Original Article

Comparison of Efficacy between Hypofractionated and Conventional Fractionated Chemoradiotherapy in the Management of Locally Advanced Carcinoma Cervix

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ABSTRACT

Introduction: *Cervical cancer is the 4th most common cancer among women in the world. Surgery, radiotherapy, or chemotherapy are the main treatment options for cervical cancer either alone or in combination.* ***Methods & Materials:*** *This quasi-experimental study was conducted at the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, from November 2020 to October 2021. A purposive sampling technique was adopted in this study including total sixty study patients divided into two arms, 30 patients in arm A (control) receiving conventional radiotherapy and 30 patients in arm B (experimental arm) recieving hypofractionated radiotherapy. Data were analyzed by SPSS version 25.0.* ***Results:*** *On per vaginal examination growth was present in 20.00% of patients, fornix obliterated in 10.00% and parametrium involved 6.67% of patients in arm A, the number is 16.67%, 13.33%, 10.00% for arm B patients on 3rd follow-up. Growth was as*

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sessed using MRI after 12 weeks of RT completion. In arm A, 21 patients and in arm B, 23 patients showed absence of growth. Almost equal numbers of patients in both arms experienced a complete response (21 in arm A and 23 in arm B). Partial responses were in nine patients in arm A and seven patients in arm B. This difference in outcome was not statistically significant (p >0.05).
Conclusion: *The study found that hypofractionated radiotherapy (37.5 Gy in 15 fractions) with concurrent weekly cisplatin is as effective as conventional radiotherapy (50 Gy in 25 fractions) with cisplatin for locoregional control in inoperable locally advanced cervical cancer.*

Keywords: *Cervical cancer, Hypofractionated Radiotherapy, Conventional Radiotherapy, Chemotherapy*

INTRODUCTION

Cervical cancer is the 4th most common cancer among women in the world. It is common in low-resource countries. This is the second leading malignancy, in terms of both incidence and mortality among Bangladeshi women[1]. According to the WHO report, it was the leading gynecological malignancy in the world[2]. In the year 2018, the number of new cases was 569,847, and 311,365 deaths were reported[3]. In 2020 the incidence became 604,127 and the death increased to 341,831 [1]. According to the International Agency for Research on Cancer (IARC), more than 50 million Bangladeshi women are at risk of developing cervical cancer, and 17686 new cases and 10362 deaths occur annually[4]. Cancer screening has become prevalent nowadays but the screening coverage in Asian countries is still low and varies from 50% in Singapore to 2.6-5 percent in India[5,6]. Patients diagnosed with early-stage turn to the advanced stage due to long queues at every step of treatment in hospitals with few and limited resources. So about 80% of the patients present in the advanced stage[7]. Radiation therapy plays an important role in advanced carcinoma cervix stages II, III, and IV[8]. Surgery, radiotherapy, or chemotherapy are the main treatment options for cervical cancer either alone or in combination. Surgery has long been a standard therapy for early-stage (I-IIA) disease[9]. Later stages are treated with a combination of external beam radiation therapy (EBRT) and intracavitary radiotherapy (ICRT) according to feasibility. Conventional fractionated radiation therapy (1.8-2.0 Gy per day, 5 days a week) is an established radiotherapy regimen for most solid tumors since the last 3 decades. Overall treatment time has a considerable effect on local control and survival. Various fractionation regimens are now practiced in clinical radiotherapy including conventional fractionation, split course radiotherapy, hyper fractionation, continuously accelerated hyper fractionation radiotherapy (CHART), hypofractionation, and accelerated fractionation[10]. In hypofractionation, overall treatment time is reduced using a high dose per fraction, with a gap of 24 hours high dose per fraction (>2-2.5 Gy) is delivered daily for 5 days. Here treatment time and fraction number are also reduced. Short-duration radiotherapy without compromising the quality of treatment is very important to maintain a properly functioning radiotherapy machine with increased longevity to combat the huge patient burden. When the treatment duration is short it not only reduces the patient burden in a hospital but also minimizes the suffering of the patients by reducing their days at the hospital and relevant costs. The chance of late compli-

cations increases with increasing dose per fraction. At a few centers, hypofractionated radiotherapy has been delivered twice weekly or four days a week[11]. Various studies with split-course radiation therapy have also practiced hypofractionation[12]. Alteration in the fractionation has been attempted mainly to improve the local control at the same time decreasing the normal tissue complications [13]. In this study, a comparison of hypofractionated and conventional fractionated chemoradiotherapy was done in terms of their efficacy.

OBJECTIVE

General Objective

- To compare short-term effectiveness between conventional fractionated (50 Gy in 25 fractions) and hypofractionated chemoradiotherapy (37.5 Gy in 15 fractions) in locally advanced cervical cancer.

Specific Objectives

- To assess and compare the tumor size status between hypofractionated and conventional fractionated chemoradiotherapy arms.
- To analyze the treatment response in different follow-ups.

METHODS & MATERIALS

This quasi-experimental study was conducted at the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, from November 2020 to October 2021. Histologically confirmed squamous cell carcinoma of the cervix with FIGO stage IIB-IVA who attended NICRH for treatment were considered as the study population. A total of 60 patients were selected as study subjects as per inclusion and exclusion criteria. A purposive sampling technique was adopted in this study.

Inclusion criteria:

- Histologically proven squamous cell carcinoma of cervical cancer
- Cervical Cancer at Stage IIB to IVA FIGO´s clinical stages
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Age 30 to 70 years

Exclusion criteria:

- Radiological or clinical evidence of distant metastasis
- History of prior pelvic radiotherapy
- Recurrent cases
- Postoperative case
- Laboratory criteria for exclusion of Hemoglobin <10 gm/dl or Serum creatinine level >1.4 mg/dl

A semi-structured questionnaire was prepared for data collection. After taking informed written consent from the patients, data were collected by face-to-face interview ensuring privacy and confidentiality by using the questionnaire. All other required data were collected from history sheets and investigation papers. Sixty patients were divided into two arms, 30 patients in arm A (control arm) and 30 patients in arm B (experimental arm). The intervention was given according to the planned radiotherapy regimen, that is conventional radiotherapy in arm A and hypofractionated radiotherapy in arm B. Concurrent chemotherapy is given using Cisplatin 40 mg/m² in 500 ml normal saline, IV weekly, 4 hours before radiation therapy. Then 1st follow-up was given 3 weeks after starting of radiotherapy. 2nd and 3rd follow-ups were given 6 weeks and

12 weeks after completion of both EBRT and brachytherapy respectively. The data were analyzed with the SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) software. For descriptive statistics means, standard deviations & ranges for numerical data and frequencies & proportions for categorical data were calculated as required. For inferential statistics, appropriate tests were used to analyze the data including the $\chi 2$ test, and t-test. Data were presented in frequency tables as per need using M S Excel 2010. Ethical clearance was taken from the ethical committee of NICRH. Informed written consent was obtained from the participants.

RESULTS

Table I: Distribution of patients according to age (*n*=60)

Age in years	Arm A *n*=30 (%)	Arm B *n*=30 (%)
31-40	04, 13.33	06, 20.00
41-50	12, 40.00	10, 33.33
51-60	09, 30.00	08, 6.66
61-70	05, 16.66	06, 20.00
Mean ± SD	51.2 ± 9.9	50.6 ± 10.2
Range	35-70	34-68

Regarding arm A, a maximum number of patients (40%) were in the age group 41-50 years. The second leading numbers of patients were found in the 51-60 years age group (30%). The mean age was 51.2 ± 9.9. In arm B, a maximum number of patients (33.33%) were in the age group 41-50 years. The second leading numbers of patients were found in the 51-60 years age group (26.66%). The mean age was 50.6 ± 10.2.[**Table-I**]

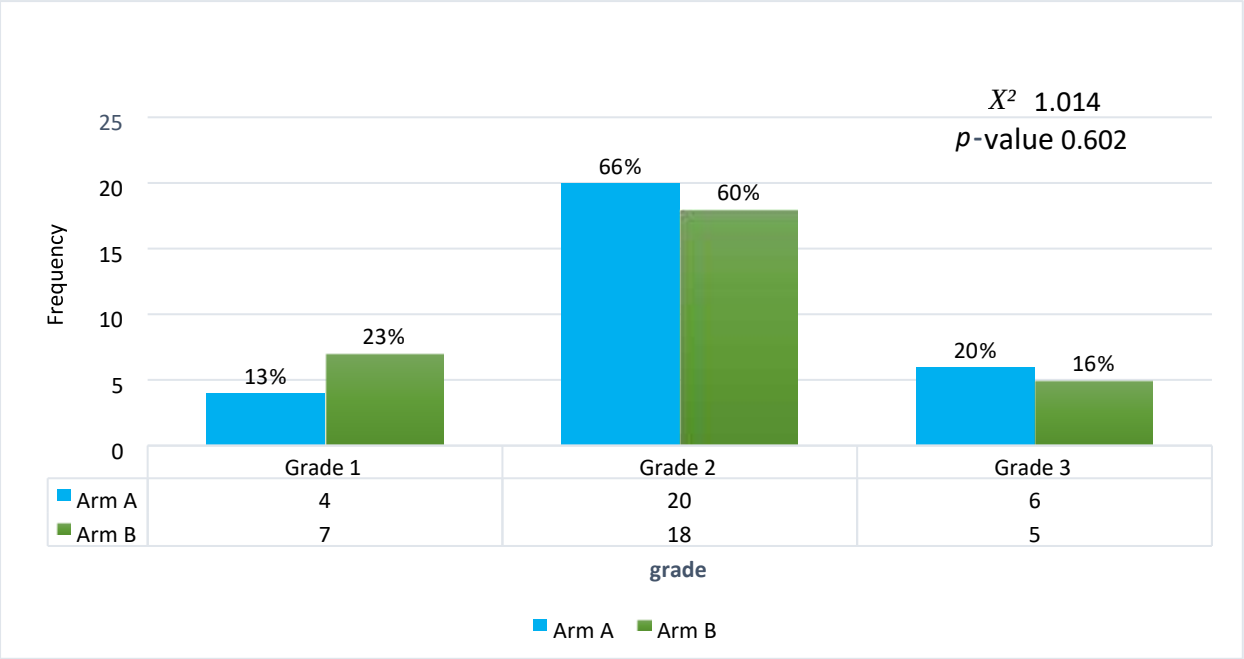

Figure 1: Distribution of patients according to tumor grade

Most of the patients had grade 2 (moderately differentiated) histologic pattern of cancer, that was 66% in arm A and 60% in Arm B. The *p*-value was 0.602 which was not statistically significant (**Figure 1**).

Table II: Pre-treatment clinical stage of the patients in both arms (*n*=60)

Stage of disease	Arm A *n*=30 (%)	Arm B *n*=30 (%)
IIB	21 (70.0)	19 (63.33)
IIIA	8 (26.67)	9 (30.00)
IIIB	01 (3.3)	02 (6.70)
IVA	0 (0.0)	0, (0.0)

In this study, 70% patients of in arm A and 63.3% patients of in arm B were stage IIB. No stage IVA patient could fulfill the selection criteria. [**Table II**]

Table III: Clinical response assessment at 1st follow-up (*n*=60)

Extent of Growth	Arm A *n*=30 (%)	Arm B *n*=30 (%)	X^2	*p*-value
PSE			0.069	0.793
Growth absent	12 (40.00)	13 (43.33)		
Growth present	18 (60.00)	17 (56.67)		
PVE			0.601	0.438
Fornix intact	14 (46.67)	17 (56.67)		
Fornix obliterated	16 (53.33)	13 (43.33)		
RVE			0.635	0.425
PM free	20 (66.67)	17 (56.67)		
PM involved	10 (33.33)	13 (43.33)		

PSE= Per speculum examination, PVE=per vaginal examination, RVE=rectovaginal examination, PM= parametrium

This table shows clinical responses observed at the first follow-up. On per vaginal examination, growth was present in 60.00% of patients, fornix obliterated in 53.33% and parametrium involved 33.33% of patients in arm A, the number is 56.67%, 43.33%, 43.33% for arm B patients. [**Table III**]

Table IV: Clinical response assessment at 2nd follow-up (*n*=60)

Extent of Growth	Arm A *n*=30 (%)	Arm B *n*=30 (%)	X^2	*p*-value
PSE			0.300	0.583
Growth absent	19 (63.33)	21 (70.00)		
Growth present	11 (36.67)	9 (30.00)		
PVE			1.001	0.316
Fornix intact	26 (86.67)	23 (76.67)		
Fornix obliterated	4 (13.33)	07 (23.33)		
RVE			0.162	0.687
PM free	27 (90.00)	26 (86.67)		
PM involved	03 (10.00)	4 (13.33)		

PSE= Per speculum examination, PVE=per vaginal examination, RVE=rectovaginal examination, PM= parametrium

This table shows clinical responses observed at the second follow-up. On per vaginal examination, growth was present in 36.67% of patients, fornix obliterated in 13.33% and parametrium involved 10.00% of patients in arm A, the number is 30.00%, 23.33%, 13.33% for arm B patients. [**Table IV**]

Table V: Clinical response assessment at 3rd follow-up (*n*=60)

Extent of Growth	Arm A *n*=30 (%)	Arm B *n*=30 (%)	X^2	*p*-value
PSE			0.111	0.783
Growth absent	24 (80.00)	25 (83.33)		
Growth present	06 (20.00)	5 (16.67)		
PVE			0.162	0.688
Fornix intact	27 (90.00)	26 (86.67)		
Fornix obliterated	3 (10.00)	04 (13.33)		
RVE			0.218	0.640
PM free	28 (98.33)	27 (90.00)		
PM involved	02 (6.67)	3 (10.00)		

PSE= Per speculum examination, PVE=per vaginal examination, RVE=rectovaginal examination, PM= parametrium

On per vaginal examination, growth was present in 20.00% of patients, fornix obliterated in 10.00% and parametrium involved 6.67% of patients in arm A, the number is 16.67%, 13.33%, 10.00% for arm B patients. No value is statistically significant. [**Table V**]

Table VI: Distribution of the patients by presence of mass on USG (*n*=60)

Mass in Cervix	Arm A *n*=30 (%)	Arm B *n*=30 (%)	X^2	*p*-value
1st follow-up				
Present	25 (83.33)	23 (76.67)	0.344	0.558
Absent	05 (16.67)	7 (23.34)		
2nd follow-up				
Present	13 (43.33)	11 (36.67)	0.278	0.598
Absent	17 (56.67)	19 (63.33)		
3rd follow-up				
Present	7 (23.34)	5 (16.67)	0.417	0.518
Absent	23 (76.67)	25 (83.33)		

The distribution of the patients by USG assessment of the cervix is shown in the above table. In most of the patients, cervical masses were present at the first follow-up. In 2nd follow up 13 patients of arm A, and 11 patients of arm B had a mass on ultrasonography. The number reduced on the third follow up However, no differences were statistically significant ($p > 0.05$). [**Table VI**]

Table VII: Assessment of patients using MRI at 3rd follow-up (*n*=60)

Mass in Cervix	Arm A *n*(%)	Arm B *n*(%)	X^2	*p*-value
Present	09 (30.00)	07 (23.34)	0.341	0.559
Absent	21 (70.00)	23 (76.67)		

Growth was assessed using MRI after 12 weeks of RT completion. In arm A, 21 patients and in arm B, 23 patients showed absence of growth. [**Table VII**]

Table VIII: Assessment of response at 3rd follow-up (*n*=60)

Outcome	Arm A *n*(%)	Arm B *n*(%)
Complete response	21 (70.0)	23 (76.67)
Partial response	9 (30.00)	7 (23.34)
Stable disease	0.0	0.0
Progressive disease	0.0	0.0
Total	30 (100.0)	30 (100.0)

Almost equal numbers of patients in both arms experienced a complete response (21 in arm A and 23 in arm B). Partial responses were in nine patients in arm A and

seven patients in arm B. This difference in outcome was not statistically significant (p >0.05). [**Table VIII**]

DISCUSSION

For most solid tumors, conventional fractionated radiation therapy (180-200 cGy per day, 5 days a week) has been an established radiotherapy regimen for the last 3 decades[10]. This fractionation scheme was developed because of tolerable acute reactions, acceptable delayed effects, and reasonable local controls. Overall treatment time has a considerable effect on local control and survival. In hypofractionation, overall treatment time is reduced using a high dose per fraction, with a gap of 24 hours high dose per fraction (>2-2.5 Gy) is delivered daily for 5 days. Here treatment time and fraction number are also reduced. In an attempt to improve the therapeutic ratio, various fractionation schedules have been attempted. Hypofractionated radiotherapy has been used in various head and neck, bladder, and gynecological malignancies[14]. Fraction size is the dominant factor in deciding the late effects. An increase in the dose per fraction also causes an increase in the late effects. In the present study, the tumor control was comparable to that of conventional treatment (70% vs 76.7%, p-value=0.829). Some other international studies supported this finding. The disease-free survival in carcinoma cervix IIIB ranges from 40-60%[8,15]. The disease-free survival of 59% seen in *Muckaden et al.* study is comparable to that of conventional fractionation[11]. On the first follow growth was present at 60% in arm A and 56.67% in arm B, fornix obliterated was in 53.33% vs 43.33%, and parametrium involved was in 33.33 vs 43.33%. In the second or third growth disappears in more patients, condition of fornix or parametrium improves in both arms. Assessment of cervix in USG, in most of the patients cervical masses were present after the completion of 1st follow-up. In 2nd follow-up onward mass disappears in most of the patients. 23.34% of arm A patients and 16.67% of arm B patients showed mass on USG. However, no differences were statistically significant (p >0.05). At 3rd follow up MRI of the pelvis was performed. Growth was found in some patients who did not have growth in USG. Seventy percent in arm A and 76.6% in arm B showed no growth in the cervix. In the current study, 70.0% of patients in the conventionally fractionated arm (Arm A) and 76.67% of patients in the hypofractionated arm (Arm B) showed complete response at the time of the last follow-up after completing treatment. In an Indian study, the complete response rate was 81% in conventional fractionated arms and 84.2% in hypofractionated arms [16]. Studies like *Shuit et al.* demonstrated that hypofractionated radiotherapy can achieve similar levels of tumor control and disease-free survival as conventional fractionation in the treatment of cervical cancer[17]. Moreover, *Chang et al.*, reported disease-free survival rates within the range of 40-60% for cervical cancer treated with hypofractionated schedules[18]. Discuss studies focusing on patient-reported outcomes and quality of life, such as those by *Sharma et al.*, which found that shorter treatment durations in hypofractionation schedules could lead to improved patient convenience and adherence without compromising treatment effectiveness[19].

Limitations of The Study:

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. Moreover, the conformal radiotherapy technique could not be done

Conclusion:

In patients receiving hypofractionated radiotherapy (37.5 Gy in 15 fractions) along with concurrent weekly cisplatin versus conventional radiotherapy (50 Gy in 25 fractions) along with concurrent weekly cisplatin, there was no significant difference in response concerning locoregional control. From the present study, it could be concluded that short or hypofractionated treatment protocol is as good as established conventional protocol in the management of inoperable locally advanced cervical cancer. In resource-challenged settings where radiotherapy treatment facilities are limited this hypofractionated therapy could be a reasonable choice.

Recommendation:

As both regimens produced almost identical outcomes, hypofractionated radiotherapy may be used instead of conventional fractionated chemoradiotherapy in the management of inoperable locally advanced cervical cancer. Further studies involving multiple centers with a large sample size may help explore the utility of hypofractionated radiotherapy.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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