comprehensive treatment of cervical cancer which include chemotherapy, surgery, external beam radiotherapy, brachytherapy and supportive care.^{28,29} This is because cervical cancer patients who received timely and appropriate treatment for the stage of their disease were more likely to have complete response to treatment, which in turn favours overall survival.¹⁰

Most definitely, the implementation of the World Health organization (WHO) strategy for elimination of cervical cancer will address the gaps of management of cervical cancer in low-resource setting, ultimately eliminating factors that contribute to poor survival of cervical cancer patients.³² This strategy targets getting 90% of girls less than 15 years vaccinated against human papilloma virus (HPV), screening 70% of women aged 35- 45 years with high quality tests and treating 90% of women who come down with diagnosis of cervical cancer.³⁰

The strength of this study is that it accrued a large number of patients across in a centre that served as an apex tertiary health institution that served for referral of cervical cancer patients across Northern Nigeria and beyond, over a 5-year period thereby giving it a good generalizability (external validity). However, the limitation of the study was it being a retrospective study with many missing dates, thereby

having the possibility of introducing recruitment bias.

CONCLUSION

Survival of cervical cancer in this study was low and similar to survival studies in Nigeria and other Sub-Saharan African countries; when compared to survival of the same disease for high income countries. Factors that are associated with survival include age and stage of disease at diagnosis, and clinical response following treatment. Multi-facet efforts need to be put in place towards designing and implementing strategies that will help address the problems of cervical cancer care in low-resource settings, which will ultimately improve its overall survival.

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