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Survival Analysis for the Recurrence of Cervical Cancer Among Patients Under Follows up Since 2012 to 2015

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Abstract
Background: Cancer is one of the leading causes of death in the world and represents a tremendous burden on patients, families and societies. The aim of the study was intended to identify the determinant risk factors for the recurrence of cervical cancer and model the recurrence rate of cervical cancer for patients who have already got their first treatment. **Methods**: A Sample of 371 cervical cancer patients who start their treatment in 2012 G.C was included. To identify risk factors of recurrence of cervical cancer and examine the association between the recurrence time with different demographic and medical variables, the proportional hazard Cox regression and the Weibull regression models were applied. **Result**: Among 371, 83(22.4%) of them experienced recurrence. The mean recurring survival time was 20.68months. Most recurrence is occurred at the beginning up to the tenth month after entry and then after the recurrence decreases. The cox model is $h_i(t, x_i,\beta)= h_o(t) \exp(\boldsymbol{\beta}_1 x_{i1}+ \boldsymbol{\beta}_1 x_{i2}+ \boldsymbol{\beta} x_{i3})$ and $h(t, x_i, \boldsymbol{\beta}_i)=1.13x10^{-4} \times 2.16t^{1.16} \times \exp(X\boldsymbol{\beta})$ was cox semi-parametric and full parametric model respectively. The recurrence is significantly dependent on aim of radiotherapy the patient took, number of cycles of chemotherapy that the patient took and smoking habits. From the Weibull regression model, the covariates that are selected by the model were stage, region of patients, marital status, number of cycles taken chemotherapy and smoking habit.**Conclusions**: Majority of the patients came to the black lion specialized Hospital, at the advanced stage of the disease especially at stage IIB and IIIB.
Keywords: Cervical cancer, Kaplan Meier, Recurrence, Proportional hazard.

Backgrounds

Recurrent cancer is when cancer cells are detected following the initial treatment with surgery (operation), radiotherapy or chemotherapy. Treatment options for recurrent cancer vary depending on the previous treatment, the location of the recurrence, and the overall condition of the patient. According to the study of (Chyong, 2004)) recurrence of the disease may depend on the extent of the disease, primary treatment and performance status/ comorbidity of the patient.

Cancer is one of the leading causes of death in the world and represents a tremendous burden on patients, families and societies (WHO, 2007). In 2008 there were 12.4 million new cases of cancer diagnosed and 7.6 million deaths from the disease (Boyle P. & Levin, 2008).

Based on projections, cancer deaths will continue to rise(American cancer society, 2006). By the year 2030 the burden is set to be more than double. There will be 26.4 million cancer cases, 17 million deaths and 75 million people living with the disease. More than half of cancer cases and 60% of deaths from cancer occur in less developed countries (World Health Organization, 2008). The lifetime risk of developing cancer is now more than one in three and by 2015 this is expected to rise to one in two (Peedell C, 2005).

Cervical cancer is the third most common cancer in women after breast and colorectal cancers and is one of the leading causes of cancer death among women in the world, (S. H. Ferlay J, Bray F, Forman D, Mathers C, Parkin DM,, 2010,). Cervical cancer is the top cancer site for women in most East African and South Asian countries both in terms of incidence and mortality. In 2008, approximately 530,000 women were diagnosed with invasive cervical cancer worldwide and 275,000 women died from it. (Arbyn M et al., 2011) (S. H. Ferlay J, Bray F, Forman D, Mathers C, Parkin DM,, 2010,) Indeed, developing countries as a whole experience a disproportionate share of the disease burden, accounting for 86% of all cervical cancer cases and 88% of all cervical cancer deaths worldwide, (Ferlay J et al., 2008) (Arbyn M et al., 2011) (Jemal A, 2011).

Cervical cancer constitutes a major public health threat to women in many low and medium resourced countries in South and Central America, sub-Saharan Africa, South and Southeast Asia where it is still the leading type of cancer among women; ((Awodele O et al., 2011; Castellsagué S et al., 2007).

WHO guidelines for cervical cancer recommend the conventional Papanicolaou test as a routine screening test in the female population (WHO, 2007) Screening coverage of 80 % or more of the female population is considered to be a successful rate of screening. However, From 1999 to 2004, only 5 % of the women in low-income countries received a Pap smear) (Alliance for Cervical Cancer Prevention, 2007). cervical cancer incidence rates have decreased dramatically since the implementation of the Papanicolaou cervical cancer screening test, or smear, in the 1940s (Elliott V. S., 2007). The Papanicolaou smear facilitates such early

detection of precancerous cervical lesions and established cervical cancer that with subsequent intervention, this cancer can often be prevented or even successfully treated (National cancer Institute, 2016).

Even though Papanicolaou smear test is available, in 2005 there were over 500, 000 new cases of Cervical cancer, of which over 90% were in developing countries. It is estimated that over 1 million women worldwide currently have cervical cancer, most of who have not been diagnosed, or have no access to treatment that could cure them or prolong their life. In 2005, almost 260, 000 women died of the disease, nearly 95% of them in developing countries, making cervical cancer one of the gravest threats to women's lives. In many developing countries, access to health services is limited and screening for cervical cancer is either non-existent or reaches few of the women who need it(WHO/UNICEF, 2006).

This study aimed:

- To estimate the survival function $\hat{S}(t)$ of cervical cancer patients.
- To estimate the survival time for the patients.
- To compare the recurrence of cervical cancer disease among different levels of risk factors.
- To find the mean survival time that the cervical cancer recurs for different characteristics of cervical cancer patients.
- To fit cox semi-parametric and full parametric model.

Methods

Study Area

The study was conducted in Addis Ababa Black lion Hospital which is the the capital city of Ethiopia. As of 2013 the city had 3.3 million inhabitants with male to female ratio of 0.91 (CSA, 2008). Regarding medical service, currently the city has 41 hospitals, 28 health centers, 35 health posts and more than 500 clinics. The Federal Ministry of Health estimates that there could be more than 150,000 cancer cases in Ethiopia each year, but available data is limited. As the nation's sole cancer referral center, Black Lion Hospital is treating only about one percent of these patients. Health experts explain that many Ethiopians with cancer never seek medical treatment and, of those who do, they may not be referred to the cancer center in Addis Ababa.

Study Design, and Source Population

The study is retrospective study that all the events - exposure and subsequent development of the recurrence of the cervical cancer had already occurred in the past; the researchers merely collect the data and investigate the risk of developing the recurrence of the disease if exposed to a particular risk factor. The source of the data was from the patients who were registered at the Black lion Specialized Hospital with the case of cervical cancer in 2012 G.C and who have been on follow up to February 2015

Sample size determination

Sample size was determined using formula:

$$n_o = \frac{\frac{Z^2P(1-P)}{d^2}}{1+\frac{1}{N}\left(\frac{Z^2P(1-P)}{d^2}-1\right)}$$ Where n_o= the sample size needed, N = the total population size in Black lion hospital in 2012 G.C (N=780), Z = the inverse of the standard normal cumulative distribution that correspond to the level of confidence, Where Z is the upper α/2 points of standard normal distribution. α =0.05 significance level, which is Z=1.96, p= 21% proportion of cervical cancer patients at which the disease relapse again (Sheibani et al., 2009.), d = the level of precision (maximum allowable error). Since $\frac{n_o}{N}$ > 5% we used $n=\frac{n_o}{1+\frac{n_o-1}{N}}$ Hence, the sample size with, *N*= 780, together with above specifications *n*=371.

Sampling procedure

Simple ransom sampling methods were used between the first two cards then an Every 2 card of systematic sampling has been used.

Exclusion criteria: Samples with not full information on their follow up card is omitted.

Data collection procedure

The data was secondary data and collected using trained enumerators from the follow up cards of patients. From the patients' card the age, the stage of the disease when they were referred to the hospital, the type of treatment the patients took (surgery, chemotherapy and radiotherapy), regions and other medical information had collected. Data collecting was carried out in the time interval of 01-03- 2015 to 16-04- 2015 G.C.

Operational definitions

Survival time: In survival the time that is to be counted starting from the day the patient took the first treatment up to the time that the disease reappears again, or survive up to the end date the study completed. It was measured in month.

Event: a case will be considered as survival event when the cervical cancer reappears again in the same place for cervical cancer patients who are already treated.

Censored: for this research, survival data was considered as censored data for any of the following reasons:

I. Patients who were completely cured from cervical cancer by their first treatment or died before coming to the Hospital.
II. Patients who took the treatment and those who did not come again to Black Lion specialized hospital despite the reappearance of the cervical cancer.
III. Patients who had come to the hospital just for the follow up, but recurrence of the cervical cancer did not observed during the study period.

Data analysis procedures

In the analysis of this data the combination different statistical soft wares such as, SPSS version 20, SAS 9.2, STATA 13 and R 3.2 have been used for cross checking the output. SAS was the most software used. STATA and SAS were mostly used of graphics. During Analysis Survival models such Hazard, semi parametrics (cox) and full parametrics Weibulll Accelerated Failure Time model were used. In multivariate survival analysis of recurrence of cervical cancer using Cox proportional hazards model by the backward Wald method three predictor variables were selected by the model. The covariates selected by the Cox proportional hazards model were the number aim of radiotherapy the patient took, number of cycles the patient took chemotherapy and smoking habit at significance of ($P \leq 0.05$).

Graphical method for proportional hazards assumption: the variables included in the final model (aim of radiotherapy, number of cycles, chemotherapy taken and smoking) were fulfilled the proportional hazards assumption because the log minus log versus time is parallel for the four variables. The assumption of proportional hazards was scaled Schoenfeld graph which indicates the relation of residual versus time. The proportional hazards assumption is fulfilled if the graph has straight line around zero. Because if the PH property holds, then we would expect the difference between covariate values at failure times versus a weighted average of the covariate values to display no temporal trends. In residual plots, we might expect the slope of the (re-scaled) Schoenfeld residuals with respect to time should be zero. So, in this graph, it is true that aim of radiotherapy, treatment taken, cycles of chemotherapy and smoking habit fulfilled the assumption as the graph of residual versus time does not show any definite pattern. This is the basic idea behind graphical methods.

Model adequacy

There is no influential observation in the data as all the dfbetas value are less than $2/\sqrt{n}$ or all dfbetas are less than cut off point for the dfbeta value 1. $2/\sqrt{371} = 0.104$ or 1

Model goodness of fit

The model goodness of fit is checked using the R^2. From the result of the LL(p) becomes 712.398 and the LL(O) is 744.46 where LL(P) model with covariate and LL(O) the null model. So R^2 is found to be 16% using equation. This indicates the model is fitted well because R^2 is small

Data Quality Management

To ensure data quality, Data were analyzed combination of different software's.

Results

Survival analysis for the time to recur of the disease

Among 371 sampled patients, 83(22.4%) of the experienced recurrence of cervical cancer. The mean survival time of the disease that was recurring was 20.68 month with standard error of 1.01 where median and standard error are 21.110 and 2.468 respectively.

The estimated Kaplan Meier recurrence survival time for the cervical cancer patients

Most events (recurrence) is occurred at the beginning up to the tenth month after entry and then after the recurrence decreases (Figure)

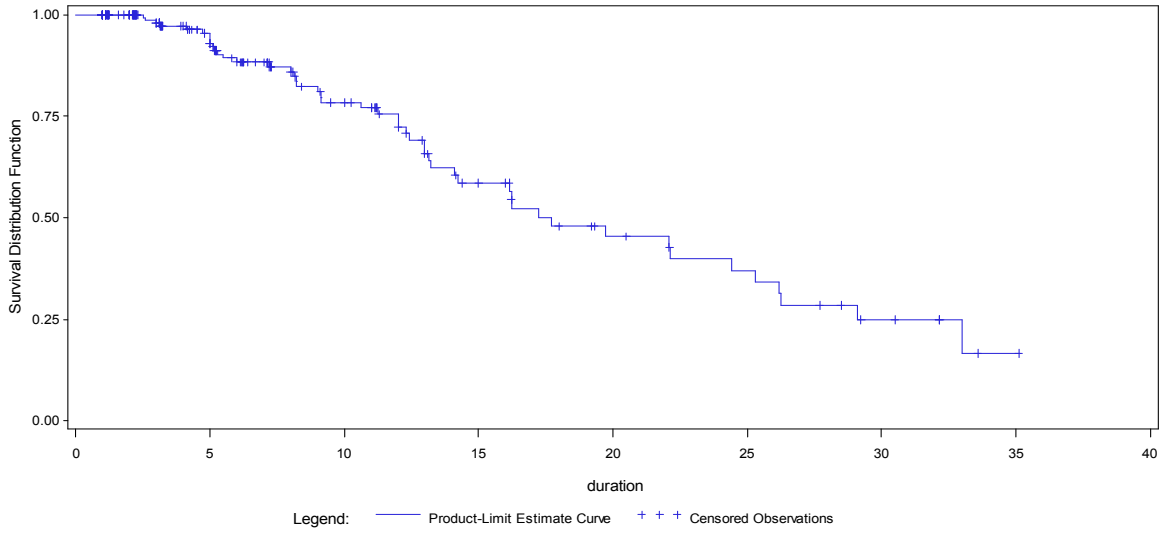

Figure 1: Kaplan Meier plot of survival time for the recurrence of cervical cancer among patients under follows up since 2012 to 2015 at black lion specialized Hospital

Comparison of survival curves

The log-rank (mantel-cox) test showed that survival curves for the variables region of patient, aim of radiotherapy taken, initial treatment the patient took, number of cycles of chemotherapy and smoking habit are all different across their level (Table 1)

Table 1: Log Rank test for comparison of survival curves for the recurrence of cervical cancer among patients under follows up since 2012 to 2015 at black lion specialized Hospital

covariate	Chi square	Df	Sign
Age	8.123	6	0.223*
Region	12.415	5	0.03
Aim of radiotherapy	6.253	2	0.016
Treatment taken	8.143	3	0.043
Number of cycles chemo taken	17.688	4	0.001
Stages of cervical cancer	17.684	12	0.123*
Marital status	3.640	2	0.162*
Smoking habit	5.75	1	0.017

*=insignificant

From the total of the patients, 37.5% have taken radiation therapy treatment of which in 21% the disease recur and 84.9% are censored. 4.6 % are those who took surgery and 5 recurrent patients. Of the total patients 189 are smokers and the disease recur in 52 of them. Non-smoker incorporates 182 of the total patient where the disease recur in 31of them. In marital status of the patients 126 are divorced and the disease re occur again in 31 of the patients. Most of the patients (143) come to the black lion hospital at stage IIIB, with this stage in 35 patients the diseases recur. In stage IIB, 95 patients are exposed to disease and 20 are recurrent.

From those patients who came to be treated, 121 have not taken radiotherapy of which 31 are recurrent, 131 took palliative aim of radiotherapy treatment of these, for 27 recurrence of cervical cancer had detected. The left 119 have taken radical aim of radiotherapy of which 25 are recurrent. Among the total number of patients 157 has not taken chemotherapy and in 26 of them diseases recur. The number of patients that took first cycle chemotherapy is 103 of which 30 are recurrent. A small number of patients (12) took fourth cycle chemotherapy of which in 2 of them the disease recurs and 83.3% are censored.

In considering age interval age of the patients, 33.42 % are in the age interval 41-50 years of this 28 patients had been diagnosed as recurrence of cervical cancer. In terms of the region 30.2 % are from Oromia region of which the disease reoccurred in 24 of them where as 78.6% are censored. The highest recurrence is in Addis Ababa region and Oromia which is 24 of the patient recurred in both regions.

The mean survival time for the patients who have not radiotherapy is 20.407 with standard error of 1.637, for palliative aim of radiotherapy the mean is 22.52 with standard error 1.62. For the cervical cancer patients taken radical aim of radiotherapy the mean and standard error are 18.24 and 2.02 respectively. Considering the chemo radiation therapy the mean and standard error are 16.872 and 1.884 respectively .The patients that took radiation has the mean and standard error of 23.411 and 1.738 respectively.

The mean and standard error for the second cycle chemotherapy are 23.21 and 2.171 respectively and for those who have not taken chemotherapy the mean and standard error are 23.672 and 1.66 respectively. From Kaplan-Meier survival estimator of considering the patients with smoking habit, has 18.396 months mean survival time until the recurrence of cervical cancer with the standard error of 1.299. The mean survival time of widowed is 22.204 with standard error of 1.793 and the mean and standard of married and divorced are 22.095 and 17.19 ,1.685and 1.528 respectively. Finally for the region of the patients, the mean survival time for those from Addis abeba region have mean and standard error of 24.105 and 1.624 respectively whereas that of cervical cancer patients from Southern Nations and Nationalities People (SNNP) and Tigray have mean and standard error of 14.427, 2.331 and 21.534, 5.409 respectively. Those from Amhara and Oromia region have mean 19.08 and 18.014 and standard error of 1.974 and 1.532 respectively

Kaplan Meier survival curve different types of variables

The survival curve is highest for those patients who took surgery at the end. It is highest for Addis Ababa's region and lowest for others region. The log-rank test of region revealed that the survival time of patients is different across the region. The patients that took second cycle chemotherapy have higher survival curve almost at the end. The survival curves are higher for patients taken palliative aim at the middle and also at the end of the study. Concerning stage of the disease, it was highest for the stage IA and stage II. The Kaplan Meier curve is higher for the patients of age group 20-30 at the beginning .patients with age group 41-50 have lowest survival curve at the end. More recurrence of age is occurred almost at middle of the curve. Nonsmokers have higher survival time than the smoker. Divorced women have lowest survival time whereas the widowed have higher survival curve at the end. From the log rank test we have observed that the survival curves are not different for the groups of marital status, this is may be why the curves are crossing each other somewhere at the middle

Cox Univariate and Multiple covariate model analysis for recurrence time of cervical cancer

Under Cox Univariate analysis variables cycles of chemotherapy, treatment taken, smoking habit and, region are significant factors for recurrence of cervical cancer. The hazard rate of cervical cancer patients in SNNP is 2.734 times greater than that of Addis Ababa region (H.R=2.734, 95% CI=1.153,6.485), for the patients in Amhara region the hazard rate is 1.786 times greater than that of Addis Ababa with(HR=1.786,95% CI=0.985,3.238).

The hazard risk of cervical cancer patients of smoker is 2.866 times greater than that of no-smoker. Cycles of chemotherapy is significant and the hazard of patients taken first cycle chemotherapy decreases 0.492 times that of patients no taken chemotherapy (HR=0.492, 95% CI=0.115, 2.102). The hazard of patients that chemotherapy two cycles their hazard increases 1.366 times that of not taken chemotherapy with (HR=1.366,95%CI=0.325,5.744). Those patients who took chemotherapy for three and four cycles their hazard decreases 0.5533 and 0.991 times that of not taken chemotherapy respectively.

The hazard of patients taken radical aim of radiotherapy is 2.91 times greater than that of patients no taken radiotherapy. Hazard rate of taking first cycle chemotherapy is 0.18 times lower than that of not taking chemotherapy (HR=0.18, 95% CI=0.025-1.279, p=0.086). The hazard of patients taking second cycle chemotherapy is 0.738 lower than that of not taking chemotherapy (HR=0.738, 95% CI=0.170-3.3213, p=0.686). The hazard rate of cervical cancer patients who took third cycle chemotherapy is 0.225 times lower than of patients not taken chemotherapy (HR=.225,95% CI=0.047-1.074,p=0.061).For the patients who took fourth cycle chemotherapy the hazard is .415 times lower than that of not taken chemotherapy (HR=..415, 95% CI=.086-2.007, p=0.274).The hazard of smoker is 1.711 times greater than that of non-smoker (HR=1.711, 95% CI=1.071-2.732, p=0.024).

The cox model is $h_i(t, x_i,\beta)= h_o(t)\ exp(\boldsymbol{\beta}_1 x_{i1}+ \boldsymbol{\beta}_1 x_{i2}+ \boldsymbol{\beta} x_{i3})$ based on this let us predict for a hypothetical women.

For women who has taken chemotherapy for one cycle (x_1) and also taken palliative aim of radiotherapy(x_2) and who is smoker (x_3) her hazard will be predicted as follows.

HR= $exp\ (\boldsymbol{\beta}_1 x_{i1}+ \boldsymbol{\beta}_1 x_{i2}+ \boldsymbol{\beta} x_{i3})$ =exp (-1.72x1+0.308x1+1x 0.537) = exp (-.845)=0.42

For women who have not taken chemotherapy, taking palliative aim of radiotherapy and who is smoker the hazard will be

$exp(\boldsymbol{\beta}_1 x_{i1}+ \boldsymbol{\beta}_1 x_{i2}+ \boldsymbol{\beta} x_{i3})$ =exp(0x0+0.308x1+0.537x1)= 2.33

For a women who has taken first cycle chemotherapy, radical aim of radiotherapy and who is non-smoker taken hypothetically the hazard will be:

$exp(\boldsymbol{\beta}_1 x_{i1}+ \boldsymbol{\beta}_1 x_{i2}+ \boldsymbol{\beta} x_{i3})$ =exp(-1.72x1+1.07x2+0x0)= 0.221

The first prediction when the person is smoker has been found to be 0.42 and when she is nonsmoker it becomes 0.221. In comparing the women who have taken chemotherapy for one cycle and not taken chemotherapy based on prediction the hazard of women that have not taken chemotherapy is higher than that of women who have taken chemotherapy.

Parametric regression models for the recurrence of cervical cancer.

The cox snell plot indicates the data is better fitted by Weibull distribution because the 45^0 lines s more expressed by Weibul distribution. Weibull regression model has the least Akaike Information Criteria (AIC) value Under ANOVA table for covariates in the final model of Weibull regression model, the risk factors which are associated with the recurrence of cervical cancer patients are region of patient, the number of cycles the patient took the chemotherapy, stage of the diseases, marital status and smoking habit of the patient.

There is an improvement in this model because the log-likelihood has decreased from -326.5 to -361 when covariates are included. Weibull distribution is selected for this data because of its AIC is small compared to the other three models and this is also supported by cox snell on the graph above. Using the regression model of equation and with the parameters found, the recurrence time of cervical cancer patients with Weibull distribution can expressed t~ Weibull ($\boldsymbol{\alpha}$,μ) , with parameters estimated μ =exp(k) where k is the intercept k=4.14 so exp (k)=exp(4.14) = 62.8. And $\boldsymbol{\alpha} = \frac{1}{\sigma} = \frac{1}{0.462} = 2.16$.

Then the time is distributed with Weibull ($\boldsymbol{\alpha}$, μ), which is Weibull ~ (2.16, 62.8) Substituting the parameters in the final Weibull model with substitution of $\boldsymbol{\lambda} = \mu^{-\alpha} = (62.8)^{-2.16} = 1.13\text{x}10^{-4}$

Finally the weibul regression model that fits this data and other identical data is given as follows.

$h(t, x_i, \boldsymbol{\beta}_i) = 1.13\text{x}10^{-4} \text{ x } 2.16t^{1.16} \text{ x exp } (X\boldsymbol{\beta})$

For the Weibull regression model the base line hazard will vary with $h_o(t) = \boldsymbol{\lambda\alpha} t^{\alpha-1}$ hence the base line hazard function for the recurrence of cervical cancer at black lion hospital is modeled to be $h_o(t) = 1.13\text{x}10^{-4}$ X2.16X $t^{1.16}$ where t is time measured in month in this model.

In Weibull model, after fixing other covariates, the hazard rate recurrence of cervical cancer patients who have taken chemotherapy for one cycle is 0.27 times lower than that of patients not took chemotherapy. For patients who took for second cycle chemotherapy the hazard rate decreases 0.52 times that of patients not took chemotherapy. The hazard rate for recurrence of cervical cancer patient's that have taken chemotherapy for three and four cycles decreases 0.704 and 0.84 times that of patients not taken chemotherapy respectively. The hazard of divorced patients is 2.12 times greater than married women fixing other covariates. The hazard of patients from Amara region is 2.13 times greater than Addis Ababa region by letting other covariates constant. The risk of hazard is 11.02 times greater for P.O than that of stage I and that of stage IIIA the hazard is 4.01 times greater than that of stage I. For smokers the hazard is 1.91 times that of non-smoker patients keeping other covariates constant.

Now let predict for the recurrence of the cervical cancer based on the fitted weibul model taking a women whose region is Amhara, stage of disease is IIIA, marital status is divorced ,cycles of chemotherapy taken for four times and smoker.

$h(t, x_i, \boldsymbol{\beta}_i) = 1.13\text{x}10^{-4} \text{ x } 2.16t^{1.16} \text{ x exp } (X\boldsymbol{\beta})$

$1.13\text{x}10^{-4} \text{ x } 2.16t^{1.16} \text{ x exp } (0.76*3+1.39*8+0.78*2-0.18*4+0.66*1)$

$=736.6\ t^{1.16}$

So, the hazard is $736.6\ t^{1.16}$ where t is the time in month at which the disease recurs.

Model assumption checking.

The test of correlation (rho) is insignificant that indicates proportional hazards assumption is fulfilled. Variables aim of radiotherapy, number of cycles taking chemotherapy and smoking habit are fulfilled the assumption because all the p values are greater than 0.05. Moreover it is also possible to see its global test and if it is greater than 0.05 the assumption have satisfied by the covariates in the model (Table 2).

Table 2 Schoenfeld residual for each covariate, recurrence of cervical cancer among patients under follows up since 2012 to 2015 at black lion specialized Hospital

Variables	rho	Chi-square	df	Prob>chi-square
Aim of radiotherapy	-0.0794	0.64	1	0.422
Number of cycle	-0.0801	0.55	1	0.459
smoking	-0.0141	0.02	1	0.897
Global test		0.81	3	0.847

Discussion

The mean survival time of the disease that was recur is 20.68 month with standard error of 1.01 where median and standard error are 21.110 and 2.468 respectively.

From the estimates, it was found that the survival of cervical cancer a patient is significantly related with aim of radiotherapy, region of the patient, the number of cycles the patient took chemotherapy, initial treatment and the smoking habit of the patients in their univariate analysis.

The log-rank test revealed that the variables age, stage and marital status are insignificant (p=0.223, 0.123, 0.162) respectively. The result is the same with one of the literature mentioned above in which age and stages

are not significant with (P=0.77) and (P=0.177) as univariate analysis (Poolkerd et al., 2006)

The cycles of chemotherapy the patient took is significant in its univariate as well as in multiple covariate of the cox proportional hazards model and its parametric result of weibull regression model shows that taking chemotherapy is a very use full treatment for those cervical cancer patients who came to black lion hospital.

The majority of cervical cancers patients are detected in late stages of cervical cancer as the descriptive analysis indicates. This is shows that women are not aware about the diseases and its prevention as that of (Bingham A, Bishop A, Coffey P, Winkler J, & Bradley J, 2003) finding on uterine cancer.

In the univariate analysis smoking is significant factor associated with recurrence free survival of patients with a p value of 0.018. This finding is supported with (O.O.Castillo et al., 2008) , in which the smoking have become Factors associated with recurrence free survival in the Univariate analysis with (p=0.015). Not only this (Yetimalar H, Kasap B, Cukurova K, & Et al, 2011) also found that smoking is a significant factor of cervical cancer disease.

The Cox‟s proportional hazard model fitted using complete case analysis found three variables that jointly serve as predictive factors on the survival of cervical cancer patients. These variables are aim of radiotherapy, number of cycles of chemotherapy taken and the smoking habit.

Results obtained from this study were found to be analogous with literature on the topic .The age of one set of cervical cancer patients is higher in age group 41-50 the cervical cancer is higher which concords with the study by (Kumari K. G., G. Sudhakar, M. Ramesh, V. L. Kalpana, & Paddaiah, 2010) identified that the age of onset of cervical cancer is higher in the other age group.

The Cox Proportional Hazard model is the most popular technique to analyze the effects of covariates on survival time but under certain circumstances parametric models may offer advantages over Cox's model. From the parametric model Weibull have been the competing model as its AIC is the smallest and also the cox snell shows that majority of data lies on 45% degree straight line. In this paper the weibul is preferable than the cox because more risk factors were identified while specifying base line with specific distribution.

Limitation of the study

As the data is gathered from the treatment card of patients, the study has limited number of variables considered as risk factors for the recurrence of cervical cancer such as family history of patients, educational level, socio economic status, number of sexual partners, use of contraceptive method, number of parity, age at marriage, number of pregnancies, menopausal status, employment status (employed or not employed) and etc., because these are the expected risk factors from experience as well as from many literatures.

Conclusions

The mean survival time of the disease that was recurring was 20.68 month. Majority of the patients came to the black lion specialized Hospital, at the advanced stage of the disease especially at stage IIB and IIIB. For most patients the aim of radiotherapy that prescribed was a type prescribed for advanced cervical cancer. In assessing the significant risk factors the Log Rank test revealed that, the type of treatment that the patient took, region of the patient, the aim of radiotherapy prescribed, cycles of chemotherapy treatment and smoking habits had significant survival probability difference for the recurrence of cervical cancer.

The result of Cox regression proportional hazards model indicates that, for the recurrence of cervical cancer of patients who had already treated, aim of radiotherapy, the number of cycles the patient took chemotherapy and smoking habits were significant.

To predict and model the recurrence time of cervical cancer using parametric regression model, the Weibull regression survival model is better fits to the data of cervical cancer patients of black lion specialized Hospital than the other parametric models.

Recommendation

The ministry of health of the country, policy makers and medical physicians should to work on awareness of the patients to follow their treatments so that the women will protect themselves from the diseases by being treated early stage of the disease because of the disease is curable.

The total population in the study years is those patients that are already registered in the hospital which do not represent the prevalence in the country level though the patients come from different region of the country.

Abbreviations

ACS	American Cancer Society
ACOG	American Congress of Obstetricians and Gynecologists
AIC	Akaike Information Criteria
SNNP	Southern Nations and Nationalities People
USPSTF	United States Preventive Services Task Force

Declarations

Ethics and consent to participate

Ethical approval was obtained from Hawassa University, college of Mathematical and statistical science; institutional review board (IRB). Once the black lion Medical Directors Has permitted, Retrospective card review was conducted.

Consent for publication

Not applicable

Availability of data and materials

The datasets in which conclusion has taken is available on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TBB has conceived the study, participated in the design of the study and performed statistical analysis, and drafting the manuscript for important intellectual content.

TMM have directly participated in the planning of the research, guided overall stage of the research, its accomplishment, and analysis. Majorly take part in the drafting the manuscript, drafting the article or revisiting it critically for important intellectual content.

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