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Comparative Study of Local Control, Response and Toxicities between Accelerated Radiotherapy versus Concurrent Chemoradiation using Conventional Fractionation in the Treatment of Locally Advanced Cervical Cancer (Stage IB2, IIA2, IIB-IVA)

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Worldwide, cervical cancer is the leading cause of morbidity and mortality in women. Even though pelvic External Beam Radiotherapy (EBRT) in conventional fractionation with concurrent chemoradiotherapy followed by brachytherapy is the standard of care of locally advanced carcinoma cervix; accelerated radiotherapy can be a useful modality of treatment. Purpose of this study was to observe the efficacy of accelerated radiotherapy versus concurrent chemoradiotherapy using conventional fractionation as treatment for locally advanced carcinoma cervix (stage IB2, IIA2, IIB-IVA) in tertiary centers of Bangladesh. It was a prospective quasi experimental observational study. The study was conducted in department of Radiation Oncology, National Institute of Cancer Research and Hospital, from December 2016 to November 2017. The study subjects were patients of histologically & radiologically proven squamous cell carcinoma of locally advanced stages of uterine cervix, attending the department of Radiation Oncology, NICRH, Dhaka. Total sample size was 60. Sample was selected by purposive sampling technique. Median EBRT time was 30 days & 38 days in arm-A and arm-B respectively. Median gap during EBRT was 1 day & 3 days in arm-A and arm-B respectively. Median OTT was 55 days & 61 days in arm-A and arm-B respectively, a statistically significant delay in chemo radiation arm-B (p value<0.0001). Regarding treatment

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response, at the end of last follow up, in arm A, 23 patients (76.6%) showed complete response (CR), where in arm B complete response was noticed in 25 patients (83.3%). Partial response (PR) were in 4 patients (13.3%) and 5 patients (16.6%) in the two arms respectively. Progressive disease was found in 1 patient (3.33%) in arm A & 2 patients (6.66%) in arm B. No statistical significance was found between two arms. Locally advanced carcinoma cervix (stage IB2, IIA2, IIB-IVA) continues to be a healthcare problem in developing countries where effective screening programs, treatment facilities or economic condition are limited. Present study suggested that early responses to treatment with pure accelerated EBRT are non-inferior to concomitant chemoradiation and the acute toxicities are lesser.

Keywords: Cervical cancer; radiotherapy; chemoradiation.

1. INTRODUCTION

"Cervical cancer is a major health problem for women worldwide. The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization (WHO) states that, with 528000 new cases every year, cervical cancer is the fourth most common cancer affecting women & second most common gynecologic cancer worldwide" [1]. "In recent times, carcinoma cervix has undergone crucial transition, both in incidence and treatment strategy. Cervical cancer rate is decreasing among women in US, although incidence remains high in Latin America, Southern and Eastern Africa, India, Polynesia and other developing countries. Such differences in incidence reflect differences in cultural attitudes toward sexual practices and the lack of awareness and spread of mass screening programmes. Highest incidence tends to occur in population that have low screening rates combined with high background prevalence of HPV infection" [2].

"Human Papilloma Virus (HPV) is the most important factor in development of cervical cancer" [3]. "The most common subtypes are HPV-16 & -18, which are found in 70% of the cases" [4]. "Women who have coitus at a young age, have multiple sex partners, have sexual partners with multiple partners, or bear children at a young age are at increased risk. Cigarette smoking, prolonged oral contraceptive use, prenatal DES exposure and immune system alteration (HIV infection) also act as risk factors for invasive cervical cancer" [2].

"The commonest symptom of cervical cancer is metrorrhagia (intermenstrual bleeding), menorrhagia (heavier menstrual flow), post-coital bleeding and post-menopausal bleeding. If chronic bleeding occurs, patient may present with symptoms related to anemia. More than 90% of cervical cancers are squamous cell carcinoma. Approximately 7% to 8% are adenocarcinoma and 1-2% are clear cell carcinoma [2]. Squamous neoplasms are often sub classified as large cell keratinizing, large cell non-keratinizing or small cell carcinomas. Invasive adenocarcinoma may be pure or mixed with squamous cell carcinoma (Adeno-squamous carcinoma). About 80% of cervical adenocarcinomas are endocervical type adenocarcinomas" [4].

As per FIGO staging, carcinoma cervix is divided into four clinical stages and staging is based upon clinical evaluation (inspection, palpation, colposcopy); roentgen-graphic examination of chest, kidney and skeleton and endocervical curettage and biopsies. Choice of treatment modality depends upon a number of factors including- Tumor size, stage, Histologic features, evidence of lymph node metastasis, risk of complications of surgery or radiotherapy and patient's performance status.

However, as a rule, "microinvasive cancers invading <3mm (stage IA1) are managed by conservative surgery. Early invasive cancers (stage IA2, IB1 and small stage IIA) are managed by radical surgery or radical radiotherapy. Locally advanced cancers (stage IB2 through IVA) are managed with combined chemotherapy and radiotherapy" [2].

In recent times the most significant development in the treatment of carcinoma cervix has been introduction of chemoradiation. After the NCI alert in 1999 [6], Cisplatin based concurrent chemoradiotherapy has become widely used in the treatment of locally advanced carcinoma cervix. But in elderly patients, patients with pre-existing medical conditions (abnormal renal, hepatic, bone marrow function), poor performance status and patients who refuse

chemotherapy; cytotoxic chemotherapy cannot be administered for which different strategy is required to enhance the effects of radiotherapy given as a single modality of treatment. Besides that, prolongation of overall treatment duration has detrimental effects on local tumor control. Hence, total treatment duration should be as short as possible (7-8 weeks).

In our settings, many patients with advanced cervical carcinoma present to us with significant co-morbidities, poor nutritional status that preclude the use of chemotherapy along with radiation. Besides that, low socioeconomic status, lack of adequate radiotherapy facilities are the issues that have impeded standardization of chemoradiation in low-income countries. Thus, newer and efficacious perspectives are needed. Altered fraction radiotherapy has also been one of the approaches that have shown promise to increase the therapeutic ratio. Theoretically hyper-fractionated (dose per fraction decreased and fraction per day increase usually twice daily) radiotherapy are attractive options, but none has proven to be any beneficial over conventional radiotherapy in carcinoma cervix and there have been reports of increased acute toxicity associated with them [6-9].

Accelerated fractionation regimen intend to reduce overall treatment time without simultaneous changes in fraction size or total dose. It aims to minimize tumor repopulation during treatment session by shortening the OTT and therefore, increasing the probability of tumor control for a similar total dose. Altered fractionation employing accelerated schedules have improved local control and survival in a number of randomized trials for head and neck [10] lung [11] and bladder [12].

In the Danish head and neck study group, where efficacy of five versus six weekly radiotherapy fractions in squamous cell carcinoma of head and neck region were compared; shortening the OTT improved loco regional control rates by 10% without significant late toxicity [10]. This schedule has not been investigated much in squamous cell carcinoma of carcinoma cervix which behaves clinically and radio-biologically in a similar pattern to its head and neck counterparts. Few studies (including randomized phase III and phase II trial) have been done since 2006 showed that accelerated fractionation regime of six fractions per week EBRT followed by ICBT has equal efficacy as concurrent chemoradiation with lesser toxicities [13-15]. So, this study on accelerated regimen of external beam radiotherapy (EBRT), six fractions per week, was designed to make a comparison between accelerated radiotherapy and concurrent chemoradiation in terms of pelvic control, response and toxicities to see whether this approach could be an effective option for the treatment of locally advanced cervical cancer in low resource countries like Bangladesh.

2. MATERIALS AND METHODS

This study was conducted to assess and compare the disease response, loco regional control and toxicities between accelerated radiotherapy and concurrent chemoradiotherapy using conventional fractionation in the treatment of locally advanced cervical cancer (stage IB2, IIA2, IIB-IVA). This was a prospective quasi experimental observational study. It took place in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka from December 2016 to November 2017. The study participants were patients of histologically & radiologically proven squamous cell carcinoma of locally advanced stages of uterine cervix attended in the Department of Radiation Oncology, NICRH, and met the inclusion and exclusion criteria of the study. Total sample size was 60. There were two arms- (Arm A & Arm B). Each arm contained 30 cases. Sampling method was purposive sampling technique. Samples were selected through inclusion and exclusion method from the patients of locally advanced carcinoma of cervix. Those who gave informed written consent were finally enrolled in the study.

Inclusion criteria:

- Adult patients of age not below 18 years and not above 75 years of age.
- Patients having Karnofsky performance status ≥70.
- Histologically proven diagnosed cases of squamous cell carcinoma of uterine cervix.
- Patients with clinically and radiologically FIGO stage IB2, IIB-IIIB.
- Patients having minimum laboratory criteria-
    - Hb %-> 10gm/dl
    - Total WBC count->4000/mm^3
    - ANC->2000/mm^3.
    - Total platelet count_>150000/mm^3

Exclusion criteria:

- Histology other than squamous cell carcinoma.

- Clinical or radiological evidence of metastasis at presentation.
- History of pelvic surgery, malignancy, exposure to chemotherapy or radiotherapy.
- Karnofsky performance status <70.
- Pregnant and lactating women.
- Recurrent cases.
- Patients with simultaneous other primaries.
- Participation in any other study on carcinoma cervix.
- Patients dropped out or lost to follow up before completion of study.

In arm-A there were 30 patients who undergone EBRT in pure accelerated regime that is 6 fractions per week, total 50Gy in 25 fractions in 4 weeks followed by intracavitary brachytherapy with ^{192}Iridium (3 insertion of 700 cGy). In Arm B patient received concurrent chemoradiotherapy; 5 fractions per week with weekly Inj. Cisplatin 40 mg/m^2, total 50Gy in 25 fractions in 5 weeks followed by intracavitary brachytherapy with ^{192}Iridium (3 insertion of 700cGy). Data were collected by taking detailed medical history, general examination, investigations, Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI).

After fulfilling the inclusion and exclusion criteria, patients were enrolled with unique ID. Subjects were briefed about the objectives of the study, risk and benefits, freedom for participating in the study and confidentiality. Informed consent was obtained accordingly. Pre-treatment evaluation included detailed history and physical examinations, complete hemogram, blood sugar, serum urea and creatinine, liver function tests, serum electrolytes, chest X-ray (CXR), ultrasonography (USG) of whole abdomen, contrast-enhanced computed tomography (CT) scan of abdomen and pelvis, biochemical and microbiological analyses of urine, cystoscopy, proctoscopy, and cardiological evaluation as and when indicated. Data were collected using data collection sheet.

Patients were assessed by follow up at 4 weeks interval up to 3 months for toxicity. CBC count was performed weekly during treatment, and blood chemistry was performed monthly.

Effectiveness of therapy, patient data such as age, sex, clinical presentation, etc. were noted. A questionnaire was used for collection of information by interviewing patients. All the collected data in the questionnaire were checked very carefully to identify errors in collecting data. Data processing work consisted of registration of schedules, editing, coding and computerization, preparation of dummy tables, analysis and matching data. The technical matters of editing, encoding and computerization were looked by researcher.

Main outcome variables were: patients with socio-demographic characteristics, includes age, sex variation, occupation, residence, socio-economic status, etc. Clinical variables were treatment responses, loco regional control of disease and acute toxicities were studied in patients diagnosed as locally advanced carcinoma of cervix. Keeping the research topic in concern, a preset questionnaire was set for data collection. During study period data collection, data summarization and report witting and all activity was under close supervision of respected guide. All clinical-statistical aspect was performed meticulously and quality assurance maintained precisely. Data processing work consisted of registration schedules, editing computerization, preparation of dummy table, analyzing and matching of data. After editing and coding, the coded data was directly entered into the computer by using SPSS version 6. Data cleaning validation and analysis was performed using the SPSS/PC software and graph and chart by MS excel. The result was presented in tables in proportion. A “P” value <0.05 was considered as significant.

3. RESULTS

Table 1 shows socio-demographic characteristics of the respondents. In terms of age, both arms were divided into 6 groups. For Arm A, maximum incidence was seen in the 5th decade (33.3%). Second leading number of patients were found in 60-69 years age group (30.0%). Mean age of the patients was 51.3 ± 10.2 years. For Arm B, majority (43.3%) was found in the age group of 40-49 years. Second leading number of patients was found in 50-59 years age group (30.0%). Mean age of the patients was 48.6 ± 11.5 years. Regarding area of residence, maximum numbers of respondents came from urban area (60.0%) followed by rural area (40.0%). Concerning level of education, most of the patients in both arms were illiterate (Arm A 63.3% and Arm B 60.0%). Approximately one-third patients of both Arm A (33.3%) & Arm B (30.0%) had below SSC level education. Only one patient in Arm A and three patients in Arm B had attained SSC level education.

Table 1. Socio-demographic characteristics of the respondents (n=60)

Characteristics	Arm A (n=30)		Arm B (n=30)	
Age (years)	**Frequency**	**Percentage**	**Frequency**	**Percentage**
20-29	0	0	0	0
30-39	2	6.6	1	3.3
40-49	10	33.3	13	43.3
50-59	8	26.6	9	30.0
60-69	9	30.0	7	23.3
>70	1	3.3	0	0
Range	32-72		30-64	
Mean ± SD	51.3 ± 10.2		48.6 ± 11.5	
Area of residence				
Rural	11	36.6	13	43.3
Urban	19	63.3	17	56.6
Level of education				
Illiterate	19	63.3	18	60.0
Below SSC	10	33.3	9	30.0
SSC	1	3.3	3	10.0

**SD = Standard Deviation*
**SSC = Secondary School Certificate*

Table 2. Assessment of major symptomatic improvement / deterioration at different follow-ups (n=60)

Clinical symptoms	Arm A (n=30)		Arm B (n=30)		*p*-value
	No	**%**	**No**	**%**	
Before RT					
P/V discharge	17	56.7	18	60.0	0.408
Lower abdominal pain	16	53.3	7	23.3	
Irregular P/V bleeding	10	33.3	13	43.3	
Post-coital bleeding	7	23.3	12	40.0	
Low back pain	6	20.0	5	16.7	
Others	12	40.0	3	10.0	
At 1st follow-up					
Lower abdominal pain & P/V discharge	12	40.0	5	16.7	0.182
P/V discharge	4	13.3	6	20.0	
Low backache & P/V discharge	4	13.3	5	16.7	
Lower abdominal pain	2	6.7	7	23.3	
Others	8	26.7	7	23.3	
At 2nd follow-up					
Lower abdominal pain	16	53.3	6	20.0	0.637
P/V discharge	4	13.3	9	30.0	
Low backache	2	6.7	4	13.3	
Lower abdominal pain & P/V discharge	3	10.0	3	10.0	
No complain	5	16.7	8	26.7	
At 3rd follow-up					
P/V discharge	2	6.7	6	20.0	0.207
Low backache	3	10.0	4	13.3	
Lower abdominal pain	5,	16.7	2	6.7	
No complain	20	66.7	18	60.0	
At 4th follow-up					
P/V discharge	1	3.3	3	10.0	0.167
Lower abdominal pain	1	3.3	2	6.7	
Low backache	1	3.3	2	6.7	
No complain	27	90.0	23	76.7	

**RT = Radiotherapy*
**P/V = Per Vaginal*

Distribution of the patients by major symptoms is given in Table 2. Before starting of radiotherapy, P/V discharge was the major complain in both arms (Arm A 56.7% vs Arm B 60%), other complains were lower abdominal pain (Arm A 53.3% vs Arm B 23.4%), irregular P/V bleeding (Arm A 33.3% vs Arm B 43.3%) and post coital bleeding (Arm A 23.3% vs Arm B 40%). At 1st follow-up, lower abdominal pain & P/V discharge topped the list (Arm A 40.0% vs Arm B 16.7%), P/V discharge and low back pain were next successive complaints. At 2nd follow-up, lower abdominal pain was the major complain followed by P/V discharge. At 3rd follow-up, 20 (66.7%) patients in Arm A and 18 (60%) patients in Arm B reported no complains. P/V discharge was present in six patients in Arm B and lower abdominal pain was present in five patients in Arm A. At 4th follow-up, most of patients in both arms reported no complains (Arm A 90% and Arm B 76.7%). P/V discharge and abdominal pain were present in minimal number of patients. Difference of symptomatic improvement between two groups was statistically non-significant (p>0.05).

Bar chart (Fig. 1) shows improvement of parametrium adhesion. Before radiotherapy, parametrium free was found in only 2 (6.7%) patients of Arm A and 1 (3.3%) in Arm B patients. Following treatment improvement was noted in both groups, but comparatively better in Arm B. At 1st follow up, 7 (23.3%) in Arm A and 12 (40.0%) in Arm B were found both parametrium free. At 2nd follow up, 18 (60.0%) in Arm A and 21 (70.0%) in Arm B were found both parametrium free. At 3rd follow up, 21(70.0%) in Arm A and 23 (76.7%) in Arm B were found both parametrium free and at 4th follow up, 22 (73.3%) and 24 (80.0%) patients were found parametrium free in Arm A and Arm B respectively. P value was found 0.128, result was not statistically significant.

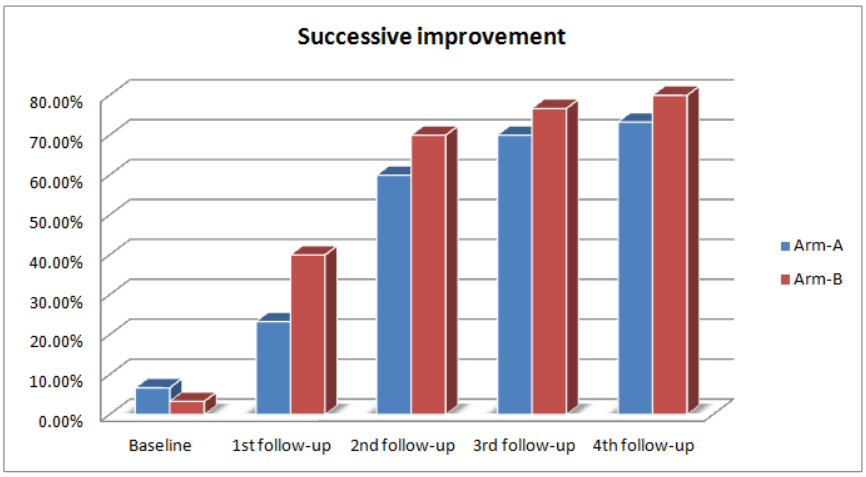

Fig. 1. Improvement of parametrium adhesion (n=60)

Table 3. Toxicities during and after therapy (n=60)

Toxicities		Arm A (n = 30) No. (%)		Arm B (n = 30) No. (%)		p value
		No	%	No	%	
1st follow-up	Anemia	17	56.7	21	70.0	0.284
	Anorexia	30	100.0	30	100.0	1.00
	Nausea	30	100.0	30	100.0	1.00
2nd follow-up	Anemia	13	43.3	14	46.6	0.371
	Anorexia	29	96.7	29	96.7	1.00
	Nausea	18	60.0	21	70.0	0.257
3rd follow-up	Anemia	5	16.6	9	30.0	0.614
	Anorexia	14	46.7	15	50.0	1.026
	Enteritis	7	23.3	11	36.6	0.253
	Nausea	9	30.0	13	43.3	1.027
4th follow-up	Anemia	0	0.0	4	13.3	0.492
	Anorexia	3	10.0	5	16.7	0.706
	Enteritis	4	13.3	6	20.0	0.105
	Nausea	5	16.7	8	26.6	0.001

No abbreviations

Table 4. Clinical response after completion of 4th follow-up for patients (n=60)

Response	Arm A (n = 30)		Arm B (n = 30)		p value
	No	%	No	%	
Complete response (CR)	23	76.7	25	83.3	0.296
Partial response (PR)	5	16.7	4	13.3	0.517
Progressive disease (PD)	2	6.6	1	3.3	0.508

**CR = Complete Response; *PR = Partial Response; *PD = Progressive Disease*

Table 3 shows different toxicities during and after treatment. Toxicities were comparable between two arms. In Arm B, nausea was a predominant complication.

Table 4 demonstrates clinical response after completion of treatment for patients of both Arm A and Arm B. According to WHO guideline of responses (criteria), complete response (CR) was 76.7% (Arm A) & 83.3% (Arm B). Partial response (PR) was 16.7% (Arm A) & 13.3% (Arm B). Progressive disease (PD) was 6.6% (Arm A) and 3.3% (Arm B). These differences RECIST were not statistically significant.

4. DISCUSSION

This was a hospital-based study conducted in Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka over a period of 8 months. In this study, about 66.7% patient's age was between 40 to 60 years. A total of 30 patients of locally advanced cervical carcinoma were included in Arm A of the study. They were divided into six age groups and their age ranged from 32 to 72 years. In Arm B of the study, maximum numbers (43.3%) were found in the age group of 40-49 years. Present study showed that frequency of cervical cancer predominance at middle to elderly age group. Highest incidence of patients was in age group between 40-49 years (38.3%), followed by 28.3% in 50–59-year age group and 26.7% in 60–69-year age group [16-20].

"All findings were consistent with result of other studies. Cervical cancer is a disease of significant worldwide morbidity and mortality. Similar study in Bangladesh reported that, status of the patients reflected advanced stage of the disease at presentation and the peak incidence was observed in 36-45 years age group. Squamous cell carcinoma was more (92.3%) in the majority of patients and adenocarcinoma was more in younger age group" C [21-31]. Another study shows "majority (43.90%) of the participants were within the age range of 26 to 35 years. Among all the subjects, the majority (77.16%) were housewives" [32].

In this study, prior starting of radiotherapy, P/V discharge was major complain in both arms (Arm A 56.7% vs Arm B 60%), other complains were lower abdominal pain (Arm A 50% vs Arm B 20%), excessive P/V bleeding (Arm A 33.3% vs Arm B 16.7%) and post coital bleeding (Arm A 23.3% vs Arm B 40%).

"The accelerated fractionation regime of six fractions per week EBRT followed by ICBT has been seen to be equally efficacious as concurrent chemoradiation in our study. Although there is no question about the benefit of chemoradiation in cervical cancer, albeit at the cost of incremental toxicity. However, the best treatment of those patients who cannot tolerate chemoradiation is not very clear. Traditionally, conventional radiation alone has been used in this subset of patients, which is a suboptimal treatment in locoregionally advanced cervical cancer. To improve local control and perhaps survival, newer avenues should be sought in this group" [31].

In this study, toxicities were comparable between two arms but nausea, enteritis were significant in Arm B.

Clinical response after completion of treatment revealed that, clinical responses were statistically non-significant between two groups.

"Concomitant chemoradiation is now the standard treatment in locally advanced carcinoma cervix and Cisplatin appears to be the ideal chemotherapeutic agent. Green et al. analyzed data from 19 randomized trials comprising 4,580 patients and concluded that concomitant chemotherapy results in improved overall survival (RR 0.71; $P < 0.0001$) and progression-free survival (RR 0.61; $P < 0.0001$). However, the absolute survival benefit was 12% maximum in early stage (I and II) disease. Patients receiving chemoradiation had a higher incidence of grades 3 and 4 hematologic and

gastrointestinal toxicities. Moreover, a recent update from a pivotal meta-analysis of chemotherapy in head and neck cancer has confirmed that the magnitude of the benefit from concomitant chemotherapy is less in older patients" [17].

In our research, the outcomes were obviously non-inferior to the control arm even though the reduction in treatment time did not result in better local control or decreased recurrence. CR looked to be somewhat greater in Arm A, although the disparity appeared to be reducing over time. Only with a longer follow-up can it be determined whether the equivalent short-term reaction persists over time or, more crucially, whether survival rates are comparable.

5. CONCLUSION

The status of the patients of cervical cancer in tertiary centres of Bangladesh reflects late presentation of the disease and advanced stage of disease at presentation. Low socioeconomic status, ignorancy, infection, poor hygiene status etc. are major factors. This method provides a rational and feasible alternative to conventional chemoradiation in patients with locally advanced cervical cancer who have contraindication to chemotherapy. Adequate health information, adequate treatment and counseling on cervical cancer need to be emphasized in our country.

6. RECOMMENDATIONS

- The study results establish the fact that this schedule of six fractions per week radiotherapy is an attractive and affordable option for carcinoma cervix patients with lesser toxicity and needs to be explored further. In the developing countries with less resources and many high-volume centers, such a plan can also help in optimization of available radiotherapy setups and treating a larger number of patients. Besides it can be viewed as an equally effective option for the elderly, patients who refuse, have contraindications to chemotherapy or have co -morbidities.
- Further study with multiple centers in different parts of Bangladesh.

7. LIMITATIONS

- The time period was not enough to conduct a quality study.
- Sample size was a great limitation to get an accurate clinical outcome.
- All relevant investigations could not be done due to financial constrain.
- It was a single centre study. Only patients admitted in NIDCH were taken for the study. So, this will not reflect the overall picture of the country. A large-scale study needs to be conducted to reach to a definitive conclusion.
- Sample were taken by purposive method in which question of bias might arise.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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