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Original Article

Factors Affecting Survival of Patients with Cervical Cancer

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Abstract

Background: Cervical cancer is the fourth leading cause of cancer-related death among women worldwide. We aimed to identify the factors affecting the survival rate of cervical cancer patients, as these factors are vital for preventing the progression and effective treatment of cancer.

Methods: In this retrospective cohort study, 254 patients with cervical cancer who were registered in The Kerman Population-Based Cancer Registry (KPBCR) between 2012 and 2022 and whose status was known to be alive or dead were enrolled. Since the proportional hazard assumption was not established for the type of treatment, the extended Cox model was used to determine the variables influencing the survival of the patients.

Results: The mean survival time of the patients was 91.28 ± 3.02 months. The results of fitting the extended Cox model showed that the risk of death increases by 1.02 per year of age at diagnosis (HR=1.02; 95% CI: 1.00, 1.04). Moreover, for a one-unit increase in body mass index (BMI), the risk of death increased by 0.93 (HR=0.93; 95% CI: 0.88, 0.98). The risk of death in patients with disease stages III&IV was 3.08 times that of patients with disease stages I&II (HR=3.08; 95% CI: 1.05, 9.03). The risk of death in patients receiving at least one of the radiotherapy and chemotherapy treatments after 18 months was 7.11 times that of patients undergoing surgery (HR=7.11; 95% CI: 1.69, 29.91).

Conclusion: The age of diagnosis, BMI, disease stage, and type of treatment significantly affect the survival of patients. Thus, raising women's awareness of periodical examinations and early diagnosis can reduce the risk of death and prevent cervical cancer progression.

Keywords: Cervical cancer; Survival; Prognostic factor; Time-dependent covariate; Extended cox model

Introduction

Despite the recent developments in preventing and treating all types of cancer, cancer as a non-communicable disease is still the second cause of death after heart disease (1). Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer-related death among women worldwide (2, 3). An estimate of cervical cancer in 2020 showed that about 604,000 women were

affected, and 342,000 deaths occurred due to cervical cancer worldwide (2) mostly in less developed and developing countries. Accordingly, it has inflicted more than 85% of deaths in developing regions (4).

Similar to other developing countries, cervical cancer in Iran is one of the five most common cancers in women, and it is the leading cause of death caused by gynecologic cancer. Although the released data suggested that the incidence of cervical cancer in Iran is relatively low, with 4.5 cases per 100,000 people per year, the mortality rate is still significant (5). Kerman Province, with an area of about 181 thousand square kilometers, is the largest province in southeast Iran. Health and treatment services offered in the cities of this province, especially the southern cities, are very limited due to the long distance from the capital of the province, and the incidence of cancer in this province has increased in recent years (6).

What is clear is that all these facts show the special position of this health problem in the world and Iran. Despite the fact that in recent decades, many studies have been conducted in the field of cervical cancer survival analyses (7-10), but in recent years, no study has been conducted in this regard in Kerman province, which is the largest province of Iran located in the southeast of Iran. Therefore, the analysis of data related to the new information of patients with cervical cancer in order to investigate the relationship between various factors with the survival rate of patients, especially in the less developed regions of the country, can be the innovation of this study. On the other hand, the results of this study can help health policymakers to better understand the life expectancy after cancer, to know the factors, effective treatment on the survival of patients, and to implement programs related to cervical cancer. Also, the use of an efficient statistical method to determine the factors affecting the survival rate of patients in the conditions where auxiliary variables are dependent on time is one of the other innovations of the present study. Also, in order to determine the influencing factors on the survival rate of patients in conditions where some of the studied variables are time-dependent, the use of the extended Cox model as an accurate and efficient statistical method is one of the other innovations of the present study.

To this end, we aimed to assess the fit indices of the extended Cox regression model on cervical cancer data to identify factors affecting the survival of patients with cervical cancer.

Methods

Participants

The Kerman Population-Based Cancer Registry (KPBCR) database is one of the oldest cancer registry databases in Iran. Since 2008, this database collects all the reports related to cancer patients from pathology laboratories, inpatient and outpatient treatment centers, urban and rural health centers, and forensic medicine all over the province. The database currently contains more than 17,000 cancer cases since 2008. In this retrospective cohort study, 254 patients with cervical cancer who were registered in KPBCR between 2012 and 2022 and whose status was known to be alive or dead were included in the study.

The independent variables in this study were age, age at diagnosis, body mass index (BMI), marital status, drug abuse, place of residence, tumor location, tumor grade, disease stage, and type of treatment, and the response variable was the time from cancer diagnosis to death or censoring interval in a month.

Ethical considerations

The protocol for this study was approved by the research council and the ethics committee of Kerman University of Medical Sciences with the code of ethics IR.KMU.REC.1401.051.

Data analysis

The Cox model is often used in medical studies as the most common model to address factors affecting survival (11). One of the advantages of this model is that a probability distribution is not required for survival times. However, the Cox model requires establishing the proportional haz-

ard (PH) assumption for all independent variables in the final model (12), and the rejection of this assumption undermines the validity of the Cox regression results. Thus, if this assumption is not established for each variable, there are various methods to solve this problem, including the stratified Cox model, the extended Cox model (used in the present study), and parametric models to enter the variable into the model. Stata software (version 17) was used for data analysis. To this end, univariate analysis was run to select the candidate variables in the multiple Cox model (variables with a p-value less than or equal to 0.2). Afterward, the proportional hazard (PH) assumption was tested using the Schoenfeld residuals test for each independent variable, but this assumption was not valid only for the type of treatment. Thus, the extended Cox model was used to enter that variable into the model. Finally, the backward elimination method was adopted to specify the most accurate model or effective variables. The variables with a *P*-value less than 0.05 were considered statistically significant.

Results

Out of a total of 254 patients examined, 81 patients (31.9%) died and the remaining patients were censored. The patients' mean age was 55.74±13.03 years, and the mean survival time was 91.28±3.02 months. Furthermore, the one-, three-, and five-year survival rates were reported in 91.3%, 78.0%, and 70.5% of the patients, respectively. The mean age of diagnosis of the disease in the patients was 50.59±13.21 years and the mean body mass index (BMI) of the patients was 24.72±4.65 kg/m^2. In addition, 79.1% of the patients were married and 9.4% reported a history of substance abuse. The data also indicated that 70.9% of the patients lived in urban areas. The tumor area in 75.6% of the patients was cervix uteri. The disease grade was not specified for 65.8% of the patients. Moreover, 76.8% of the patients were suffering from the SCC cell type, and 11.0% of them were at the disease stages III & IV. Finally, 35.8% of the participants had received at least one of the radiotherapy and chemotherapy treatments (Table 1).

Table 1: Characteristics of risk factors for death-censored and 1, 3 and 5 year overall survival rates cervical cancer

Variable	***Mean±SD / N (%)***			***Overall Survival (%)***		
	Alive	Dead	Total	1-Year	3-Year	5-Year
Age(yr)	54.87±12.93	57.59±13.13	55.74±13.03	-	-	-
Age at diagnosis(yr)	48.41±12.67	55.25±13.22	50.59±13.21	-	-	-
BMI (kg/m^2)	25.32±4.38	23.43±4.497	24.72±4.65	-	-	-
Marital status						
Single	6 (75.0)	2 (25.0)	8 (3.1)	87.5	75.0	75.0
Married	138 (68.7)	63 (31.3)	201 (79.1)	91.5	79.1	71.7
Divorced/deceased spouse	29 (64.4)	16 (35.6)	45 (17.7)	91.1	73.3	64.5
Tobacco						
No	162 (70.4)	68 (29.6)	230 (90.6)	91.7	79.6	73.0
Yes	11 (45.8)	13 (54.2)	24 (9.4)	87.5	62.5	53.0
Region						
rural	46 (62.2)	28 (37.8)	74 (29.1)	82.4	70.3	64.2
urban	127 (70.6)	53 (29.4)	180 (70.9)	95.0	81.1	73.1
Tumor location						
Cervix uteri	126 (65.6)	66 (34.4)	192 (75.6)	90.6	77.1	67.8
Endocervix	42 (79.2)	11 (20.8)	53 (20.9)	94.3	83.0	80.8
Exocervix	5 (55.6)	4 (44.4)	9 (3.5)	88.9	66.7	66.7
Grade						
Well differentiated	17 (81.0)	4 (19.0)	21 (8.3)	95.2	81.0	81.0
Moderately differentiated	22 (61.1)	14 (38.9)	36 (14.2)	94.4	80.6	67.8
Poorly differentiated	19 (63.3)	11 (36.7)	30 (11.8)	93.3	73.3	59.8
Not determined	115 (68.9)	52 (31.1)	167 (65.7)	89.8	77.8	71.5
Cell type						
Non SCC	40 (67.8)	19 (32.2)	59 (23.2)	89.8	74.6	69.2

SCC	133 (68.2)	62 (31.8)	195 (76.8)	91.8	79.0	70.9
Stage						
0 (No Stage)	42 (97.7)	1 (2.3)	43 (16.9)	-	-	-
I & II	31 (83.8)	6 (16.2)	37 (14.6)	97.3	91.9	86.3
III & IV	10 (35.7)	18 (64.3)	28 (11.0)	82.1	53.6	32.9
Unknown	90 (61.6)	56 (38.4)	146 (57.5)	89.0	73.3	65.4
Treatment type						
No treatment	99 (78.6)	27 (21.4)	126 (49.6)	91.3	82.5	79.6
Surgery	32 (86.5)	5 (13.5)	37 (14.6)	94.6	86.5	86.5
Radiation and/or chemotherapy	42 (46.2)	49 (53.8)	91 (35.8)	90.1	68.1	52.0

Following the Cox univariate analysis, the age of disease diagnosis, BMI, history of drug abuse, stage of the disease, and the type of treatment were entered as the variables into the multiple extended Cox model (P<0.05) (Table 2).

Table 2: Univariate survival analysis of cervical cancer patients using the Cox proportional hazard model

Variable	***HR (95% CI for HR)***	***P-value***
Age	1.01 (0.99- 1.03)	0.228
Age at diagnosis	1.03 (1.02- 1.05)	<0.001
BMI (kg/m^2)	0.92 (0.87- 0.96)	0.001
Marital status		
Single	Ref	
Married	1.29 (0.31- 5.26)	0.725
Divorced/deceased spouse	1.50 (0.34- 6.52)	0.590
Tobacco		
No	Ref	
Yes	2.11 (1.16- 3.81)	0.014
Region		
rural	Ref	
urban	0.71 (0.45- 1.12)	0.144
Tumor location		
Cervix uteri	Ref	
Endocervix	0.53 (0.28- 1.00)	0.050
Exocervix	1.39 (0.51- 3.82)	0.521
Grade		
Well differentiated	Ref	
Moderately differentiated	2.08 (0.68- 6.32)	0.196
Poorly differentiated	2.24 (0.71- 7.05)	0.167
Not determined	1.72 (0.62- 4.77)	0.294
Cell type		
Non SCC	Ref	
SCC	0.98 (0.58- 1.63)	0.926
Stage		
I & II	Ref	
0 (No Stage)	0.14 (0.02- 1.18)	0.071
III & IV	5.87 (2.33- 14.82)	<0.001
Unknown	2.73 (1.18- 6.34)	0.019
Treatment type		
Surgery	Ref	
No treatment	1.58 (0.61- 4.10)	0.348
Radiation and/or chemotherapy	4.67 (1.86- 11.74)	0.001

HR: Hazard ratio, CI: Confidence interval

The data from the Schoenfeld residuals test established the proportional hazard (PH) assumption for all significant variables except the treatment type in the final Cox model (Table 3).

Table 3: Examining the proportional hazard assumption using the Shoenfeld test

Variable	*Chi-square*	*Df*	*P-value*
Age at diagnosis	0.13	1	0.716
BMI	0.01	1	0.940
Tobacco (Yes)	0.88	1	0.348
Stage (III & IV)	3.39	1	0.065
Stage (0)	0.97	1	0.325
Stage (Unknown)	1.67	1	0.195
Treatment type (No treatment)	0.68	1	0.408
Treatment type (Radiation and/or chemotherapy)	6.06	1	0.013
Global	19.77	8	0.011

Df: Degree of freedom

Thus, the treatment type is a time-dependent variable so there was no difference between the survivals rates for any type of treatment received before 18 months. However, there was a significant difference in the survival rates in the patients receiving different treatments after 18 months (Fig. 1). To this end, the extended Cox model was run to specify the factors affecting the survival of patients with cervical cancer and determine the goodness fit index of the model on the collected data.

Data analysis via the multiple extended Cox model indicated that the risk of death increases by 1.02 for a one-year increase in age at diagnosis (HR=1.02 [95% CI: 1.00, 1.04]) and by 0.93 for a one-unit increase in body mass index (HR=0.93 [95% CI: 0.88, 0.98]). The history of drug abuse was not significant. However, given the *P*-value for this variable (*P*=0.070), it can also be considered a risk factor affecting the survival of cervical cancer patients (HR=1.76 [95% CI: 0.95, 3.24]). The risk of death in the patients at the disease stages III & IV was 3.08 times that of the patients at disease stages I & II (HR=3.08 [95% CI: 1.05, 9.03]). Furthermore, the risk of death in patients receiving at least one of the radiotherapy and chemotherapy treatments after 18 months was 7.11 times that of the patients undergoing surgery (HR=7.11 [95% CI: 1.69, 29.91]) (Table 4).

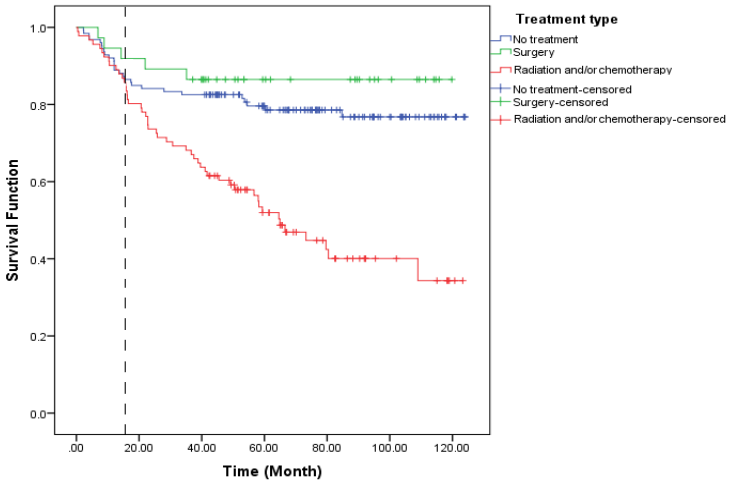

Fig. 1: Kaplan-Meier survival curve of cervical cancer patients by treatment type

Table 4: Multiple survival analysis of cervical cancer patients using extended Cox model

Variable	*HR (95% CI for HR)*	*P-value*
Age at diagnosis	1.02 (1.00- 1.04)	0.015
BMI (kg/m²)	0.93 (0.88- 0.98)	0.011
Tobacco		
No	Ref	
Yes	1.76 (0.95- 3.24)	0.070
Stage		
I & II	Ref	
0 (No Stage)	0.16 (0.02- 1.40)	0.098
III & IV	3.08 (1.05- 9.03)	0.039
Unknown	1.76 (0.65- 4.78)	0.268
Treatment type (Before 18 months)		
Surgery	Ref	
No treatment	1.53 (0.45- 5.21)	0.496
Radiation and/or chemotherapy	1.87 (0.54- 6.42)	0.320
Treatment type (After 18 months)		
Surgery	Ref	
No treatment	0.96 (0.20- 4.53)	0.957
Radiation and/or chemotherapy	7.11 (1.69- 29.91)	0.007

Discussion

In this study, to identify factors affecting the survival of patients with cervical cancer, the extended Cox model was run as an alternative to the Cox model due to the failure to establish the PH assumption for the type of treatment as a variable in this study. Multivariate analysis through the backward elimination method showed that the extended Cox model with the presence of five auxiliary variables including age at diagnosis, BMI, history of drug abuse, disease stage, and type of treatment was the most accurate in determining the factors affecting the survival of cervical cancer patients.

The data in this study indicated that the age at diagnosis was an effective factor in the survival of cervical cancer patients so the risk of death increased by 1.02 for each year increase in the age at diagnosis. This finding was similar to the results reported in a study by Quinn et al. on women with cervical cancer from 1973 to 2015 in the United States (13). In addition, other studies have confirmed the age of disease diagnosis as a predictor of survival in cervical cancer (8, 14). Hence screening and diagnosis of the disease at a younger age are recommended.

Also, it was found that body mass index affected the survival of cervical cancer patients. Thus, for a one-unit increase in body mass index, the risk of death decreases by 7%. Similarly, body mass index is a predictive factor for survival in American patients with cervical cancer with HR=0.78 (15). Fourteen percent of cervical cancer patients undergoing chemotherapy had experienced severe weight loss and had a higher risk of death. Moreover, the patients diagnosed with stages 3 and 4 of the disease, compared to patients in the early stage of the disease, were 3.4 times at risk of severe weight loss (16). Hence, following these findings, people with severe diseases seem to experience significant weight loss and are at a greater risk of death compared to people with a normal weight.

Another finding of this study was that a history of drug abuse was not a significant risk factor. However, given the *P*-value for this variable (*P*=0.070), it can also be considered a risk factor affecting the survival of cervical cancer patients. Similarly, the patients who smoked or used alcohol or drugs had a significantly lower survival rate (17), which is an alarming sign for them to stop smoking or using alcohol or drugs.

We noted that the patients diagnosed with disease stages III and IV had 3.08 times higher risk of death compared to the patients diagnosed with early stages I and II. Accordingly, cervical cancer patients in advanced stages III and IV had a lower survival rate than patients in the early stages (18), which is in line with other studies (14, 19, 20).

The present study confirmed the proportional hazard (PH) assumption for all variables except the treatment type. Thus, there was no difference between the survival rates for any type of treatment taken before 18 months. However, there was a significant difference in the survival rates in the patients receiving treatments after 18 months. Thus, since the PH assumption was not established for the type of treatment, the extended multiple Cox model was used to investigate the effect of this and other variables affecting the survival of patients with cervical cancer. The patients who received at least one of the radiotherapy and chemotherapy treatments after 18 months of diagnosis had 7.11 times higher risk of death compared to patients who underwent surgery after 18 months of diagnosis. Thus, it can be claimed that receiving at least one of the radiotherapy and chemotherapy treatments after 18 months is a risk factor affecting the survival of patients with cervical cancer. In a similar vein, patients in Bhutan who received at least radiotherapy or chemotherapy had 3.1 times higher risk of death compared to patients who only had surgery (8). Cervical cancer treatment depends on various factors such as the stage of the disease (the most vital factor in choosing treatment), location, type, degree of differentiation of the tumor, size of the primary lesion, the growth pattern of the primary tumor, age, general health of the patient, possible side effects, and the decision for having a child (21-23). Surgery is often the main treatment for cervical cancer, especially if the cancer is diagnosed in early stages such as stage IA, IB1, and IIA1 (24). Radiotherapy is used for cancers in stages IIB, IIIB, IIIB, and IVA, or tumors that have expanded greatly (25). Chemotherapy is also used to treat patients in stages IVA and IVB of the disease (25, 26). Thus, following our findings, it seems the greater risk of receiving at least one of the radiotherapy and chemotherapy treatments for cervical cancer patients depends on the patient's condition and the progression of the disease. Thus, surgery is a more effective treatment for cervical cancer, and the mere reliance on radiotherapy and chemotherapy may be ineffective and involve a high mortality risk.

In this study, the mean survival time was 91.28 months, and the one-, three-, and five-year overall survival rates were 91.3%, 78.0%, and 70.5%, of the patients with cervical cancer, respectively. In the studies conducted in Iran, in West Azerbaijan Province, the mean survival time was 86.31 months, and the one-, three-, and five-year overall survival rates were 96.9%, 85.2%, and 73.1%, of the patients with cervical cancer, respectively (14) and in Yazd Province, the overall five-year survival rate of patients was 75.9% (27). In the studies conducted in other countries, in Malaysia, the mean survival time was 65.8 months, and the one-, three-, and five-year overall survival rates were 94.1%, 79.3%, and 71.1%, of the patients with cervical cancer, respectively (28) and in South Korea, the 5-year relative survival rate was 79.2% (29). The results of the studies show that the 5-year survival rate was higher than the present study.

In general, the survival rate of cervical cancer patients in this study is lower than other provinces and countries. Perhaps the reason for this difference can be attributed to factors such as time of diagnosis, correct or incorrect diagnosis of the stage of the disease, appropriate or inappropriate treatment, timely treatment or delay in treatment, as well as other factors. Therefore, this difference in the survival rate of the present study with other studies is a clear reason for the necessity of conducting the present study in order to identify the risk factors that have led to a decrease in the survival of patients with cervical cancer in the present study compared to other studies.

This study shed light on the survival of cervical cancer patients, especially in less developed regions. It also revealed a solution for using time-

dependent variables, besides when the PH assumption is not established.

Conclusion

Some variables including age at diagnosis, BMI, history of drug abuse, disease stage, and type of treatment can significantly affect the survival of cervical cancer patients. Thus, the risk of death in patients with higher diagnosis age, lower BMI, drug abuse, more advanced disease stage, and reception of at least one of the radiotherapy and chemotherapy treatments after 18 months is higher than in patients undergoing surgery. Raising women's awareness of periodic examinations and early diagnosis, weight control, and not consuming drugs can reduce the risk of death and improve the survival time of patients. Early diagnosis lowers the risk of radiotherapy and chemotherapy and improves their efficiency in treating cervical cancer.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interests.

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