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Indicators of Survival and Prognostic Factors in Women Treated for Cervical Cancer at a Tertiary Care Center in Bangladesh

N HOSSAIN[a], H HOQUE[b], S PARVIN[c], M JAHAN[d], S MONIRA[e]

Abstract:

Background: Cervical cancer remains a major cause of cancer deaths among females in low and middle-income countries. Local survival studies are crucial for assessing overall management effectiveness, as they reflect the level of care provided and awareness among the population about screening and early diagnosis.

Objectives: To analyze disease-free survival (DFS) among patients treated for cervical cancer and investigate clinical, management, and outcome-related independent factors associated with survival.

Materials & Methods: A retrospective study was conducted on 393 cervical cancer patients from January 2014 to 2020 at the Gynecological Oncology Department of the National Institute of Cancer Research and Hospital (NICRH), analyzing demographic and clinical data, tumor characteristics, treatment options, and outcomes, including recurrence, as predictors of survival.

Results: Three hundred ninety-three patients included in this study. The mean average age was 49 years, range 28-85 years. Total follow-up times(months), mean 38; range (6-108) months. Among them 61% were postmenopausal, with a majority of women having a parity of 59% and an average marriage age of 14.93±3.95. The most common presenting symptom was irregular bleeding, with 62.8% of patients being illiterate. Tumor characteristics included FIGO stage I, II, and III, with squamous cell carcinoma being the most common histopathological type. Patients received initial surgery (21.6%), radiotherapy (74%), and palliative care (4%). The mean duration of follow-up (DFS) was 2.20 years in <24 months and 3.35 years in >24 months. Residual disease and recurrence were 6.4% and 30.5%, with local recurrence being the most common (22.6%) and liver being the most common site of distal recurrence (38.3%). Survival was independently associated with age, grade II, and FIGO stage III.

Conclusion: Age, grade, and FIGO clinical stages adversely affect the overall survival of cervical cancer patients

Key words: Disease Free Survival (DFS), Prognostic factors, Treatment, Cervical Cancer

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Introduction

Background: Cervical Cancer (CC) is a health crisis impacting women and their families across the world, especially in low-resource settings[1]. In low- and middle-income countries (LMICs), CC continues to be the second most prevalent cancer in morbidity and one of the leading causes of cancer deaths among females[2,3].

In 2020, an estimated 604,237 women were diagnosed with cervical cancer globally, representing 6.5% of all female cancers[1]. CC killed an estimated 314,843 women in 2020, 20% of whom were in less developed regions of the world, where access to prevention, screening, and treatment services is severely limited[1]. Due to the lack of valid prevention and screening methods, it is worth noting that the morbidity of cervical cancer has still increased in less-developed countries in recent years.

The prognosis and survival of patients with cervical cancer depend, 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 also includes surgical, radiation, and chemotherapy protocols.

a. Dr. Nasrin Hossain, Associate Professor, Dept. of Gynecological Oncology, National Institute of Cancer Research Hospital (NICRH), Mohakhali, Dhaka, Bangladesh
b. Dr. Humaira Hoque, Junior Consultant, Dept. of Gynecological Oncology, National Institute of Cancer Research Hospital (NICRH), Mohakhali, Dhaka, Bangladesh
c. Dr. Salma Parvin, Junior Consultant, Dept. of Gynecological Oncology, National Institute of Cancer Research Hospital (NICRH), Mohakhali, Dhaka, Bangladesh
d. Dr. Merina Jahan, Junior Consultant (Obst. and Gynae), National Institute of Cancer Research Hospital (NICRH), Mohakhali, Dhaka, Bangladesh
e. Dr. Sirajum Monira, Medical Officer, Dept. of Gynecological Oncology, National Institute of Cancer Research Hospital (NICRH), Mohakhali, Dhaka, Bangladesh

Address of Correspondence: Dr. Nasrin Hossain, Associate Professor, Dept. of Gynecological Oncology
National Institute of Cancer Research Hospital (NICRH), Mohakhali, Dhaka, Bangladesh, Mobile: 01711395089, E-mail: nasrinhossain23@gmail.com

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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 case of recurrence or metastasis, the prognosis remains poor. In developing and under developing countries, 5 years survival rates declined considerably due to inadequate treatment and advanced stage at diagnosis[2,3,4].

The indicator of clinical prognosis is the key factor in the therapeutic decision-making process. For cervical cancer, the therapeutic strategy generally depends on the clinical stage, which is established by the FIGO[2]. The clinical assessment of the anatomic extent, the error rate between the final histopathological classification and FIGO staging is about 25% in patients with early stages[5,6]. Hence, it is inevitable to enhance the FIGO staging system for more precise and practical prognostication of cervical cancer patients, optimizing the life quality of long-term survival and individualized treatment.

It is crucial to investigate survival in cervical cancer at the local level to provide an approach to the effectiveness of the overall management as it reflects the level of care of the patients. Thus, we conducted this study to provide insight into survival and disease-free survival among women treated and followed up for cervical cancer, and it investigated the clinical, management, and outcome related independent factors of survival.

Materials & Methods:

This retrospective study included women with CC who were treated and followed up at the Gynecological Oncology Department, National Cancer Institute of Research and Hospital (NICRH), Dhaka, Bangladesh, between June 2014 to December 2020, who met the inclusion criteria. Patients with missing follow-up data were excluded. The institutional ethical committee approved the study, and informed consent was obtained from all patients. The following data were collected i) All baseline demographic and clinical data including age, parity, age of marriage, marriage before menarche, menopausal status, and educational level ii) Tumor characteristics including FIGO stage, grade, histopathology. iii)Management data, including surgery, radiotherapy with or without concurrent chemotherapy (induction, adjuvant), systemic chemotherapy, and palliative care. iv) Outcome data during follow-up of the patient by taking history, physical examination, and all necessary investigations to find out the residual disease, DFS and recurrence pattern of disease. If suspected recurrence, it was biopsy proven.

Statistical Analysis:

All statistical data were analyzed by using SPSS (22.0 version). Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean and standard deviation (SD). Kaplan-Meier survival analysis was carried out to estimate the mean, overall survival (OS), and disease-free survival (DFS). Cox-regression analysis was used to select prognostic factors. P-value <0.05 was considered statistically significant.

Results:

Baseline demographic and clinical characteristics; Three hundred ninety-three patients fulfilled the inclusion criteria. The mean (SD) age was 49.63±9.86, range (years) 28-85. Total follow-up times were range (6-108) months, average of 38.78±25.78. Table 1 shows, 237 (59.5%) had 1-4 children, and 159(40.5%) had more than five children. Average married age: 14.93±3.95 years, and 116(29.5%) had married before menarche. Most women were postmenopausal, 240 (61.1%) and 153(38.9%) perimenopausal. At educational level, 209 (53.2%) were illiterate.

Table I: showed the majority were in the age group ≥45(73.6%) years. Majority parity was 1-4(59.5%). The average married age was 14.93±3.95 years. Majority (70.5%) were not married before menarche. 61.1% of

Table-I

Baseline demographic and clinical characteristics (n=393)

Characteristics	Frequency	Percentage
Age in years		
<45	104	26.4
≥45	289	73.6
Parity		
1-4	234	59.5
≥5	159	40.5
Married age	14.93±3.95	
Married before menarche		
Yes	116	29.5
No	277	70.5
Menopausal		
Yes	240	61.1
No	153	38.9
Education level		
Illiterate	209	53.2
Primary	166	42.2
Secondary	18	4.6

patients were menopausal. Maximum patients were illiterate (53.2%).

Table II showed tumor characteristics; the most common presenting symptoms were irregular bleeding 247(62.8%), postmenopausal bleeding 102 (26%), and intermenstrual bleeding 44(11.2%). Regarding the type of growth, 65.6% was exophytic/cauliflower type, then endophytic growth, ulcerative growth, and no visible growth were 16.53%, 10.17%,7.63%, respectively. It was observed that a maximum of 174 (44%) were FIGO stage IIB followed by 117(29%) were stage IIIB, then stage IIA, IB1, IB2, IB3 were 7%, 2.5%, 4.6%, 3% respectively. Least common stage was IIIA (1%). Majority (72.5%) were grade II (72.5%) followed by grade I (14.5%) and grade III (13%). Regarding histopathology, the majority (86%) were squamous cell carcinoma (SCC), and 14% were adenocarcinoma (ADC).

Table II

Tumor characteristics (clinical and pathological) (n=393)

Characteristics	Frequency	Percentage
Symptoms: menstrual bleeding		
Intermenstrual bleeding	44	11.2%
Irregular bleeding	242	62.8%
Post menopausal bleeding	102	26%
Type growth		
Exophytic growth/Cauliflower/	258	65.6%
Endophytic growth	65	16.5%
Ulcerative growth	40	10.1%
No visible growth	30	7.6%
FIGO stage		
Stage IB1	10	2.5%
Stage IB2	18	4.6%
Stage IB3	12	3%
Stage IIA	26	7%
Stage IIB	174	44%
Stage IIIA	2	1.5%
Stage IIIB	117	29%
Un stage	34	8.6%
Grade		
Well differentiated	57	14.5%
Moderately differentiated	285	72.5%
Poorly differentiated	51	13%
Histological type		
Squamous cell carcinoma	338	86%
Adenocarcinoma	55	14%

Table II showed 65.4% were exophytic growth, 16.53% were endophytic growth, 10.1% were ulcerative growth, and 7.63 % had no visible growth. It was observed that maximum (44%) were FIGO stage IIB followed by stage IIIB (29%), stage IIA(7%), stage IB1 (2.5%), IB2(4.6%),IB3(3%) and IIIA were only 1.5%. Majority (72.5%) were moderately differentiated followed by 14.5% were well differentiated and 13% were poorly differentiated. Majority (86%) were squamous cell carcinoma and 14% were adenocarcinoma.

Table III: Distribution of initial treatment with CC; surgery was 22%, majority of patients received radiotherapy among them Induction CT+ RT(CCRT+EBRT) 52%, CCRT 20%, Only EBRT 2%. Initially palliative care received 4% of cases.

Table-III

Distribution of initial treatment received with cervical cancer(n=393)

Treatment options:	Frequency	Percentage
Surgery	85	22%
Radiotherapy		
CCRT	82	20%
EBRT alone	8	2%
Induction CT+RT (CCRT/EBRT)	203	52%
Palliative care	15	4%

Table III showed majority (74%) received radiotherapy and only 22% had surgery

Table IV shows follow-up and outcome following disease: the majority of patients follow-up more than 24 months 213(54%) and the rest were ≤24 months 181(46%). Residual disease had 25 (6.5%). Recurrence developed in 120(30.5%) patients. Most common site of recurrence is local 89(22.6%), next distal recurrence, and both local and distal recurrence were 16(4.1%) and 15(3.8%) respectively. Among the distal recurrence, liver is the most common 12(39%) sites, then bone, cervical LN, lung and others were 8(26%), 5(16%),4(13%) and 2(6.4%) respectively.

Table V: showing factors associated with DFS among cervical cancer patients(n-393), mean DFS was higher in Stage IB2 (67.20±6.17) than Stage IIB (33.60±40.66), Stage IIIB (33.73±24.70). It also observed that DFS survival was higher in grade I (49.17±39.88), than in grade II (38.57±22.13), grade III (27.97±19.23)

Table-IV

Outcome status following treatment

	Frequency	Percentage
Overall follow up time		
≤24 months	181	45.9
>24 months	213	54.1
Residual disease	25	6.4
Recurrence (total)	120	30.5
• Local recurrence (cervix pelvis)	89	22.6
• Distal recurrence	16	4.1
• Local and distal recurrence	15	3.8
Site of distal recurrence(n=31)		
• Liver	12	39%
• Bone	8	26%
• Lung	4	13%
• Cervical LN	5	16%
• Others	2	6%

Table-IV showed 45.9% had follow up 24 months and 54.1% had follow up > 24months.It was observed that residual disease and recurrence were 6.4% and 30.5% respectively, Among the recurrence; local recurrence (22.6%), distant recurrence (4.1%) and both local and distant recurrence (3.8%). Liver is the commonest site of distal recurrence (39%), then bone (26%), cervical LN (16%), lung (13%).

Table-V

Prognostic factors associated with survival

Variables	Mean ± SD
Figo stage	
Stage IB1	45.33±18.20
Stage IB2	67.20±6.19
Stage IB3	38.60±71.2
Stage IIA	43.60±40.66
Stage IIB	33.54±24.84
Stage IIIA	43.60±40.66
Stage IIIB	33.73±24.70
Un stage	47.98±18.54
Grade	
Grade I	49.17±39.88
Grade II	38.57±22.13
Grade III	27.97±19.23
Histopathology	
SSC	43.89±25.64
ADC	25.75±21.25

Table V showed; mean disease-free survival was higher in stage IB2 (67.20±6.19) months and lower were stage IIB (33.54±24.84) and stage IIIB (33.73±24.70) months. It also observed higher disease-free survival in grade I than grade III which were 49.17±39.88 vs 27.97±19.23 respectively. SSC had more survival than ADC.

Table-VI

Prognostic factor for survival related cox-proportional hazard model analysis

Variables	HR	P value	95% of CI	
			Lower	Upper
Age				
<60 vs >60	2.12	0.001	1.660	2.708
Histology				
SCC vs ADC	1.78	0.001	1.414	2.258
Grade				
I vs II	1.69	0.011	1.314	2.191
I vs III	2.88	0.001	2.193	3.597
II vs III	1.18	0.025	1.466	2.182
FIGO stage				
I vs II	1.65	0.016	2.013	3.851
I vs III	2.73	0.001	2.377	4.680
II vs III	0.84	0.091	0.947	1.173

Table VI shows; >60 years, adenocarcinoma, grade III and FIGO stage III were statistically significant and higher risk of recurrence (P<0.05).

Figure 1 shows, the mean disease-free survival according to follow-up time was 2.20 years in d"24 months and 3.56 years in more than >24 months. The cox multivariate hazards regression model showed, Age (HR=2.12, p-0.001), histopathology (HR=1.78, p- 0.001), grade II (HR=2.88, p-0.001), FIGO stage III (HR=2.73, p-0.001) (Table: VI)

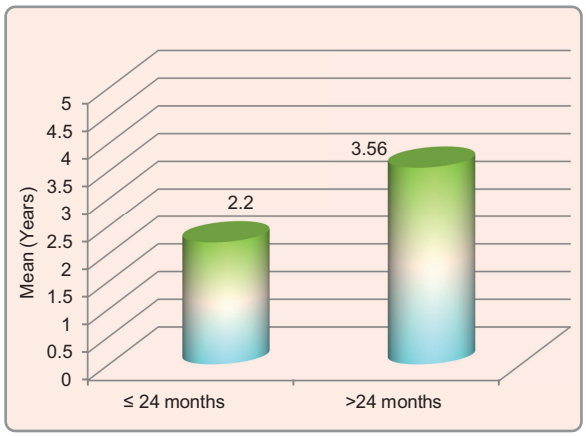

Figure 1: *Disease free survival according to follow up time*

Figure shows mean disease-free survival were 2.20 years in ≤24 months and 3.56 years in >24 years.

Discussion:

Cervical Cancer ranks as the second most common cancers for Bangladeshi women at the reproductive age after breast cancer[6,15]. In different settings, the prognostic significance of the disease varies considerably according to sociodemographic factors, the stage at which it is diagnosed, and the accessibility to effective cause and treatment. In our study, the median follow-up time was 38 months (range 6-108). Median follow-up time is considerably shorter than that reported in the other studies[2,8,9]. Analysis of various factors influencing survival in CC patients is usually presumed that cancer in younger patients is biologically much more aggressive than in older age[10]. Still, the present study revealed that ages >60 years had a worse prognosis than <60 years (HR:2.12, p=0.001). Another study[17] showed that age is not the factor worsening the prognosis of survival.

In the current study, the FIGO clinical stage is one of the main prognostic factors in CC[1] patients (HR;2.73, p=0.001). Stage III and Stage II had worse prognosis than stage I, that is reduced disease-free survival and higher risk of recurrence. Others studies[9,16] found that the clinical stage of CC had prognostic factors in the survival but was statistically significant. Another studies[9,14,17] found that the advanced stage affected survival where, FIGO stage IIIB was found worse than FIGO stage IB & IIB. Another study[16] showed that FIGO stage I &II tended to have better OS, LFFS, and DFS than FIGO stage III, but the difference is not significant.

One of the most significant prognostic factors in CC is histopathology. In the current study comparing the SCC vs ADC found that adenocarcinoma had a worse survival outcome (HR:1.78, p-0.001). Mean DES in SCC and ADC were 43.25±25.64 and 25.75±21.25, respectively. Our study findings correlated with other studies[7,10,15].

Another significant prognostic factor was the grade of the tumor. In this present study, we found that grades I, II had worse prognostic factors (HR: 2.88, p-0.001) than grade I, which was correlated with other studies[2,7,9,11,12]. They also revealed that grade II, III were worse prognostic factors. Other studies[13,16] indicated no prognostic role of the tumor grade is SCC. The same observation was noted in a recent retrospective analysis of an Indian study, showing no correlation between poor differentiation & advanced stage with reduced survival[8].

In this study, 30% developed recurrence during their follow up time. This corresponds with other studies that found 25% and 27% failure rate during their observation[1,2]. In the present study, among the sites of recurrence, the liver is the common site (39%), subsequently bone (25%), cervical LN (16%), and the least common site lung (13%). One studyx revealed that the incidence of lung metastasis from cervical cancer is low, with an average incidence of 2.1% -6.1%. In another study[8,12], blood-borne metastasis with CC was mainly found in the liver, lungs, and bones. This finding was similar to the present study finding.

In present study, mean disease-free survival depends upon the clinical stage of disease. In CC stage IB2, IIB and IIIB DFS were 67.20±6.19, 33.54±24.84, and 33.73±24.70, respectively. Several other studies revealed[1,6,7,14] that the clinical stage has a significant effect on survival. But, another study[10,12] clearly shows that the stage is not an independent factor that could

help predict the clinical course; it also depends on the other factors that they had analyzed. In this study, DES was also depending upon the differentiation/grade of disease. Grade I had mean DFS (49.17±39.88) followed by grade II (38.57±22.13) and grade III (27.97±19.23). Our study, we found that mean DFS was more (43.89±25.64) in SCC than ADC (25.75±21.25). Other studies[7,15,16] also reported ADC had poorer survival than SCC.

Limitation:

This study has some limitations; major limitation is the retrospective design and follow up time was slightly short (median 38 months). Another, we applied a cox-proportional hazards regression to investigate the impact/tumor characteristics on survival. At the same time, a novel model based on a deep-learning neural network model has proven to be more effective in predicting a patient's survival.

Conclusion:

In this study, the independent prognostic factors in disease-free survival (DFS) of cervical cancer were assessed. Age, clinical stage, grade, and histopathology were the significant prognostic factors for cervical cancer patients.

Conflict-of-interest: There is no potential conflict of interest.

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