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Retrospective Analysis of Cervical Cancer Staging in two Cohorts and its Application in 2018 Revised FIGO Staging for Cancer Cervix

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Abstract

Introduction: *cervical cancer is the second most common cancer of women in Bangladesh. Information about the extent of any cancer is critical for treatment planning .For the management of cervical cancer clinical staging is the first and foremost task and disease stage is the single most important prognostic factor.*

Objective: *To know the distribution of clinical stages of cervical cancer, to validate the revised 2018 FIGO staging system for cervical cancer with a particular focus on stage 1B and to know the differences in distribution of stages among two cohort groups.*

Methods: *Retrospective analysis was conducted among two cohorts of cervical cancer patients. First group of cervical cancer patients underwent Examination Under Anesthesia (EUA) for clinical staging during December 2011 to July 2017 and second cohort was the same type of patients undergoing same procedure by different group of observer from August 2017 to June 2019. Chi square test was done to know the difference in stages between two groups. P value <0.05 was considered as significant difference.*

Results: *In the first (8.12.11-1.7.17) cohort (n—479) maximum (68.21%) patients were between 41 to 60 years old. Similarly in the second (2.8.17—30.6.19) cohort (n—256) maximum (63.45%) patients were between 41 to 60 years of age. Significant difference observed in the measurement of the size of the tumour when it was 2.1 to 4 cm in size. (p value-0.001) . Great difference observed in performing cystoscopy during EUA (p value -0.001) between two cohorts. In the first cohort 27.39% and in 2nd cohort only 2.73% patients underwent cystoscopy. Differences also observed in diagnosing stage 11A, B and 4 A diseases.*

Conclusion : *The 2018 FIGO staging system for cervical cancer is useful to distinguish stage 1B disease and it is very fruitful in taking decision regarding management. An important information obtained from this analysis is that great variation can occur in diagnosing stages of cervical cancer by different group of observer.*

Key wards: *Cervical cancer, Clinical staging ,Observer variation, FIGO 2018, Revised staging.*

Introduction:

According to the GLOBOCAN data 2018, cervical cancer is the fourth most common cancer in women worldwide, and is the second most common in low and middle income countries (LMIC)[1]. While its incidence in developed countries is low (6-9.5 per

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lac) and still declining, countries which do not have access to screening program have a high incidence up to 43.1 per lac[2]. In 2018 ,there were an estimated 569847 new cases and 311365 deaths worldwide annually. More than 85% of these cases are in developing countries.

The hallmark of treatment of this cancer depends on correct staging and a good staging system is the ability to define anatomical extent of the disease which is the indicator of survival outcomes. Thus the treatment guide is allocated. Staging also allows comparison of outcome of treatment between centers. Cancer staging is an evolving process, can be done clinically or surgically. Cervical cancer staging is traditionally done by clinical examination. But now-a-days MRI, CT and PET are widely used where available and often recommended in contemporary guidelines like the NCCN guidelines[2].

The purpose of the staging system is to provide uniform terminology for better communication among health professionals and to provide appropriate informations to the patients regarding prognosis which results in improved treatment. This is a constantly evolving process as more new therapeutic modalities, imaging technologies and surgical approaches are developed, more prognostic information become available.

Since 2009 the International Federation of Gynaecology and Obstetrics (FIGO) staging system for cervix has been revised for the first time in 2018. Considerable progress has been made in the use of imaging modalities to evaluate extent of invasion of cervical cancer[3]. Although the availability and ability of various imaging technique has been increased substantially both in high and LMICs, the capabilities to asses the abdomen ,pelvis and retroperitoneal lymph nodes by different imaging modalities varies considerably. Moreover interpretations made by the radiologists varies considerably between person to person.

According to GOG report, the errors in FIGO clinical staging ranges 24% for stage 1B to 67% for stage 11A . MRI is coming up for detection of stromal , parametrial , bladder and vaginal wall invasion. But MRI is costly and technically difficult to interprete. So most of the time we have to depend upon clinical Examination Under Anesthesia (EUA) for proper and correct staging of cervical cancer which is more informative and objective, specially for operable cases.

Advances in Minimally Invasive Surgery (MIS) has led to the widespread use of this technique for paraaortic lymph node sampling in advanced stage cervical cancer (stage 3 and 4) to determine the need for extended field radiation for stage 3C2 disease. Interestingly some poor-resource country like Srilanka is using MIS routinely for retrieval of paraaortic nodes by laparotomy or laparoscopy[4].

FIGO has included preoperative radiological and postoperative histopathological evaluation of pelvic and paraaortic lymph nodes in cervical cancer staging system and reclassified the stage 3 disease as stage 3A(involvement of lower one third of vagina) , stage 3B (involvement of pelvic sidewall), stage 3C1(involvement of pelvic lymph nodes) and stage 3C2 (involvement of paraaortic lymph nodes). When lymph node involvement is diagnosed histopathologically then it should be noted as “p” and when it is diagnosed radiologically should be noted as “r” . This cohort study done to adopt resived FIGO staging for stage 1B only . In this study due to lack of information about radiological or pathological findings revised FIGO staging for stage 3 and 4 could not be adopted .

The FIGO Gynaecologic Oncology Committee determined that the staging classification needed revision to maintain unanimity worldwide, incorporate new technology where feasible, thereby improve it,s utility and applicability.Preoperative imaging and postoperative pathological assessment of the pelvis and paraaortic lymphnodes should be incorporated in to the staging system of cervical cancer with some flexibility to its use according to available resources.

Methods:

A retrospective analysis was conducted among two cohort groups of patients at the gynaecological oncology department of Bangabandhu Sheikh Mujib Medical University (BSMMU) . Both the cohorts consisted of clinically or histopathologically diagnosed cervical cancer patients (total no-735) attending OPD of the department during December 2011 to June 2019. All the patients had similar type of laboratory

investigations for staging purpose.Commonly x-ray chest, IVU,CT and MRI of the whole abdomen done preoperatively. Then after getting anesthesia fitness, all of them had EUA with cystoscopy where indicated and proctoscopy or sigmoidoscopy where indicated. All the findings were noted in a predesigned cervical cancer staging proforma sheet ,one part of which is preserved in the department. For the purpose of analysis the patients were divided in to two cohorts depending on the changeover of the group of observer. First cohort included the patients undergoing EUA between December 2011 to July 2017 which consisted of 479 cases. The second cohort included same type of 256 cases who had unique laboratory investigations and EUA between August 2017 and June 2019. Variables analysed were age, size of tumour, cystoscopy done or not done, biopsy taken or not taken and distribution of stages with particular focus on stage 1B disease. On the basis of revised FIGO staging system the stages were distributed as 1B1,1B2 and 1B3 according to size of the tumour recorded in the data sheet. Differences between two cohorts were analysed by Chi-square test. P value < 0.05 was considered as significant difference.

Results:

In the first cohort (n=479) maximum (68.21%) patients were between 41 to 60 years old. In the second cohort (n =256) 63.45 % patients were in the same age group with no significant difference. But significant difference (p=0.021) between two cohorts was observed in prevalence of cervical cancer in the age group 41 to 50 years. Another difference (p=0.037) was observed in the age group 61 to 70 years .In the first group 5.6% and in the second group 9.76% were in this age group (Table I).

Highly significant difference (p=0.001) was found in the measurement of the tumour size when it exceeded 4 cm. In the first cohort 6.05% were measured as >6 cm. On the other hand no tumour in second cohort was measured as> 6 cm.(Table-II). Significant differences also observed in the measurement of tumour with size between 2.1-4cm.

A great difference was observed in performing cystoscopy during the procedure (p=0.001).In the first cohort 27.39% patients had cystoscopy and in the second cohort only 2.73% had cystoscopy (Table -III).

Another significant difference was observed in the diagnosis of operable and inoperable cases. In the first cohort about 50% cases were operable (up to stage II A) and in the second cohort it was 37% (p=0.001). Observer variation also found in the diagnosis of stage II A and stage II B disease. In the first cohort 15.43% were stage II A but in the second cohort it was 6.64% (p=0.001). On the other hand 28.26% and 50.78% cases were diagnosed as II B in first and second cohort respectively (p=0.001). Another significant difference was observed in the diagnosis of stage II A (P=0.007) (Table-IV).

Table-I

Age Distribution of the study population

Age	08-12-11 to 01.08.17 (n=479)		02-08-17 to June 19 (n=256)		p-value
	Number	Percentage	Number	Percentage	
20-30 yrs	18	3.75%	8	3.125%	0.658
31-40 yrs	98	20.45%	53	20.70%	0.006*
41-50 yrs	193	40.29%	81	31.64%	0.021*
51-60 yrs	134	27.92%	84	32.81%	0.171
61-70 yrs	27	5.6%	25	9.76%	0.037*
71- 80 yrs	8	1.6%	5	1.953%	0.077
81- 85 yrs	1	0.20%	0	0.0	0.464
Total	479	100.0%	256	100.0%	

Chi-square test was done, *significant . P- Value <0.05 = Significant

Table-II

Size of Tumor diagnosed during EUA

Size	08-12-11 To 01.08.17 (n=446)		02-08-17 To June 19 (n=247)		p-value
	Number	Percentage	Number	Percentage	
< 1 cm	7	1.56%	6	2.37%	0.424
1.1- 2 cm	81	18.1%	45	17.78%	0.985
2.1- 4 cm	209	46.86%	147	58.10%	0.001*
4.1 – 6 cm	122	27.35%	49	19.36%	0.028*
> 6 cm	27	6.05%	0	0.0	<0.001*
Total	446	100.0%	247	100.0%	

Chi-square test was done, *significant . P- Value <0.05 = Significant

Table-III

Cystoscopy done during EUA

Cystocopy	08-12-11 To 01.08.17 (n=376)		02-08-17 To June 19 (n=256)		p-value
	Number	Percentage	Number	Percentage	
Done	103	27.39%	7	2.73%	<0.001*
Not Done	273	72.60%	249	97.26%	
Total	376	100.0%	256	100.0%	

Chi-square test was done, *significant . P- Value <0.05 = Significant

Table-IV

Distribution of stages diagnosed during EUA

Stage	08-12-11 To 01.08.17 (n=454)		02-08-17 To June 19 (n=256)		p-value
	Number	Percentage	Number	Percentage	
IA_2	2	.43%	5	1.953%	0.050
IB_1	91	19.9%	20	7.8125%	<0.001*
IB_2	35	7.6%	40	15.62%	0.001*
IB_3	26	5.6%	13	5.07%	0.716
IIA	71	15.43%	17	6.64%	0.001*
IIB	130	28.26%	130	50.78%	<0.001*
IIIA	17	3.6%	5	1.953%	0.186
IIIB	60	14.34%	23	8.98%	0.092
IVA	20	4.34%	2	0.78%	0.007*
IVB	2	.43%	1	0.39%	0.921
Total	454	100.0%	256	100.0%	

Chi-square test was done, *significant . P- Value <0.05 = Significant

Discussion :

Staging of cervical cancer by clinical examination is the key to the management of this cancer. Clinical staging is the most commonly used way of staging of carcinoma cervix. But sometimes it is inaccurate in defining the extent of the disease. There are many factors on which correct staging depend . Important factors are - examination done with or without

anesthesia, obesity of the patient, tightness of abdominal wall, presence of other pathology in the pelvis and aboveall the experience of the observer. A report from the university of Southern California indicated only 52% correlation between clinical stage and subsequent exploration findings[5]. Most patients are upstaged on the basis of surgical exploration, with the most likely sites of occult metastasis being the pelvic and paraaortic lymphnodes. Other sites of occult diseases are parametrium, peritoneum and omentum. Upto 14% patients may also be downstaged usually because of some benign pathological diseases are discovered during surgery, such as pelvic inflammatory disease, endometriosis and fibroids.When doubt exists during the clinical staging procedure, the tumour should be assigned in the earlier stage.Overstaging and understaging are the most problematic issue in the management of carcinoma cervix and it mostly affect therapeutic desecion .Because decision making about the operability is the key to the management of the cases. FIGO stages strictly correlate with the prognosis of the patient and strict adherence to the rules of clinical staging is necessary, without which there is every chance of observer variation.

This was a retrospective comparison of results of clinical staging among two cohorts. In addition earlier stage IB was restaged according to new 2018 FIGO staging system. The restaged IB disease consisted of 2018 stage IB1(tumour size < 2 cm), stage IB2 (tumour size 2-3.9 cm) and stage IB3 (tumour size > 4cm) .On restaging of the first cohort (n=454) ninety one (19.9%) patients were found stage IB1. On the other hand in the second cohort (n=256) it was only twenty (7.8%) . Statistically this difference was highly significant (p value =< 0.001). Significant difference also observed in restaging stage IB2 (first cohort-7.6% and second cohort -15.62%, p value=0.001). No difference was found in restaging stage IB3 (P= 0. 716) These differences indicate that significant amount of observer variation may occur in the measurement of the size of the tumour. In previous FIGO criteria ,only clinical and imaging findings were used for staging .The main change in the revised 2018 FIGO criteria was the addition of surgical risk factors in the staging system[6] which mainly affected the staging of cervical cancer. The new staging system clearly showed the significant survival differences among the three subgroups. Using data of 62,212 women in America[7], 5 year survival in the FIGO 2018 schema was 91.6% for stage 1B1 tumours, 83.3% for stage 1B2 neoplasms and 76.1% for stage IB3 lesions. In a Chinese report[8] of 362 cervical cancer patients with restaging IB, the 5- year overall survival (OS) rates of patients with FIGO 2018 stage IB1, IB2 and IB3 were 95.3% , 95.1% and 90.4% .

Tumour size is considered to be an important prognostic factor for stage I cervical cancer and increasing tumour size is indicative of increasing chance of lymph node involvement, higher recurrence rate and lower survival rate[(9-11)]. A recent study[12] demonstrated that the survival rates were significantly different between 2018 FIGO stage IB1 and stage IB2 disease.

In this analytic study difference also observed in staging IIA and IIB diseases between two in groups of observer in two cohorts. In the first cohort (04-12-11 to 01-07-17) stage IIA and stage IIB diseases were 15.43 % and 28.26% respectively. In the second cohort (02- 08-17 to 30-6-2019) these were 6.64% and 50.78% respectively. These differences were statistically significant (p= 0.001) . Stage 11A is the operable disease and stage IIB is inoperable condition. So to provide highest benefit to the patient , strict adherence to the rules of clinical staging should be maintained. No difference was found in diagnosing stage IIIA and stage IIIB disease. In new FIGO 2018 staging system for cervical cancer, stage III is reclassified IIIA ,IIIB, IIIC1 and IIIC2 . Stage III C has been introduced and classified as 1 and 2 according to pelvic and paraaortic lymph node involvement respectively. Lymph node involvement is diagnosed either by imaging or histopathologically. We could not reclassify stage III diseases as both the imaging and histopathological reports were not available. Metastases to local lymph nodes is the primary mode of cervical cancer metastasis.[13] Lymph node metastasis is the most important direct prognostic factor for the decline in the survival rate of early stage cervical cancer,[14] but it was not until 2018 that nodal status was included in the FIGO staging system. Noordhuis et al[15] found that patients with early stage cervical cancer who did not have lymph node metastasis had a 5-year over- all survival (OS) rate of 90% compared to only 65% for patients with lymph node metastasis .

Cystoscopy is one of the essential ancillary aids during examination under anesthesia for cervical cancer staging , specially for the diagnosis of stage IVA diseases. We found a significant difference in performing cystoscopy between two cohorts. In the first cohort 27.39% patients underwent cystoscopy and 4.34% patients were diagnosed as stage IVA disease. But in the second cohort only 2.73% patients underwent cystoscopy and only 0.78% patients were diagnosed as stage IVA disease. The difference was statistically significant (p=0.007).

This was a small sample retrospective study with certain inherent biasness. Due to the limited information obtained, we could not make any prognostic differences between the stages and substages.Further prospective research is needed for the prognostic discrimination of observer variation, histological grade and lymph node status.

In conclusion, revised 2018 FIGO staging system is based on tumor size and Lymph node involvement. It seemed to accurately reflect the survival rate with a distinct statistical tendency for poorer 5-year DFS and OS rates with increasing stage.

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