original article

Indicators of survival and prognostic factors in women treated for cervical cancer at a tertiary care center in Saudi Arabia

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BACKGROUND: Investigating survival in cervical cancer at the local level is crucial to determine the effectiveness of overall management, as it reflects the level of care provided and awareness among the population about screening and early diagnosis.

OBJECTIVES: Analyze overall survival (OS) and disease-free survival (DFS) among patients treated for cervical cancer and to investigate clinical, management- and outcome-related independent factors associated with survival.

DESIGN: A retrospective medical record review.

SETTING: Gynecology oncology unit in a tertiary care center.

PATIENTS AND METHODS: All women with cervical cancer who were treated and followed up between January 1999 and December 2017. Baseline demographic and clinical data, tumor characteristics, treatment options and outcomes including recurrence were collected and analyzed as factors and predictors of survival.

MAIN OUTCOME MEASURES: OS and DFS among patients treated for cervical cancer.

SAMPLE SIZE: 190 patients.

RESULTS: The 190 patients had a mean (SD) age of 54.2 (13.1) years (median 52.0, interquartile range, 46-62), and median (IQR) follow-up time was 37.0 (12.0-69.0) months. Tumor characteristics showed FIGO stage (I [19.0%], II [48.9%], III [18.4%], IV [13.6%]), grade (I [15.8%], II [46.8%], III [35.8%]) and the most frequent histological type was squamous cell carcinoma (77.4%). Patients received initial radiotherapy with concurrent chemotherapy (53.2%), initial radical hysterectomy (24.7%), systemic chemotherapy (6.3%) and palliative care (4.7%). Mean OS and DFS were 97.1 (82.2, 111.9) and 85.2 (70.4, 100.0) months, respectively. Recurrence and mortality rates were 25.8% and 46.8%, occurring after a median (IQR) time=13.0 (6.0-28.0) and 20.0 (9.0-45.0) months, respectively. Survival was independently associated with grade II (hazard ratio [HR]=3.6, 95%CI: 1.3-9.7, *P*=.012), grade III (HR=4.5, 95%CI:1.6-12.6, *P*=.004), number of regional organs involved (1-3 organs: HR=7.8, 95%CI: 1.2, 49.1, *P*=.030), and recurrence (HR=2.23, *P*=.001).

CONCLUSION: Survival was about 8 years in our institution, which is predicted by the tumor grade, regional organs involved and recurrence. Remarkably, this study found a high percentage of patients diagnosed at an advanced stage, which probably impacts survival and stresses the need for improving early detection.

LIMITATIONS: Retrospective design, resulting in recall bias and missing data.

CONFLICT OF INTEREST: None.

Cervical cancers are malignant proliferations that originate from the cervix, the lower cylindrical end of the uterus. Squamous cell carcinoma, which grows in the squamous tissue of the ectocervical and more particularly in the external os, and adenocarcinoma, which grows in the glandular tissue of the endocervical canal, represent the most frequent histopathological types of cervical cancer. Other types include adenosquamous cancers, which combines both squamous and glandular cells, in addition to rare types such as small cell neuroendocrine carcinomas, lymphomas and sarcomas.[1]

Cervical cancer ranked among the top four female cancers with a globally estimated incidence of 569 847 new cases in 2018 corresponding to 15.1 new cases per 100 000 women and a cumulative risk of 1.36% from birth to 75 years old. It also represents one of the major causes of cancer-related mortality in females, responsible for 311 365 deaths worldwide in 2018, 90% of them occurring in underdeveloped and developing countries.[2-4]

In contrast to the worldwide picture, the incidence and prevalence of cervical cancer in Saudi Arabia is significantly lower, accounting for less than 3% of all new female cancers.[5] This epidemiology is explained by the societal and traditional standards that would play an important role in reducing exposure to human papilloma virus (HPV) infections, which constitute one of the leading risk factors for cervical cancer.[6]

Prognosis and survival of patients with cervical cancer depends, on the one hand, on the tumor stage and grade at diagnosis, and on the other hand on state-of-art management, which should be based on accurate staging and includes an arsenal of surgical, radiation and chemotherapy protocols.[4] In developed countries, up to 95% of early-stage cases and up to 85% of advanced stage cases of cervical cancers are well controlled at 3 years of follow-up after the start of treatment; in the case of metastasis or recurrence the prognosis remains poor. In developing and underdeveloped countries, 5-year survival rates decline considerably due to inadequate treatment and advanced stage at diagnosis.[4,7]

It is crucial to investigate survival in cervical cancer at the local level to provide an approach on the effectiveness of the overall management, as it reflects the level of care of the patients and the awareness among the population about screening and early diagnosis. Thus, we conducted this study to provide insight into survival and disease-free survival among women treated and followed up for cervical cancer and to investigate the clinical, management- and outcome-related independent factors of survival. Secondarily, we analyzed the medium-term prognosis of treated cervical cancer by estimating the 5-year survival rate and exploring the associated factors.

PATIENTS AND METHODS

This retrospective study included all women with cervical cancer who were treated and followed up at the Gynecology Oncology Unit, King Abdulaziz University, Jeddah, Saudi Arabia, between January 1999 and December 2017. Patients with missing follow-up data were excluded. The study was approved by the unit of biomedical ethics research committee in our center. The following data were collected: 1) baseline demographic and clinical data including age, parity, height and weight with calculation of the body mass index (BMI), medical history (hypertension, diabetes, other cancer, and more.); 2) tumor characteristics including FIGO stage, grade, histological type, locoregional organ involvements (parametrium, pelvis, vagina, and other organs), distal metastasis, and hydronephrosis; 3) management data including cut-through hysterectomy, radical hysterectomy, radiotherapy with or without concurrent chemotherapy (initial, adjuvant), systemic chemotherapy and palliative care; 4) outcome data including events occurring during the follow-up period (recurrence, death) and 5-year status (alive with/without disease, deceased, censored); 5) time variables including date of diagnosis, date of recurrence if any, date of death if any, and date of last follow-up.

Statistical analysis was performed with IBM SPSS version 21.0 for Windows (Armonk, NY). Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean and standard deviation (SD) or median (interquartile range), as appropriate. Kaplan-Meier survival analysis was carried out to estimate mean and overall survival (OS) and disease-free survival (DFS), with the 95% confidence interval (CI), as well as to analyze factors associated with survival. Results are presented as mean (95%CI) survival with log rank level. Cox regression was used to investigate independent factors associated with survival; results are presented as hazard ratio (HR) with 95%CI. Factors for 5-year survival were analyzed by comparing the characteristics of patients who were alive at 5-year follow-up versus those who died before 5 years. The independent t-test was used to analyze normally distributed numerical variables, while the chi-square test or Fisher exact test were used to analyze categorical ones. Binary logistic regression was carried out using multivariate model to analyze independent risk factors of 5-year survival. The level of statistical significance was set to <.05, to reject the null hypothesis.

Table 1. Baseline demographic and clinical characteristics (N=190).

Age (years)	54.2 (13.1)
Nationality	
Saudi	52.0 (27.4)
Non-Saudi	138.0 (72.6)
Parity	
0	18.0 (9.5)
1-5	71.0 (37.4)
>5	47.0 (24.7)
Missing data	54.0 (28.4)
BMI category (kg/m²)	
Underweight (<18.5)	18.0 (9.5)
Normal (18.5, 24.9)	47.0 (24.7)
Overweight (25, 29.9)	59.0 (31.1)
Class I obesity (30-34.9)	22.0 (11.6)
Class II obesity (35.0, 39.9)	35.0 (18.4)
Class III obesity (40+)	8.0 (4.2)
Medical history	
Hypertension	58.0 (30.5)
Diabetes	36.0 (18.9)
Bronchial asthma	4.0 (2.1)
Renal failure	2.0 (1.1)
Other cancer	2.0 (1.1)
HIV	2.0 (1.1)
Hypothyroidism	1.0 (0.5)
Tumor characteristics	
FIGO stage	
IA	3.0 (1.6)
IB	33.0 (17.4)
IIA	5.0 (2.6)
IIB	88.0 (46.3)
IIIA	1.0 (0.5)
IIIB	34.0 (17.9)
IVA	13.0 (6.8)
IVB	13.0 (6.8)
Grade	
I	30.0 (15.8)
II	89.0 (46.8)
III	68.0 (35.8)
Histological type (biopsy)	
Squamous cell carcinoma	147.0 (77.4)
Adenocarcinoma	22.0 (11.6)
Mixed adenosquamous	2.0 (1.1)
Other	4.0 (2.1)
Locoregional involvement	
Parametrium	150.0 (78.9)
Right pelvis	45.0 (23.7)
Left pelvis	38.0 (20.0)
Bladder	35.0 (18.4)
Rectum	17.0 (8.9)
Vagina	102.0 (53.7)
Distal metastasis	
Yes	158.0 (83.2)
No	32.0 (16.8)
Hydronephrosis	
Yes	149.0 (78.4)
No	37.0 (19.5)

Data are n (%) except for age (mean, SD).

RESULTS

Baseline demographic and clinical characteristics

One hundred ninety patients fulfilled the inclusion criteria. The mean (SD) age was 54.2 (13.1) years (median 52.0, interquartile range, 46-62), 71 (37.4%) had 1-5 children and 47 (24.7%) had more than 5 children **(Table 1).** The medical history showed hypertension (30.5%), diabetes (18.9%), and bronchial asthma (2.1%). Tumor characteristics showed FIGO stage IIB (88, 46.3%), IIIA and IIIB (35, 18.4%), and IV A and IV B (26, 13.6%); and the majority of the participants were grade II (89, 46.8%) or III (68, 35.8%). The most frequent histological type was squamous cell carcinoma (n=147, 77.4%), followed by

Table 2. Management and outcomes (N=190)

Cut-through hysterectomy	
No	187 (98.4)
Yes	3 (1.6)
Radical hysterectomy	
No	134 (70.5)
Initial	47 (24.7)
After RT/CT	9 (4.7)
Radiotherapy	
No	42 (22.1)
Initial	119 (62.6)
Adjuvant	29 (15.3)
Chemotherapy	
No	63 (33.2)
Concurrent	101 (53.2)
Adjuvant	25 (13.2)
Systemic chemotherapy	
No	178 (93.7)
Yes	12 (6.3)
Palliative care	
No	180 (94.7)
Yes	9 (4.7)
Missing data	1 (0.5)
Follow-up and outcome	
Total follow-up time (months)	37.0 (46-62)
Persistent tumor	
Yes	7 (3.7)
Recurrence	
Recurrence rate	49 (25.8)
Time-to-recurrence (months)	13.0 (6.0-28.0)
Mortality	
Mortality rate	89 (46.8)
Time-to-death (months)	20 (9.0-46.5)
5-year follow-up status	
Alive without disease	53 (27.9)
Alive with disease	8 (4.2)
Deceased	73 (38.4)
Unknown (FU<5 years)	56 (29.5)

Data are number (%) or median (IQR) unless noted otherwise. Because of missing data, not all values sum to the total.

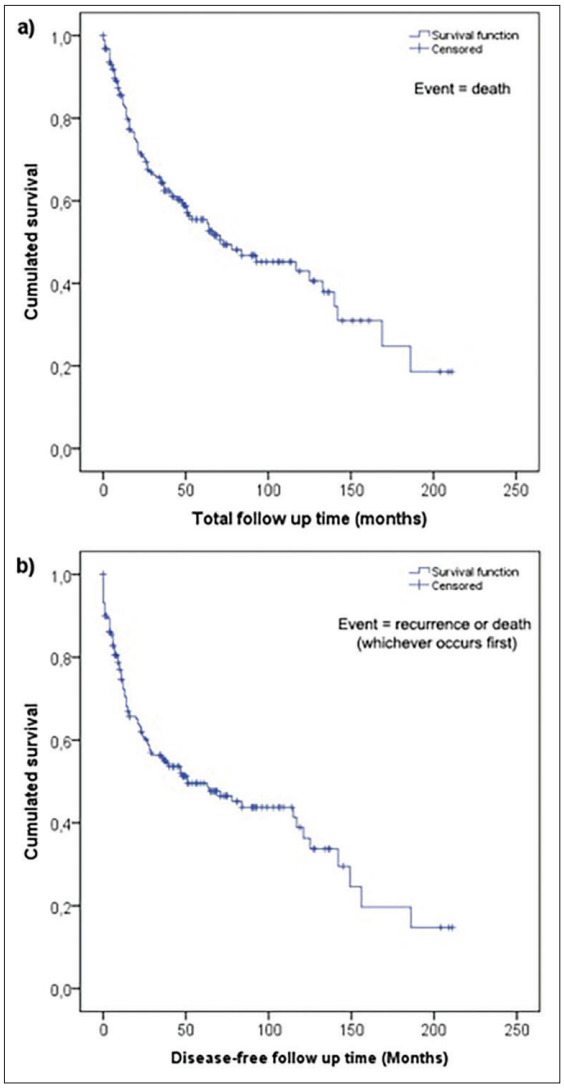

Figure 1. Overall survival (a) and disease-free survival (b) curves.

adenocarcinoma (n=22, 11.6%). Distal metastasis was diagnosed in 16.8% of the patients and the most frequent locoregional involvement was the parametrium (n=150, 78.9%) followed by vagina (n=102, 53.7%) and right pelvis (n=45, 23.7%), and hydronephrosis was reported in 149 (19.5%) of the patients.

Management and outcomes

Patients received initial radiotherapy and concurrent chemotherapy (119, 53.2%), systemic chemotherapy (12, 6.3%) and palliative care (9, 4.7%) **(Table 2).** There were 47 (24.7%) patients who had radical hysterectomy as initial treatment. Recurrence occurred among 49 (25.8%) patients after a median (IQR) follow-up time of 13.0 (6.0-28.0) months; while mortality occurred among

Table 3. Factors associated with overall survival among cervical cancer patients (N=190) (Kaplan-Meier survival analysis).

Predictor	Survival time (months)			*P* value
	Mean	95%CI		
FIGO stage				
I	120.2	97.6	142.8	<.001
II	110.9	91.0	130.8	
III	37.8	26.3	49.2	
IV	33.9	16.2	51.6	
Grade				
I	129.3	107.3	151.2	.001
II	88.1	68.7	107.5	
III	82.9	58.1	107.7	
Parametrium				
No	109.3	88.2	130.5	.020
Yes	88.4	72.5	104.3	
Right pelvis				
No	109.6	92.7	126.6	<.001
Yes	46.7	27.3	66.1	
Left pelvis				
No	105.8	89.4	122.2	<.001
Yes	50.2	27.3	73.2	
Bladder				
No	103.9	87.8	120.1	.001
Yes	46.2	29.3	63.1	
Rectum				
No	101.7	86.1	117.2	.001
Yes	31.8	15.9	47.7	
Vagina				
No	96.4	81.4	111.4	.036
Yes	88.2	68.5	108.0	
No local involvements				
0	116.9	95.6	138.2	<.001
1-3	97.1	78.7	115.4	
4+	57.4	36.2	78.7	
Distal metastasis				
No	108.9	92.4	125.4	<.001
Yes	33.4	17.7	49.2	
Hydronephrosis				
No	109.6	92.9	126.4	<.001
Yes	31.5	20.5	42.6	
Cut-through hysterectomy				
No	98.5	83.5	113.6	.021
Yes	19.0	16.7	21.2	
Radical hysterectomy				
No	90.3	73.6	106.9	.007
Initial	107.2	86.4	127.9	
After RT/CT	30.5	11.3	49.7	
Radiotherapy				
No	87.8	62.6	112.9	.889
Initial	93.9	76.5	111.5	
Adjuvant	89.4	65.1	113.8	
Chemotherapy				
No	77.9	57.9	97.9	.272
Concurrent	102.2	81.7	122.6	
Adjuvant	85.9	60.3	111.6	
Systemic CT				
No	97.9	82.8	113.2	.469
Yes	47.9	24.2	71.5	
Palliative care				
No	101.8	86.4	117.2	<.001
Yes	12.1	1.8	22.5	
Recurrence				
No	118.1	98.1	138.1	<.001
Yes	56.8	40.4	73.1	

Table 3 (cont.) Factors associated with overall survival among cervical cancer patients (N=190) (Kaplan-Meier survival analysis).

Log rank test. Time variable=time from diagnosis to last follow up, event=death. CI: Confidence interval.

89 (46.8%) after a median (IQR) follow-up time of 20.0 (9.0-45.0) months. Five-year status showed 53 (27.9%) alive without disease, 8 (4.2%) alive with disease, and 73 (38.4%) deaths; while status was unknown in 56 (29.5%) as their follow-up time was less than 5 years.

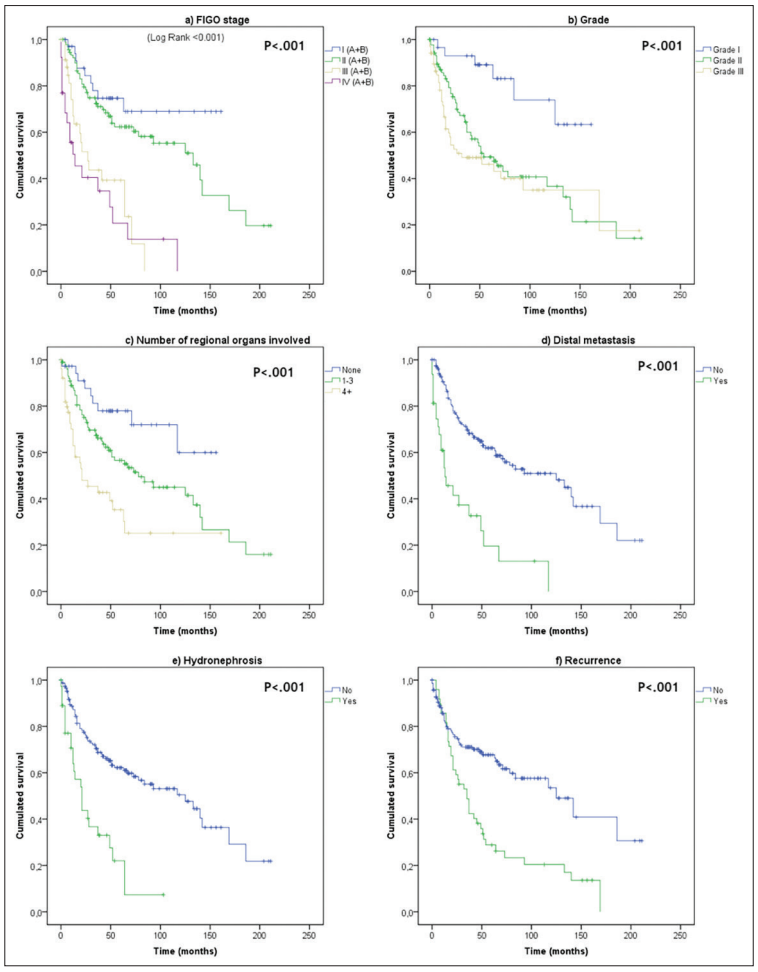

Figure 2. Kaplan-Meier curves by statistically significant factors for overall survival (log-rank test).

Survival analysis

Mean (95% CI) and median (95% CI) survival was 97.1 (82.2, 111.94) months and 73.0 (30.9, 115.1) months, respectively. Mean (95% CI) and median (95% CI) DFS was 85.2 (70.4, 100.0) months and 51.0 (18.5, 83.5) months, respectively **(Figures 1a,b).** Mean OS decreased significantly with FIGO stage (*P*<.001), tumor grade (*P*=.001), and the involvement of regional organs such as parametrium (*P*=.020), bladder (*P*=.001), rectum (*P*=.001), and others **(Table 3)** as well as the number of local organs involved (*P*<.001). Most remarkably, the presence of distal metastasis reduced the mean OS from 108.9 to 33.4 months (*P*<.001), while the presence of hydronephrosis reduced it from 109.6 to 31.5 months (*P*<.001). The mean OS decreased from 118.1 to 56.8 months in case of recurrence (*P*<.001). Patients who benefited from initial radical hysterectomy showed longer OS (mean survival=107.2 months) compared to those who received conservative treatment (90.3 months) or radical hysterectomy after radiotherapy and chemotherapy (30.5 months), and the difference was statistically significant (*P*=.007). No association of OS was observed with radiotherapy and chemotherapy modality. Kaplan-Meier analysis for the most significant factors are depicted in **Figures 2a-f.**

The Cox multivariate hazards regression model showed tumor grade II (HR=3.57, *P*=.012), grade III (HR=4.49, *P*=.004), number of locoregional organs involved (1-3 organs: HR=7.76, *P*=.030) and recurrence (HR=2.23, *P*=.001) to be the only independent factors of OS **(Table 4).** Baseline demographic and clinical and management factors associated with 5-year OS were analyzed after exclusion of patients who had unknown status at 5 years of follow-up. Of the 134 patients included in this analysis, 61 were alive at 5 years of follow-up: 5-year survival rate=45.1% (95% CI=36.9%, 54.3%), 5-year mortality rate=54.5% (95% CI=45.7%, 63.1%). Several factors were statistically significant (results not presented in tables); however, grade (grade II: OR=0.15, *P*=.027, grade III: OR=.09, *P*=.010) and recurrence (OR=0.18, *P*=.001) were the only independent factors for 5-year survival **(Table 5).**

DISCUSSION

Cervical cancer ranks eighth among the most common cancers for Saudi women at the reproductive ages.[8] In different settings, the prognostic significance of the disease varies considerably according to sociodemographic factors, stage at diagnosis, accessibility to effective care, and adherence to prescribed treatment.[9] In the present study, women with cervical cancer had an average 8 years of OS (mean survival time of 97.1 months), while the mortality rate was 46.8% after a mean time of 20.0 months. Patient survival was associated with several tumor characteristics, including tumor stage (II and III), FIGO stage,an increase in local involvement, distant metastasis and hydronephrosis. However, using a Cox regression model, the hazard associated with survival increased significantly only in women with an advanced tumor grade (II and II), increased number of involved regional lymph nodes, and recurrent tumors.

The mean survival time was considerably longer than that reported in other studies **(Table 6).** Pardo and Cendales[10] found that the mean survival time was 3.69 (2.58) years in a cohort of 455 women treated for cervical cancer in Colombia. Carneiro et al[11] revealed a slightly longer mean survival time (4 years) in 1851 Brazilian patients. Other reports showed mean survival times of 5.68 years and 6.88 years among 138 and 964 cases, respectively.[12,13] Considering the median values,

studies conducted in India and Malaysia showed median survival times ranging between 12 months and 5.48 years,[14,15] which was shorter than our reported value (6.08 years). To the best of our knowledge, only one study[16] has reported better survival data than that revealed in our analysis. That study was a large investigational study based on two equally-randomized ethnic groups and relying on the Surveillance Epidemiology and End Results (SEER) database indicated that American white non-Hispanic women had a significantly longer mean survival time (18.47 years) as compared to white Hispanics (15.85 years, $P<.001$).[16] Therefore, our applied treatment strategies seem to provide promising therapeutic outcomes when compared to other settings.

On the other hand, the 5-year survival rate among our patients (n=134) was 53.2%. In the literature, survival rates were different across different countries. For example, studies conducted in developed countries reported higher figures. In the United States, the 5-year survival ranged from 62.8% to 67.6% during the period between 1999 and 2015.[17,18] Similar rates were reported in Canada (67%)[19] and the United Kingdom (67.4%).[20] However, reports in Australia and China revealed that 73% and 82% of women with cervical cancer, respectively, were alive after 5 years of diagnosis.[21,22] Contrastingly, the combined 5-year survival rate from cancer of the cervix is less than 50% in underdeveloped countries. Data from South Africa indicated that 5-year survival rates were 37.9% to 45.7%, while they did not exceed 40% for any of the Sub-Saharan African country between 2006 and 2011.[23] Nevertheless, Jayant et al[9] showed a 60.5% survival in a rural region in India.

Considering local estimates, El Sayed et al[24] showed that the 4-year survival rate was 79% at King Abdulaziz University Hospital, 68.3% at King Faisal Specialist Hospital,[25] and ranged between 64.5% and 72.4% at King Fahad Medical City following a concurrent postoperative regimen comprising radiotherapy and chemotherapy.[26,27] It is evident that the discrepancy in survival rates is linked with the applied screening programs aimed at detecting cervical cancer at an early stage because the survival of patients in stage IA was as high as 95.1%, while it was 5.3% in stage IV patients.[9] Additionally, postoperative management protocols, such as chemotherapy or radiotherapy, might impact recurrence rates and progression-free survival.[22] Further, in the present study, the 5-year survival analysis included all patients who died before achieving 5 years of follow-up, regardless of the date of diagnosis. This inclusion bias probably skewed the mortality rate, explaining the relatively low 5-year survival rate in our series.

Table 4. Predictors of overall survival among cervical cancer patients (N=190).

Predictor	Hazard ratio	95%CI		*P* value
FIGO stage				
I	Reference level			
II	0.6	0.2	1.9	.418
III	1.7	0.5	5.6	.380
IV	1.3	0.3	6.3	.780
Grade				
I	Reference level			
II	3.6	1.3	9.7	**.012**
III	4.5	1.6	12.6	**.004**
Parametrium (yes)	0.4	0.1	1.7	.195
Right pelvis (yes)	3.2	1.1	9.5	**.038**
Left pelvis (yes)	0.5	0.2	1.6	.260
Bladder (yes)	0.9	0.4	2.1	.836
Rectum (yes)	1.4	0.6	3.3	.428
Vagina (yes)	0.8	0.5	1.3	.335
No regional organs involved				
0	Reference level			
1-3	7.8	1.2	49.1	**.030**
4+	5.4	0.5	57.5	.166
Distal metastasis (yes)	2.5	0.8	8.0	.128
Hydronephrosis (yes)	0.6	0.3	1.4	.231
Recurrence (yes)	2.2	1.4	3.6	**.001**

Multivariate Cox hazards regression model. Time variable=time from diagnosis to last follow up, event=death.

We demonstrated that grade II and III tumors were independently associated with reduced overall survival as compared to grade I tumors. Previous studies on the prognostic significance of tumor differentiation have shown conflicting results. In a retrospective study of the National Cancer Institute's SEER program in the United States, Matsuo et al.[28] showed that moderately- and poorly-differentiated tumors predicted decreased cause-specific survival among a total of 31 536 patients. In a German study based on the pathological examination of 467 samples from women with squamous cell cervical carcinoma, poorly-differentiated tumors (grade

Table 5. Predictors of 5-year overall survival among cervical cancer patients (n=134).

Predictor	Odds ratio	95%CI		P value
FIGO stage				
I	Reference level			
II	1.69	0.18	16.17	.647
III	0.46	0.04	5.08	.528
IV	NC	NC	NC	.999
Grade				
I	Reference level			
II	0.15	0.03	0.81	**.027**
III	0.09	0.02	0.57	**.010**
Right pelvis (yes)	0.46	0.07	3.19	.435
Left pelvis (yes)	0.29	0.03	2.47	.258
Bladder (yes)	0.55	0.08	3.72	.543
Vagina (yes)	0.69	0.24	1.95	.483
No. local involvement				
0	Reference level			
1-3	0.60	0.06	5.94	.660
4+	3.87	0.13	117.68	.438
Distal metastasis (yes)	NC	NC	NC	.999
Hydronephrosis (yes)	0.46	0.06	3.32	.442
Recurrence (yes)	0.18	0.07	0.47	**.001**

Multivariate binary logistic regression. Independent variable = survival at 5 years of FU. NC: not computable. Model fit measures: deviance=127, AIC=157, R2(McFadden)=0.291, R2 (Nagelkerke)=0.441.

III) had a significant impact on reducing recurrence-free survival, but had no effect on overall survival.[29] Nonetheless, there was no difference in survival rates between grade I and II tumors. When these grades (II and III) were merged, both recurrence-free and overall survival were longer in low-grade tumors when compared to high-grade tumors.[29] Other early studies indicated no prognostic role of the tumor grade in squamous cervical cancer.[30-32] The same observations were noted in a recent retrospective analysis of Indian women (n=167), showing no correlation between poor differentiation and advanced disease stage and reduced survival.[33] Seemingly, variations in sample sizes as well as the prognostic models used in the aforementioned studies are responsible for the variation in their findings.

Recurrence was also associated with shortened survival and low 5-year survival rates; as it reduced the mean survival by approximately 50% (from 9.8 to 4.7 years; hazard ratio=2.23) and the 5-year survival rate by 82%, as demonstrated by the Cox regression and multivariate binary regression models, respectively. A study by Poolkerd et al. reported low survival rates among patients with recurrent cervical cancer, with a median survival of 8 months after recurrence and 2-year survival rate of approximately 22% and 15% in local and distant recurrence, respectively.[34] Survival rates in case of recurrence may be further reduced by the treatment aim being palliative in several cases, as observed in our findings, in line with data reported by Poolkerd et al. showing a drop of 2-year survival from approximately 22% in treated patients to 4% in those who received only supportive care.[34]

Considering the previously mentioned predictors of survival, it is important to tailor effective prevention strategies. However, studies showed uneven progress in efforts aimed at reducing disease incidence across different countries owing to unequal treatment and the presence of several geographic, financial, cultural, and language barriers to screening.[35] In Western countries, primary prevention entails education regarding safe sexual practices as well vaccination against HPV. In Saudi Arabia and other Muslim countries, although the incidence of cervical cancer is significantly lower than other countries due to the predominant religious and cultural factors, the incidence of the main pathogenic factor (HPV infection) among Saudi women with invasive cervical cancers is very high (89%-96%),[8] and similar to that reported in women of Western societies (85-99%),[36] which stresses the relevance of promoting vaccination locally to fight against this cancer. Of note, the most common viral genotypes among Saudi women are genotypes 16/18 (in 75% of cases),[8] which are covered by the locally available vaccines; the quadrivalent (genotypes 6, 11, 16, and 18) and bivalent (genotypes 16 and 18) vaccines.

Further, the recent recommendations of the US Preventive Services Task Force[35] underscored the relevance of screening women aged 30-65 years using cytological testing every 3 years, high-risk HPV testing every 5 years, or both tests every 5 years to detect the disease at early stages. In the Saudi context, based on our results, women can benefit from early detection to start management, to control regional organ involvement, reduce recurrence, and ultimately improve OS and DFS outcomes. Studies conducted in the United Kingdom indicated that the impact of cervical cancer screening largely contributes to reducing disease-attributable mortality (by more than two-thirds) rather

Table 6. Local and international data on cervical cancer overall survival.

Author (year)	Country	N	Outcome	Value
Afinan et al (2019) (present study)	Saudi Arabia	190	Mean survival time	8.08 years
			Median survival time	6.08 years
			5-year survival rate	53.2%
El Sayed et al[24] (2017)	Saudi Arabia	60	4-year survival rate	79%
El-Senoussi et al[25] (1998)	Saudi Arabia	164	4-year survival rate	68.3%
Al Asiri et al[26] (2013)	Saudi Arabia	74	5-year survival rate	64.5%
Asiri et al[27] (2014)	Saudi Arabia	102	5-year survival rate	72.4%
Muhamad et al[15] (2015)	Malaysia	5859	Median survival time	5.48 years
			5-year survival rate	71.1%
Vishma et al[14] (2017)	India	380	Median survival time	<1 year
Liu et al[22] (2018)	China	98	5-year survival rate	82%
Carneiro et al[11] (2017)	Brazil	339	Mean survival time	~4 years
			5-year survival rate	74.0%
Mascarello et al[13] (2013)	Brazil	964	Mean survival time	6.88 years
			5-year survival rate	58.8%
Pardo and Cendales[10] (2009)	Colombia	455	Mean survival time	3.69 years
Benito et al[12] (2017)	Spain	139	Mean survival time	5.68 years
Khan et al[16] (2016)	USA	4000	Mean survival time	15.85-18.47 years depending on race
Benard et al[17,18] (2017)	USA	30 357 (2001-2003) 60 263 (2004-2009)	5-year survival rate	63.5% in 2001-2003 62.8% in 2004-2009

than reducing the incidence of cancer.[37,38] As such, it is necessary to promote regular attendance of women, including female university students, to screening through increasing their awareness levels regarding concurrent HPV coinfection and enhance the implementation of organized screening programs in uncovered areas.[39-41] Such aspects should be stressed since only 15.8% of patients in our analysis were diagnosed at an early stage (stage I) of the disease, indicating the importance of early detection.

This study has some limitations, which may impede generalizability of the findings. The major limitation is the retrospective design, which can result in recall bias and missing data. This would limit the effects of unrevealed significant factors and/or predictors of survival. Another consequent limitation of the retrospective design is the lack of adequate power to calculate a sample size at which the outcomes could be statistically reliable. Finally, we applied a Cox proportional hazards regression to investigate the impact of patient/tumor characteristics on survival, while a novel model, based on deep-learning neural network models, has proven to be more effective in predicting patients' survival;[42,43] the use of such a model in our setting may be recommended to improve treatment decision-making and outcomes by providing more accurate predictions.

In summary, cervical cancer treatment in the current study enabled an average OS of 97.1 months (~8 years), indicating a more prolonged survival time than that frequently reported in low- and middle-income countries. However, the 5-year survival rate (53.2%) was less than other rates estimated in developed countries but higher

than those in developing countries. Survival was impacted by all investigated tumor characteristics, including FIGO stage, tumor grade, involvement of local organs, distant metastasis, and hydronephrosis; however, it was independently associated with tumor grade, number of regional organs involved, and recurrence. There is a need to improve early detection of cervical cancer by conducting efficient screening programs regularly to detect the disease at manageable stages and hence improve patient survival. Awareness should be raised among Saudi women about prevention and the risk of concurrent HPV infection on cervical cancer incidence.

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