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Prognostic Impact of Histopathology in Patients with Advanced Stage Cervical Carcinoma Treated with Radiotherapy

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Summary:

Introduction: Cervical cancer is the fourth most common cancer in women worldwidev . Most patients in developing countries including Bangladesh present at advanced stage. Histopathological types of cervical cancer influence the treatment outcome when treated by radiation therapy.

Objective: To determine the disease free survival (DFS) in different histopathological types in advanced stage cervical carcinoma treated with radiotherapy.

Methods: A prospective cohort study was conducted in Gynaecological oncology outpatient department (GOPD) of National institute of Cancer Research & Hospital (NICRH), Dhaka for one year from September'2016 to July'2017. Advanced stage (IIB-IVB) cervical cancer who completed radiation therapy and histopathological type either squamous cell carcinoma or adenocarcinoma of cervix were included in this study.

Results: The median follow-up time was 1.82 years; range was 8 to 24 months. Average disease free survival (DFS) was 1.53years in squamous cell carcinoma (SSC) and 1.51 years in adenocarcinoma (ADC). Local recurrences was higher in adenocarcinoma group (62.5%) than squamous cell carcinoma (30.5%) & the difference was statistically significant (p = 0.001). Loco-regional recurrence and distal recurrence were also higher in ADC than SSC but results were not statistically significant (p=.345, p=.795). In multivariate analysis it was shown that histopathological type and stage of disease were found to be independently significant prognostic factors for DFS, hazard ratio were 1.766 (p=.018) and 2.173 (p=.006).

Conclusion: Adenocarcinoma was a poor prognostic factor for patients with locally advanced cervical carcinoma. Advanced stage of disease was also significant predictor for disease free survival.

Key ward: cervical carcinoma, advanced stage, histopathological, radiotherapy.

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Introduction:

Cervical cancer is a major global public health problem and the fourth world wide leading cause of cancer death in women[1].

In Bangladesh, cervical cancer is the second common cancer in women after breast[2]. To reduce mortality from cervical cancer and improve survival, it is necessary to identify the prognostic factors.

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Among the gynecological malignancies, the most common cases attending GOPD of NICRH is cervical cancer[3]. Most of them are in advanced stage disease & treated with radiotherapy. Early stage of cervical cancer is defined as FIGO stages I to IIA and advanced stage in defined as stage IIB to IVBt . Several studies have reported that histopathological type is an important prognostic factor in advanced stage cervical canceru – –'v . Other factors such as clinical stage, cell differentiation, treatment modality are also prognostic factors for cervical cancerv 'w .

The present study was carried out to find out the prognostic impact of histopathological type of cervical cancer on disease free survival (DFS), local (cervical)/ loco-regional (pelvic) recurrence and distal recurrence after completion of treatment with RT.

Methods:

It was a prospective cohort study conducted in gynecological oncology outpatient department (GOPD)

of National Institute of Cancer Research &Hospital (NICRH) during the period of September 2016 to September 2017 (one year). Sampling technique was purposive. Advanced stage (IIB-IVB) cervical cancer who completed radiation therapy and histopathological type either squamous cell carcinoma or adenocarcinoma of cervical cancer were included in this study and early stage (IB-IIA) cervical cancer, patients with incomplete treatment and any malignancy other than cervical cancer were excluded from this study. Formal permission was taken from the ethical committee of the NICRH, Dhaka. Cervical cancer cases were diagnosed by history, clinical examination and histological confirmation of biopsy specimen from cervix. Inform consent was taken from each patient before enrollment. Data were collected in a pre-designed data collection sheet. Clinical and pathological data were collected from medical records, pathology reports, and cancer registry reports. Follow-up schedule was every 03 months. Every patient was evaluated by history taking, complete physical examination. If there was any suspicious of recurrence on clinical evaluation, than USG/CT scan of whole abdomen & pelvis and chest X –Ray was advised. All recurrence was confirmed by tissue diagnosis. Data were analyzed using SPSS software. A p value <0.05 was regarded as statistically significant.

Result:

One hundred and fifty biopsy proven advanced stage (IIB – IVB) cases of cervical carcinoma were included in this study. Mean age was 48 yrs (range 35-66 yrs). Mean follow-up time was 1.82(yrs) and range was (0.08-2 yrs). Table 1: showing clinicopathological characteristic of the study population. Figure 1: shows average DFS was 1.53 years in Squamous cell carcinoma and 1.51 years in Adenocarcinoma but findings was not statistically significant. Figure2: shows adenocarcinoma histopathological type was associated with shorter DFS. The differences was not statistically significant (<0.05).

Table-I

Clinicopathological characteristics (n=150)

Characteristics	SCC		ADC	
	Frequency	Percent (%)	Frequency	Percent (%)
Age				
• <50	69	46	18	12
• >50	49	32.6	14	9.3
Parity				
• <2	16	10.6	1	1
• >2	102	68	31	20.6
Menopausal Status				
• Premenopausal	53	35.3	19	12.6
• Postmenopausal	65	43.3	13	8.6
FIGO Stage				
• Stage ll B	81	54	13	8.6
• Stage lll A	4	2.6	0	0
• Stage lll B	33	22	19	12.6
Histopathological Type	118	78.7	32	21.3
Grade				
• Grade 1	33	22	5	3.3
• Grade 2	73	48.6	19	12.6
• Grade 3	12	8	8	5.3
Treatment				
• CCRT	18	12	10	6.6
• RT	96	64	22	14.6
• EBRT	4	2.4		

Table II: showing local (cervix) recurrence (62.5%) in ADC than SSC (30.5%) and found statistically significant (p=0.001). local pelvic recurrence was higher in ADC (12.5%) than SSC (8.5%). Distal recurrence was also higher in ADC than SSC which was 6.2% VS 5.1% respectively .Both of the differences were not statistically significant (> 0.05). Table III: shows univariate analysis, shorter disease-free survival in both SSC and ADC in relation to advanced stage of cervical cancer. Table IV: shows local recurrence was higher in stage IIIB (50%) and local regional recurrence was also higher in stage IIIB (57.1%). Both of the differences were statistically significant (<0.05%). Multivariate analysis revealed that histopathological type and stages of cervical cancer were independent significant predictors for DFS of the patients. Hazard ration of histopathological type and stages were being 1.76 (q= .018) and 2.17(q =.006). (Table VI)

Table-II

Relationship of different histopathological type of cervical cancer with recurrence

	SSC		ADC		p value
	No	%	No	%	
Local recurrence	36	30.5	20	62.5	0.001
Loco- recurrence (regional)	10	8.5	4	12.5	0.345
Distal recurrence	6	5.1	2	6.2	0.795

Table-III

Univariate analysis showing DFS in different stages of cervical cancer patients

	Stage IIB	Stage IIIB	P value
SCC			
Disease free survival	1.59±0.39	1.50±0.32	0.670
ADC			
Disease free survival	1.55±0.37	1.20±0.36	0.592

Table-IV

Relationship of local recurrence, local regional recurrence and metastasis according to different stages of cervical carcinoma

	Stage IIB		Stage IIIA		Stage IIIB		P value
	No	%	No	%	No	%	
Local recurrence	24	42.9	4	7.1	28	50.0	0.005
Loco- regional recurrence	6	42.9	0	00	8	57.1	0.005
Distal recurrence	4	50.0	0	00	4	50	0.163

Table-V

Multivariate analysis showing DFS in relation to different variable

DFS	HR	95% CI		P value
		Lower	Upper	
Age	1.005	0.657	1.538	0.980
Histology	1.766	1.100	2.836	0.018
Stage (II VS III)	2.173	1.256	3.760	0.006
Grade (I&II VS III)	1.453	0.855	2.467	0.167
Treatment duration	0.641	0.375	1.095	0.103

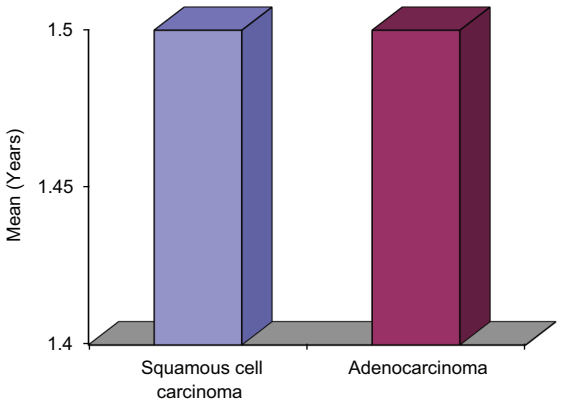

Fig.-1: *Disease free survival according to squamous cell carcinoma and adenocarcinoma*

Figure shows average disease free survival of 1.53 years in squamous cell carcinoma and 1.51 years in adenocarcinoma.

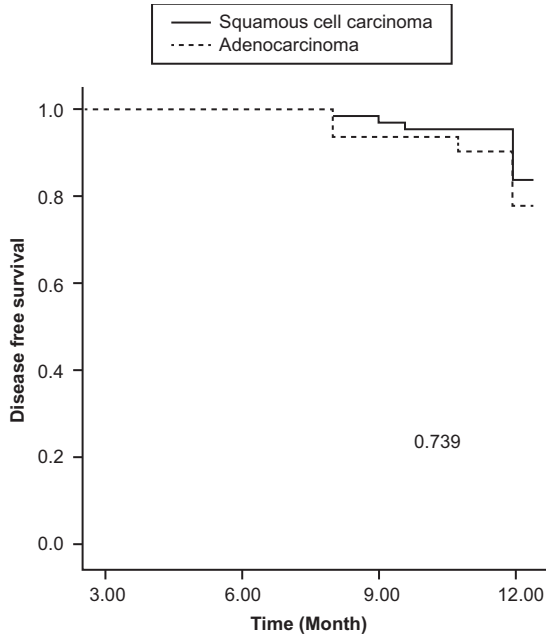

Fig.-2: *The kaplan- Meier survival curve showing graphic presentation DFS of SSC and ADC*

Discussion:

The factors, which affect the prognosis of patients with cervical cancer, are very complex and interactive and they jointly affect the prognosis of patients. This study revealed that Histopathological type was an important prognostic factor in advanced stage cervical cancer treated by radiation therapy.This study showed that, Disease free survival was longer in squamous cell carcinoma cases (1.53 years) than adenocarcinoma (1.51 years).

In case of squamous cell carcinoma, 83.9% of patients were disease free for more than 01 years and in adenocarcinoma, 75% of patients were disease free for more than one year. Similar findings were found in several other studiesv ‘w . In one studyx , patients with ADC had a poorer survival than SSC, particularly among the patients with advanced stage and indicate a strong impact of Adenocarcinoma compared with squamous cell carcinoma. Another studyy reported that the DFS and OS (overall survival) of patients with adenocarcinoma were significantly shorter than that of patients with SSC. One Japanese study[1]p reported that non-squamous histopathological type was the first independent risk factor when all relevant factors were taken into account. One Chinese study[11] reported that adenocarcinoma was an independent factor OS (HR= 7.83; 95% CI=2.23-27.4; p=0.001), LFES (Local failure free survival) (HR = 5.67; 95% CI= 1.68- 19.1; p=0.005) and DFS (disease free survival) (HR= 6.47; 95% CI= 2.26-18.5: P= 0.001). The 4 years DFS rates for ADC and SSC were 45.3% versus 71.9% (p=0.006) respectively.

In this study, among total number of SSC (118) cases, local recurrences was 36 (30.5%) and total number of ADC (32) cases, local recurrences was 20 62.5%). Local (cervical) recurrence was significantly higher in ADC than SSC (p=0.001). Local pelvic recurrence occurred in 10 patients of SSC (8.5%) and 4 patients in ADC (12.5%). Local regional recurrence is higher in ADC than SCC. Distal recurrence was also high in ADC type (6.2%) than SSC (5.1%). Several other studies have similar finding [11′13′1]t ′1v . In one study[1]v reported that in case of SCC, 25.0% case had loco regional recurrence and 36.1% had distant failure. In case of ADC, 32.7% developed loco-regional recurrence and 49.1% had distant recurrence. Eifel al[1]w analyzed 229 patients with cervical carcinoma and reported that the incidence of the pelvic recurrence was 17% for ADC and 13% for SSC. Also reported that distant metastasis were more frequent in patient with adenocarcinoma than SSC (37% VS 21% p=0.01). In this study finding ADC has higher local recurrence, pelvic recurrence, metastasis than SSC. One Taiwan study[11] reported that local failure free survival for adenocarcinoma and Squamous cell

carcinoma were 55.4% versus 83.9% (p=0.01) respectively. One study conducted in Thailand[13] included 611cervical cancer patients and reported that (6.2%) developed recurrence of disease. Among them local recurrence was 21 (55.3%), distal recurrence was 15 (39.5%) and combined 2 (5.2%). One Japanese study[1u] reported that distant failure rates of SSC and ADC cases were 36.1% and 49.1% respectively.

In present study, multivariate analysis shows that histopathological type and advanced stage cervical carcinoma were independent prognostic factors in disease free survival of SSC and ADC. Advanced stage cervical adenocarcinoma has shorter disease free survival than squamous cell carcinoma. These findings correlated with several other studiesy [´12´13]. One European study [13] reported that advanced stage cervical carcinoma tended to have poor survival. The 4 years OS, LFES(local failure free survival) and DFS were for stage I+II and stage III were 76.2% versus 70.1% (p=0.33), 80.4% versus 72.3% (p=0.59) and 70.8% versus 60.7% (p=0.52) respectively. Another study[12] reported that FIGO stage was a independent prognostic for OS & DFS. OS and DFS as a function of FIGO stage were 87.9% (95% CI 77.1%-93.8%) and 83.3% (95% CI 71.8% - 90.5%) for stage II, 59.1% (95% Cl 47.6%- 68.9%) and 66.6% (95% CL 54.6%- 76.1%) for stage III. One Thailand studyy reported that FIGO stage IIB compared with FIGO stage III +IV were associated with poor survival among patients with advanced stage ADC (HR 2.9; 95% 2.0- 4.4 and HR 4.5 95% CI 2.6- 7.9 respectively) and SSC (HR 1.7; 95% CI 1.4-2.0 and HR 3.7 95% Cl 2.8-4.9 respectively).

In this study revealed that local recurrence was more common in stage IIIB (50.0%) than stage IIB (42.9%). This finding was similar to several other studies[13´1t ´1v] reported that local recurrence was more common according to advance stage cervical carcinoma.

In current study local regional recurrence is higher in stage IIIB (57.1%) than stage IIB (42.9%). Loco-regional recurrence is higher in advanced stage cervical carcinoma in following study [13´1t ´1v] .

In present study, 37% of cases with stage IIB or III had local recurrence after RT and 14.6% of cases with stage IIB or III had distant metastasis after RT. Nakano et at[1x] reported that the rate of distant failure after RT was 14% for stage II disease and 25% for stage III disease.

Conclusion:

Histopathological type of adenocarcinoma is a significant and independent prognostic factor for disease free survival and local recurrence in advanced stage cervical carcinoma patient treated with radiotherapy. Advanced stage cervical carcinoma is also significant and independent prognostic factor in DFS, local recurrence and metastasis. This finding may be useful for further tailored treatment-strategies and follow-up planning among patients in each histopathological type.

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