The Survival of Patients with Cancer of the Cervix in Nairobi, Kenya

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SUMMARY

Cervical cancer ranks as the second most frequent cancer among women globally. The majority of patients present in advanced disease stages, leading to high mortality rates. Information on the survival of cervical cancer patients in Kenya is lacking which is necessary in estimating the burden of the disease and informing policy shifts in management of the disease. The objective of this study was to estimate the cure fraction, the survival time and rate and, identify covariates that significantly affect the survival of patients with cervical cancer in Nairobi, Kenya. A retrospective, descriptive non-intervention study of selected patients with cancer of the cervix was carried out in Nairobi, Kenya. 211 patients with an initial diagnosis of cancer of the cervix between January 2006 and June 2007 were followed up for five years respectively. 108 (51.18%) of them were confirmed dead within that period, 15 (7.11%) were still alive and 88 (41.70%) were lost to follow up. Most of the patients were from low income areas (60.19%) within Nairobi, followed by those from middle income areas (37.91%) with the smallest proportion coming from high income areas (1.90%). The patients' ages ranged from 14 to 76 years; the median mean age was 46 years while the mean was 46.45 years. The probability of surviving beyond the maximum amount of time (60 months) was estimated at 0.198 using the Kaplan-Meier estimator. The cumulative proportion surviving at the end of the study interval was 0.67 at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV. The median survival time at stage I is 60 months, 23.02 months at stage II, 10.14 months at stage III and 9.73 at stage IV. The Cox regression model was used to identify covariates that significantly affect the survival duration of cervical cancer patients. The age of patients, stage at diagnosis and level of education significantly affected the survival. Patients with an initial diagnosis at stage II, stage III and stage IV had an increased risk of death 6.29, 13.71 and 15.47 times respectively those at stage I. Therefore, early detection of cervical cancer and prompt treatment should be taken up to improve the overall survival of the patients.

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Introduction

Cancer of the cervix is a serious public health problem globally, especially in developing countries where it is the second most common cancer in women. Every year, approximately half a million new cases of cancer of the cervix are reported globally, 80% of which occurs in developing countries, where the disease is

also the leading cause of cancer-related death among women [1]. The huge disparities in morbidity and mortality between developed and developing countries exist largely because over the last few decades, developed countries have implemented effective programmes for its prevention, in some countries reducing incidence and mortality by up to 80% [1, 2].

Most cervical cancer cases (99%) are linked to genital infection with human papillomavirus (HPV) especially type 16 or 18 [3]. HPV is a common sexually-transmitted virus that does not always cause symptomatic disease in infected individuals. Existing evidence indicates that more than 97% of all cancers of the cervix are associated with persistent infection of HPV. Cancer of the cervix is a disease with a long latent period [4, 5, 6]. In sub-Saharan Africa, the causes of high mortality rates are associated with poor access to medical facilities, poor nutrition, late presentation with the disease, poor quality care, low rate of follow-up, and women not completing treatment due to economic barriers. Cultural factors also play a role in the rates of cervical cancer including: early marriage, polygamous marriage, and high gender parity. These factors afflict women and girls living in rural areas at much greater rates [7].

In Kenya, recent estimates indicate that every year 2454 women are diagnosed with cervical cancer and 1676 die of the disease. Cervical cancer ranks as the second most frequent cancer among women in Kenya. About 38.8% of women in the general population are estimated to harbour cervical HPV infection at a given time, and 60.9% of invasive cervical cancers are attributed to HPVs 16 or 18 [7].

The survival of cancer patients is an important indicator of their prognosis. Currently, there are no survival studies that have been conducted on cervical cancer in Kenya, unlike in other parts of the world. This study therefore comes up with the findings on the five year survival rates and survival duration of patients with cervical cancer considering the initial stage of diagnosis and other covariates such as education level, age, smoking behaviour, alcohol intake, grade of cervical cancer, treatment given, residence and HIV status of patient.

Methodology

Study design

A retrospective, descriptive non-intervention study was carried out in which cervical cancer cases diagnosed in January 2005 and June 2007 were followed up to January 2010 and June 2012 for five years respectively to determine an individual's survival duration. It involved the use available information from medical records on cervical cancer patients and follow up of patients by contacting and interviewing the patients or their next of kin to determine the vital status of patients in case of missing on unclear details from available records. Follow up was also done using medical records at the Nairobi hospice for patients who had been referred there.

Study site

This study was conducted at Kenyatta National Hospital in Nairobi, Kenya. This facility was ideal for this study because it provides high quality and specialized cancer treatment and it has the capacity to handle all referrals in Kenya. This makes it a hospital of choice for a large proportion of cancer patients.

Study population

The study population were women who were residents of Nairobi, had a new diagnosis of cervical cancer between January 2005 and June 2007 and were

aged between 14 and 79 years. Women were excluded if they were aged beyond 80 years because the cure fraction is less reliable for this age group [8] or were diagnosed based on death certificate or autopsy.

Sampling

Using the WHO manual 'Sample size determination in Health studies' [9] the sample size was estimated as follows:

Test survival rate	50%
Anticipated survival rate	40%
Level of significance (α)	5%
Power of the test (β)	90%
Confidence level (Z)	95%

Using the formula

$$n = \left\{Z_{1-\alpha}\sqrt{[P_0(1-P_0)]} + Z_{1-\beta}\sqrt{[P_a(1-P_a)]}\right\}^2 / (P_0 - P_a)^2$$

For $P_0 = 0.50$ and $P_a = 0.40$ the sample size is 211.

The purposive sampling method was used. Criteria used were according to the explained inclusion and exclusion criteria.

Data management and analysis

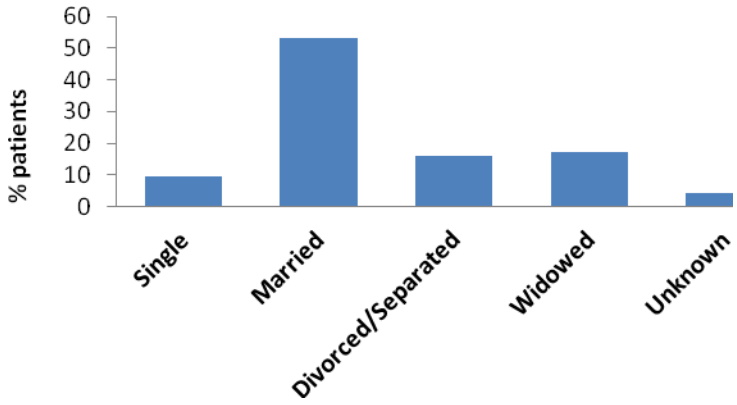
Excel was used to capture data and produce some descriptive graphics. R version 2.15.1[10] and SPSS statistical software were used for statistical analysis. Survival analysis was performed using the Kaplan-Meier estimator. The Life Table was used to estimate both the cure fraction and the relative survival of patients. The log-rank test was performed to compare the expected number of events at each stage of diagnosis against the observed values. The Cox Regression model was used to study the association between the survival with potential risk factors and other covariates.

Results

Description of the dataset

211 patients with an initial diagnosis of cancer of the cervix between January, 2006 and June 2007 were followed up for five years respectively. 108 (51.18%) of them were confirmed dead within that period, 15 (7.11%) were still alive and 88 (41.70%) were lost to follow up. The patients' ages ranged from 14 to 76 years; the median age was 46 years while the mean was 46.45 years. 53.08% of these patients were married as depicted in Figure 1.

Figure 1: Marital Status of patients

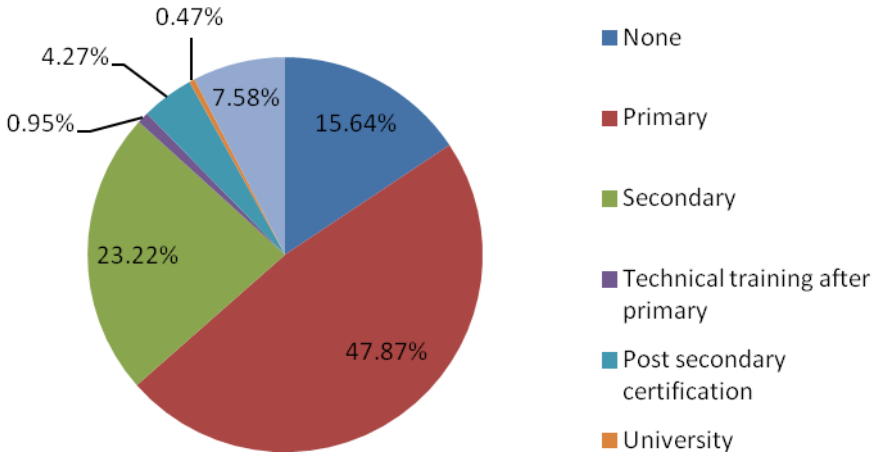


In addition 49.76% and 47.39% of the patients had never engaged in cigarette smoking and alcohol intake respectively. Only 1.42% and 3.32% had a history of smoking and drinking alcohol respectively while the rest their drinking and alcohol intake behaviour could not be ascertained.

The residential areas in Nairobi were classified as high, middle and low income areas [11]. 60.19% of the patients were from low income areas, 37.91% from middle income areas with the smallest proportion coming from high income areas (1.90%).

The largest proportion of patients highest level of education attained was primary at 47.87% and the least having attained university education at 0.47% (Figure 2).

Figure 2: Level of education of patients



Diagnosis

There is evidence that most of the participants were not engaging in regular screening for cervical cancer; most of the cases were diagnosed at advanced stages that is as from stage II (Table 4) and most of them were also diagnosed histologically (Table 1). 57.35% were diagnosed histologically and at the same time at late stages of the tumor that is as from stage II (Table 1). Most of the tumors were poorly differentiated (19.43%). The HIV status of most patients could not be ascertained from medical records of the patients which were heavily relied on to provide accurate information.

Table 1: Patients' diagnostic details

	Number of patients	% patients
Method of diagnosis		
Histology	121	57.35
Cytology	48	22.75
Others	42	19.90
Stage		
Stage I	15	7.11
Stage II	50	23.70
Stage III	63	29.86
Stage IV	30	14.22
Unknown	50	25.12
Grade		
Well differentiated	14	6.64
Moderately differentiated	38	18.01
Poorly differentiated	41	19.43
Undifferentiated/Anaplastic	10	14.22
Unknown	108	25.12
HIV Status		
Negative	48	22.7
Positive	25	11.8
Unknown	138	65.4

Treatment

The treatment given to individual patients indicate that 46.45% of the patients were surgically treated, 60.19% received external radiotherapy while only 4.74% received Brachytherapy and 14.22% were given chemotherapy (Table 2).

Table 2: Treatment options given to patients

	Frequency	Percent
None / Unknown	45	21.33
S	36	17.06
S+ EBR	46	21.80
S + EBR + B	2	0.95
S + EBR + B + C	3	1.42
S + EBR + C	11	5.21
EBR	50	23.70
EBR + C	10	4.74
EBR + B + C	3	1.42
EBR + B	2	0.95
C	3	1.42

Key

S – Surgery

EBR – External Beam Radiation

B – Brachytherapy (Internal Beam Radiation)

C – Chemotherapy

Cure fraction

The cumulative proportion that survived at the end of the study interval was 0.67 at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV (Table 3). The greatest number and proportion of terminal events occurred as from stage II.

Table 3: Proportion surviving at the end of the Study Interval

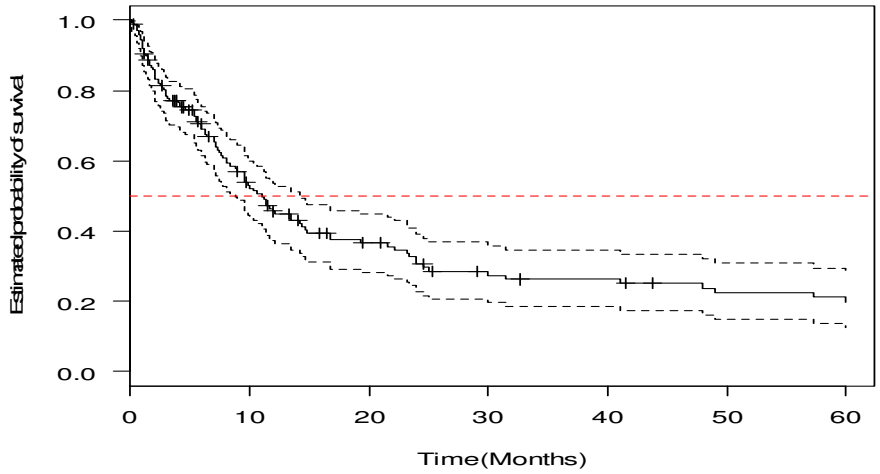
Stage	Proportion Surviving
Stage I	0.67
Stage II	0.36
Stage III	0.15
Stage IV	0.00
Unknown	0.09

Survival time

Right censoring was done on observations that were either alive or lost to follow up. The probability of surviving beyond five years is estimated at 0.198 using the Kaplan-Meier estimator. The survival curve, Figure 3 gives a visual representation of the survival trend. Drops in the survival curve occur whenever the

terminal event occurs to a patient. The survival curve describes the relationship between the probability of survival and time as inverse. The red dotted line shows that at 10 months about 50% of patients were still alive (Figure 3). The Figure shows a sharp drop in the survival of patients within the first few (approximately 15) months, indicating that most of the patients experienced the event early.

Figure 3: Survival curve



Comparing Survival with Stage as Strata

Using the log-rank test, the survival at different stages of diagnosis were significantly different (χ^2 = 20, df=4, ρ<0.05) indicating that the survival at different stages of diagnosis are significantly different as shown in Table 4.

Table 4: Survival difference

	No. of Patients	Observed	Expected	(O-)^2/E	(O-E)^2/V
Stage I	15	2	12.5	8.81	10.19
Stage II	50	21	30.8	3.10	4.43
Stage III	63	32	26.8	1.02	1.39
Stage IV	30	19	12.6	3.25	3.76
Unknown	53	34	25.4	2.94	3.88

$$Chi\ Square\ test\ statistic = \frac{\Sigma(Observed - Expected)^2}{Expected}$$

$$The\ log rank\ test\ statistic = \frac{\Sigma(Observed - Expected)^2}{Variance\ of\ (Observed - Expected)}$$

The median survival time of patients declined sharply with advancement in stages at initial diagnosis (Table 3).

Table 5: Median Survival Times

Stage	Median Time (Months)
Stage I	60.000
Stage II	23.023
Stage III	10.136
Stage IV	9.730
Unknown	8.057

The effects of covariates on the survival

To check whether all the nine variables deserved to be included in the final Cox Proportional Hazards regression model, stepwise regression was used. The AIC was lowest when four covariates are removed that is grade, HIV status, Drinking behaviour and Smoking behaviour as shown in Table 6. They were therefore excluded in subsequent analysis.

Table 6: Stepwise regression

Covariate	Df	AIC
none		922.04
Age	1	925.26
Education	2	926.12
Income zone	2	927.85
Treatment	10	932.43
Stage	4	939.79

After removing the variables that do not deserve to be in the model, Table 7 shows that the age of a patient, stage at initial diagnosis and level of education significantly affects the survival, and some treatment options also significantly affect the survival as well. Three treatment options which are S + EBR + B + C, S + EBR + C and EBR significantly affect the survival of patients ($p < 0.05$). There is evidence of a steady increase in the risk of death with advancements in stage at initial diagnosis. Patients with an initial diagnosis at stage II, stage III and stage IV have an increased risk of death 6.29, 13.71 and 15.47 times respectively those at stage I. Patients who had attended school beyond primary school were at a reduced risk compared to those who attended none/primary education.

Table 7: Final Cox PH regression model

	HR	95 % CI LL	95 % CI UL	p
Age	9.782e-01	0.95977	0.9971	0.02400
Level of education				
None/Primary	1			
Post primary education	4.953e-01	0.30030	0.8170	0.00590
Unknown education level	8.400e-01	0.38277	1.8434	0.66000
Income zone				
High income zone	1			
Medium income zone	5.414e+07	0.00000	Inf	1.00000
Low income zone	4.109e+07	0.00000	Inf	1.00000
Stage				
Stage I	1			
Stage II	6.294e+00	1.42400	27.8220	0.01500
Stage III	1.371e+01	3.08593	60.9422	0.00058
Stage IV	1.547e+01	3.28162	72.8937	0.00054
Unknown stage	1.122e+01	2.51520	50.0218	0.00150
Treatment				
None/Unknown	1			
S	7.306e-01	0.36332	1.4691	0.38000
S+ EBR	9.154e-01	0.51936	1.6134	0.76000
S + EBR + B	2.251e-01	0.02905	1.7436	0.15000
S + EBR + B + C	1.086e-01	0.01413	0.8353	0.03300
S + EBR + C	2.553e-01	0.10209	0.6382	0.00350
EBR	4.799e-01	0.27368	0.8415	0.01000
EBR + C	3.838e-01	0.14550	1.0123	0.05300
EBR + B + C	1.919e-08	0.00000	Inf	1.00000
EBR + B	7.799e-01	0.09626	6.3197	0.82000
C	4.119e-01	0.05238	3.2397	0.40000

Discussion

This study has demonstrated that the probability of surviving beyond five years when a patient is diagnosed with cancer of the cervix is estimated at 0.198 using the Kaplan-Meier estimator and the cumulative proportion surviving at the end of the study interval is 0.67 at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV. The median survival time at stage I is 60 months, 23.02 months at stage II, 10.14 months at stage III and 9.73 at stage IV. A

similar study of 261 patients with cancer of the cervix registered by the Kampala population-based cancer registry, Uganda, between 1995 and 1997 had overall observed and relative survival for 3 years was 52.4% and 59.9% respectively [12]. This indicates that the more than 50% of patients in Kampala survived beyond three years while in this study only 26.3% of patients survived beyond three years.

According to the Cox regression model that was used in this study to identify covariates that significantly affect the survival of patients with cancer of the cervix; the age of patients, stage at diagnosis and level of education proved to be significant. Some treatment options also proved to significantly affect the survival of patients. Only 7.11% of patients were ascertained to have had a diagnosis at stage I which shows that most of the patients were diagnosed at advanced stages. Also among cases that were treated by radiotherapy in Nairobi between 1974 and 1979 patients with an initial presentation at stage I was only 7% [13]. Similar studies conducted in Africa show that the stage at diagnosis is mostly advanced; the case of Kampala, Uganda where they recorded 27.9% of patients with an initial diagnosis at stage I is more than three times the proportion in this study. This difference is attributed to high levels of health awareness and easy access to medical facilities in Kampala [12]. This explains why the survival is low. In another study stage proved to be the only covariate that influences the survival significantly [2].

Stage is important in determining the nature of treatment; at KNH patients between stage I and III are given radiotherapy treatment while those at stage IV are given chemotherapy treatment. Brachytherapy otherwise called internal beam radiation allows use of a higher total dose of radiation to treat a smaller area and in a shorter time than is possible with external beam radiation treatment. 60.67% of patients had an initial diagnosis between stage I and III and 60.19% were given external radiotherapy treatment. From an oncologist's perspective at KNH, the amount of radiation therapy for curative cases should be about 80 gray (Gy) but most patients receive about 50Gy. This is because most of the patients in this study were being referred to Mulago Hospital in Kampala, Uganda for brachytherapy but because most of them come from low income zones they could not afford it. 60.19% of patients in this study received external radiotherapy while only 4.74% received Brachytherapy. In the Kampala study only one in four patients (16 out of 63) had received both external beam and internal radiation, almost half of the patients (30 out of 63) received radiotherapy treatment by external beam alone and nine cases by internal radiation alone [12].

In another study the following variables were analyzed: age; tumor staging; histopathological type of tumor; level of education; skin color; and year of diagnosis in association with the survival using Cox proportional hazards regression model. As for level of education, those with 11 years of schooling or more showed a significantly better survival [14]. On the other hand this study showed that patients who had attended school beyond primary school were at a reduced risk compared to those who attended none/primary education.

Conclusion

The findings of this research show that the survival of patients is poor compared to other studies carried out in Africa. Patients with distant metastasis have an increased risk of death compared to those with localized cancer of the cervix. Early detection of

cervical cancer through regular screening and prompt and comprehensive treatment should be taken up to improve the overall survival of the patients.

Recommendations

An integrated national patient record keeping system linking all the medical facilities should be put in place by the government. This will make it easier to estimate disease burden and also assess interventions. For statistical analysis, actual statistics would be available rather than the use of estimates and better projections can be made.

Government intervention to reduce the burden of the cost of cancer treatment on the patients is very necessary. This is because as noted in this study cancer of the cervix affects mostly the poor who cannot afford cancer treatment. In most cases they are undertreated because they cannot meet the high costs associated with cancer treatment.

Improved awareness is an integral part of controlling cervical cancer. This can be done by having health education on cervical cancer incorporated in the teaching curriculums just like it has been done for HIV / AIDS, carrying out medical camps and community mobilization activities among other channels that can be used to make people aware. This will encourage women to attend regular screening therefore increasing chances of diagnosis at the precancerous stage which is 100% curable. As discovered in this study there have been cases of uptake of herbal therapy and seeking religious intervention and in turn ignoring prescribed medication; this has posed a great danger to the health of such patients who eventually go back to the hospitals when the situation is much worse. Therefore extensive and expansive awareness will reduce the high mortality associated with cancer of the cervix among women.

Decentralizing cancer treatment will to cut down on cost of transportation and associated costs as many patients are referred to Kenyatta National Hospital (KNH) given there are only two referral hospitals in Kenya. The amount of time one has to wait before they undergo especially curative treatment will be reduced. Long queues are witnessed at the Radiotherapy unit at KNH which make the conditions of patients to worsen in this event.

There is need for improved and more efficient equipment required in cancer treatment as the existing ones are greatly strained and some of them are archaic.

Further research on the time to remission and relapse, and treatment should be carried out to give more insight into the burden of the disease and disease management.

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