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A Comparative Study on Response and Toxicity of Concurrent Chemo-Radiotherapy and Radiotherapy Only in the Treatment of Cervical Cancer

HN Ashikur Rahaman* and Shravana Kumar Chinnikatti

Department of Clinical Oncology, Enam Medical College and Hospital, Savar, Dhaka, Bangladesh

***Corresponding author:**
HN Ashikur Rahaman

journalhouse111@gmail.com

Department of Clinical Oncology, Enam Medical College and Hospital, Savar, Dhaka, Bangladesh

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Abstract

Introduction: Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female cancers. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries. The high mortality rate from cervical cancer globally could be reduced through a comprehensive approach that includes prevention, early diagnosis, effective screening and treatment programmes.

Objective: This experimental study was carried out to compare the response and acceptable toxicity in concurrent chemo-radiotherapy and radiotherapy only in the treatment of cervical cancer.

Methods and Materials: The study had conducted in the Department of Radiation Oncology, Enam Medical College Hospital, Savar, Dhaka and in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka from July 2018 to June 2019.

Type of Study: Experimental study-Randomized Control Clinical Trial. Patients with carcinoma cervix attained at the Radiation Oncology Department of EMCH and NICRH during the study period had included in the study according to the inclusion of an exclusion criterion.

Results: A total of 80 patients (40 patients in Side A and 40 patients in Side B) who have biopsy-proven cervical carcinoma with no history of previous treatment were selected from the Department of radiotherapy Enam Medical College Hospital, Savar, Dhaka and in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital. All patients on both sides received external beam radiation with 50 Gy in 25 daily fractions over five weeks. Followed by three insertions of Brachytherapy were given by 21 Gy (one insertion per week for 7 Gy). Patients in Side A received injection Cisplatin 40 mg/m^2 in IV infusion on the first day of each treatment per week in addition to radiotherapy. In this study, it was observed that a significant symptomatic improvement was found in Side A after treatment than Side B and no severe unwanted reaction was noted in most of the patients. Systematic toxicity developed in both groups and comparatively more in Side A (chemoradiation) but that was not statistically significant and well managed with conservative treatment. Regarding performance status patients treated with concurrent chemoradiation showed better performance status than the patient treated with radiotherapy alone.

Conclusion: In this study, it was observed that patients of carcinoma cervix treated with concurrent chemoradiotherapy were effective for symptomatic improvement and suitable with acceptable toxicity for advanced cancer of the uterine cervix than those with radiation only.

Keywords: Cervical cancer; Concurrent chemoradiotherapy; Efficacy; Toxicity

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Introduction

Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female cancers. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries. The high mortality rate from cervical cancer globally could be reduced through a comprehensive approach that includes prevention, early diagnosis, effective screening and treatment programmes. There are currently vaccines that protect against common cancer-causing types of *Human Papillomavirus* and can significantly reduce the risk of cervical cancer (WHO 2018). It is the second-most common cause of female-specific cancer after breast cancer, accounting for around 8% of both total cancer cases and total cancer deaths in women (WHO 2014). About 80% of cervical cancers occur in developing countries [1]. Most women present with locally advanced stage in developing countries compared with developed countries where most people present with early-stage cancer [2]. In developing and undeveloped countries, a much more severe prevalence of this malignancy is associated with a generally worse economical and sanitary condition, lack of effective screening, as well as under implemented prevention strategy, where a lot of women were exposed to the risk of, or already affected by, high-risk CC, which remains a major health problem for women in these countries, though important advancement and progress has been witnessed in the last few years [3]. Carcinoma of the cervix is most common in Bangladeshi women comprising about 25% of all female cancer [4]. In Indian women, the uterine cervix is the commonest site of cancer and accounts for 20% of all malignant tumors in the females. The age-adjusted incidence is approximately 30 per 100000 populations per year, with approximately 120000 new cases diagnosed every year in India. The disease usually occurs in women from a low socioeconomic background, similar to other developing countries of Latin America, Africa, etc. Cancer of the cervix is also the common cause of cancer-related mortality in women of India (age-adjusted mortality of 4.3 per 100000 populations per year) and worldwide [5]. Total number 2805 patients from July 2018 to June 2019 were treated at the Department of Radiation Oncology, Enam Medical College Hospital, among them 760 patients were female and 138 patients that mean 18.15% of the patients were suffered from carcinoma cervix (Radiotherapy OPD, EMCH 2018-2019). It is common knowledge that the most important cause of cervical cancer is persistent *Papilloma virus* infection. The *Human Papilloma Virus* (HPV) is detected in 99% of cervical tumors, in particular the oncogenic subtypes such as HPV 16 and 18. While Papanicolau smears are used in the classical primary screening technique, HPV DNA testing, introduced in 2008, is well diffused in developed countries and is taking off in developing countries with a potentially significant reduction in the numbers of advanced cervical cancers and deaths [6]. In the HPV vaccination era, we expect that cervical cancer incidence had reduced, especially in those developed countries where large-scale immunization has been introduced. Most developed countries have introduced IIPV vaccines into routine vaccination programs and more than 60 million doses have already been distributed in 2010, which could guarantee a protection rate of 70%. However, cervical cancer 'still represents a major public health problem even in developed countries [7]. The disease is extremely rare in virgins. The incidence is higher in married women than single women and increases with the number of pregnancies. There is a fivefold higher incidence among prostitutes. It is commoner in women of lower socioeconomic groups. This is thought to be due to the early age of first intercourse [8]. The cervix is easily accessible to examination and the epithelial shed from it can give reliable evidence of early cancer of precancerous changes. The test is universally known as the "Pap's Smear"-test. Vaginal cytology can reveal cervical cancer in its preclinical stage when it is completely curable-with 5 years survival rates of 97%-100%. The Pap's Smear provides a strong suspicion of malignancy, which requires confirmation by cervical biopsy. More than 97% of uterine cervix tumors are squamous cell carcinoma. Approximately 7% to 10% are classified as adenocarcinoma and 1% to 2% is clear cell mesonephric type [9]. VIA test is very cost-effective and is usually done in every Medical College Hospital in Bangladesh by which cervical cancer may be diagnosed easily and early. VIA or Visual Inspection with Ace-tic acid sounds like a scary way to test for cervical cancer, but in reality, it is quite simple [10]. In CC patients without distant metastasis, several factors have been demonstrated as directly associated with a worse prognosis, including locally advanced disease, bulky tumor, deeply invasive disease, and pelvic lymph node or parametrical involvement. Patients with the aforementioned characteristics are at higher risk of recurrence and generally have a shorter survival period. 4-8 primarily applied conventional treatment modality for high-risk CC is Radiotherapy (RT) with or without hysterectomy; however inefficient local control and lymph node metastasis remain the major causes of treatment failure [11-13]. Therefore, treatment strategy combining RT with chemotherapy has been evaluated in a lot of clinical trials, initially in several pilot studies published 15 years ago, most of which were Randomized Controlled Trials (RCTs) [8,14,15]. In these trials, Concurrent Chemo Radiotherapy (CCRT) was the experimental treatment mode most widely assessed. Chemotherapy, at first, was applied exclusively as palliative care for patients with unfavorable prognosis.

Aims and Objective

General objectives

To compare the response and toxicity occurs in between Concurrent Chemo-Radiotherapy (CCRT) and Radiotherapy (RT) only in the treatment of cervical cancer.

Specific objectives

1. To observe the change of symptoms such-P/V discharge, P/V bleeding, Pelvic pain, Fever, etc
2. To observe the toxicity such as nausea, vomiting, stomatitis, alopecia, pigmentation, and myelosuppression (hematological), etc
3. To compare the symptomatic response to both modalities
4. To compote the toxicity on both modalities

Methods and Materials

Type of study: Experimental study-Randomized Control Clinical Trial.

Place of study: The study had conducted in the Department of Radiation Oncology, Enam Medical College Hospital, Savar, Dhaka and in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh

Period of study: July 2018 to June 2019

Patient selection: Patients with carcinoma cervix attained at the Radiation Oncology Department of EMCH and NICRH during the study period had included in the study according to the inclusion of an exclusion criterion

Inclusion criteria:

1. Patients: Clinically diagnosed and histologically proved squamous cell cervical carcinoma
2. FIGO stage: Stage IIb to stage Iva
3. Age group: Less than 60 years
4. Performance status: Karnofsky performance status score >60

Exclusion criteria:

1. Patients: With prior treatment
2. FIGO stage: Pre-invasive to some case of stage IIa and stage IVb
3. Age group: More than 60 years
4. Performance status: Karnofsky performance status score <60

Study population: The patients who were clinically diagnosed and histologically proved carcinoma cervix (squamous cell carcinoma) attained in the OPD of Radiation Oncology Department EMCH and NICRH.)

Simple size calculation for two proportions:

$$n = \frac{z^2 pq}{d^2} = 288$$

Here p= Prevalence of disease-25%=(0.25) [4]

Q=1-p 0.75

Z= 1.96 (Z value of Standard Normal Distribution at 95% confidence level)

D= Acceptable error in the estimate of 'p' usually set a at 5% = (0.05)

n = Sample size

$$n = \frac{(1.96)^2 \times 0.25 \times 0.75}{(0.05)^2} = 288.12 \approx 288$$

Corrected sample size

$$nc = \frac{n}{1 + \frac{n}{N}}$$

n= 288, No. of patients of carcinoma cervix attained at OPD of Radiotherapy Department in 1 year

N=138

$$nc = \frac{288}{1 + \frac{288}{138}} = 93.2 \approx 93$$

Using above formula the expected sample size was 93; but many considerable cases as 80 cases in study period due to time limitation.

Sampling technique

Systematic random sampling:

***The procedure of study*:** A total of 80 patients with histologically proved cervical carcinoma (squamous cell carcinoma) had selected randomly according to pre-defined inclusion and exclusion criteria and divided into two sides. Every alternate patient had enrolled for each side.

***Pre-treatment evaluation*:** Following procedure was followed to evaluate the patient's condition before treatment:-

General:

a) History

b) Physical examination

c) Examination under general anesthesia if needed

d) Location and type of lesion was recorded prior to treatment

Diagnostic procedures:

a) Biopsy for histopathological diagnosis

b) Pap's smear

c) Per-vaginal examinations

d) Per-speculum examinations

e) Per-rectal examinations

f) Bimanual examinations (rectovaginal, abdomino-vaginal) paying particular attention to detect the extension of the lesion

Laboratory studies:

a) Complete blood picture including T.C, D.C, Hb%, ESR and platelet count

b) Urinalysis (Urine routine and microscopic examination)

c) Liver function test (Serum bilirubin, SGPT, SGOT, Alkaline phosphatase)

d) Kidney function test (Serum creatinine, Creatinine clearance rate if needed)

e) ECG

Radiographic studies:

a) Chest X-ray (P/A and lateral view): to rule out comorbid conditions and general anesthesia evaluation

b) Ultrasonography of the whole abdomen

c) CT scan of abdomen and pelvis (optional)

d) MRI scan of pelvis/whole body PET scan (optional)

e) Cystoscopy/Sigmoidoscopy/Barium enema/IVU: if clinical suspicion of the bladder, rectal or ureteric involvement

f) Registration procedures: The patient was registered

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after pretreatment evaluation completed and meets the eligibility criteria

Side A (study group): 40 patients had treated with concurrent chemo-radiation by Cisplatin 40 mg/m^2 weekly for 5 weeks on day 1, 8, 15, 22 and 29 with a radiation dose-50 Gy in 25 fractions, 2 Gy per day/fraction, 5 days in a week for 5 weeks by Linear Accelerator (LINAC) machine (15 MV photon energy) both in SSD and SAD technique, AP, PA, Rt LAT, Lt LAT portal (usually 4 field box) and Intra-Cavitary Radiotherapy (ICRT)-21 Gy in 3 insertion, 7 Gy weekly insertion for 3 weeks treated by flexitron HDR Co-60, 20 channel machine.

Arm-B (control group): 40 patients had treated by radiotherapy only with a radiation close- 50 Gy in 25 fractions, 2 Gy per day/fraction, 5 days in a week for 5 weeks by Linear Accelerator (LINAC) machine (15 MV photon energy) both in SSD and SAD technique, AP, PA, Rt LAT, Lt LAT portal (usually 4 field box) and Intra-cavitary Radiotherapy (ICRT)-21 Gy in 3 insertion, 7 Gy weekly insertion for 3 weeks treated by flexitron HDR Co-60, 20 channel machine. All patients had received weekly till the completion of the treatment, all findings of the local and systemic examination had recorded and compare with previous findings and had documented.

Data analysis

Data analysis was done according to the objectives of the study by using a statistical package for a social science software program. Statistical significance had taken at $p \leq 0.05$ by using a Chi-Square Test.

Stage IA1: Stage IA1 cervical cancer can be managed conservatively to preserve fertility, with conization without lymphadenectomy, because the risk of nodes metastasis is <1%. The cone's margins must be free of disease. If a non-fertility-preserving therapy hysterectomy is performed, ovaries need not be removed. In the presence of LVSI, lymphadenectomy is recommended **(Table 1)** [16].

Stage IA2: Stage IA2 with no LVSI can be treated by conization (if fertility is to be preserved) or extra fascial hysterectomy. In the case of LVSI pelvic lymphadenectomy is indicated with radical trachelectomy or radical hysterectomy. In patients with a surgical contraindication, brachytherapy may represent an alternative option.

Stages IB1 to HA1: Stages IB and IIA cervical carcinoma can be cured by radical surgery including pelvic lymphadenectomy or radiotherapy. The two procedures are equally effective but differ in terms of morbidity and type of complications. In the only randomized trial directly comparing radical hysterectomy and radiation therapy only in 343 women with stage IB-IIA disease, overall and disease-free survivals at 5 years were similar for the two groups (83% and 74%, respectively), and 66% of the patients in the surgical arm had adjuvant radiation for the presence of risk factors. The rate of severe morbidity was 28% in the surgery group and 12% in the radiotherapy group (level of evidence I) [12]. There is no published evidence that concurrent chemoradiation would be useful in patients with early cervical cancer (stages IB1 and IIA <4 cm). Fertility-preserving surgery consisting of radical trachelectomy or conization with/without chemotherapy can be offered to young patients with early-stage cervical cancer wishing to preserve their fertility (level of evidence IV).

Stages IB2 to IVA: Chemoradiation Historically, radiotherapy has been the mainstay in the treatment of locally advanced cervical cancer, with a local control rate ranging between 88% and 95% for stage IB, 70%-80% for stage IIB, and 30%-40% for stage III and 5-year survival >80% for stage IB, 65% for stage IIB, and 40% for stage III.

Results

A total number of 80 patients with histological proved cervical carcinoma had selected randomly according to pre-defined inclusion and exclusion criteria and divided into two sides. 40 patients for Side-A (Study group) had treated with concurrent chemo-radiation by Cisplatin 40 mg/m¬2 weekly for 5 weeks on day 1, 8, 15, 22 and 29 with a radiation dose-50 Gy in 25 fractions, 2 Gy per day/fraction, 5 days in a week for 5 weeks by Linear Accelerator (LINAC) machine (15 MV photon energy) both in SSD and SAD technique, AP, PA, Rt LAT, Lt LAT portal (usually 4 field box) and Intra-cavitary Radiotherapy (ICRT)-21 Gy in 3 insertion, 7 Gy weekly insertion for 3 weeks treated by flexitron HDR Co-60, 20 channel machine and 40 patients for Side-B (Control group) had treated by radiotherapy only with a radiation dose- 50 Gy in 25 fractions, 2 Gy per day/fraction, 5 days in a week for 5 weeks by LINAC machine (15 MV photon energy) in SSD and SAD technique, AP, PA, Rt LAT, Lt LAT portal (usually 4 field box) and ICRT-21 Gy in 3 insertion, 7 Gy weekly insertion for 3 weeks. All the patients had received weekly till the completion of the treatment, all findings of the local and systemic examination had recorded and compare with previous findings and had documented.

The column chart showed the age distribution of the study population. The study populations had divided into 4 age groups. Age ranges from 20-60 years. The pick age incidence of cervical cancer had found in age groups of 40-50 years **(Figure 1)**.

Table 1: Cervical cancer treatment according to stage PLND (Pelvic Lymphadenectomy); LVSI (Lymphovascular Space Invasion); CT (Chemotherapy); NACT (Neoadjuvant Chemotherapy); RT (Radiation Therapy).

Stage	Treatment	Issue
IA1	Conization or Simple hysterectomy ± salpingo-ophorectomy and PLND if LVSI	Conservative surgery
IA2	Conization/radical trachelectomy or modified radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB1, IIA	Radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB2, IIB-IV	Combination CT/RT with Cisplatin	NACT to large bulky tumors prior to CT/RT

The column chart showed the socio-economic status of the study population. The socio-economic status of the study population was categorized according to the poor, middle class and rich. Most of the populations on both sides were in the poor group followed by the middle class **(Figure 2)**.

In this study, it had been observed that on both sides most of the patients belonged to illiterate and primary education status. Less numbers found to have HSC in Sides A and only one patient had in Sides B **(Figure 3)**.

In this study majority of the patient was multiparous. 25 (62.5%) of the study population had given birth to 3-4 children in Side A and 22 (55%) in Side B **(Figure 4)**.

The study populations had divided into 4 age groups. Age ranges from 20-60 years. The pick age incidence of cervical cancer had found in age groups of 40-50 years. Most of the populations in both arms were in the poor group followed by the middle class. Among the study population in both arms were in the poor group followed by the middle class. Among the study population, most of the patients belonged to illiterate and primary education status. Only one patient had found to have HSC in arm-A. In this study, it had been observed that in both arms the majority of the patient was multiparous. 25 (62.5%) of the study population had given birth to 3-4 children in Side-A and 22 (55%) in Side-B. Almost all the study population had presented with P/V watery discharge with pelvic pain. Majority of the patient presented with P/V bleeding, fever and anorexia **(Figure 5)**. It had been observed that Kamofsky Performance Status Scale (KPS) score on both sides was 60-80 in most of the study population **(Figure 6)**.

The bar chart showed the distribution of the study population according to the presence of symptoms. Almost all the study population had presented with P/V watery discharge with pelvic pain. Majority of the patient presented with P/V bleeding, fever and anorexia.

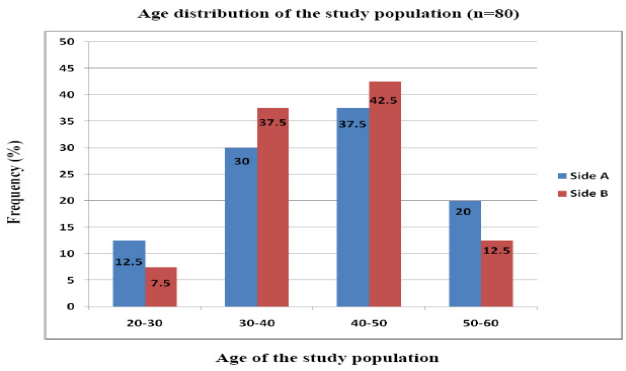

Figure 1 Age distribution of the study population (n=80), n=Number of study population.

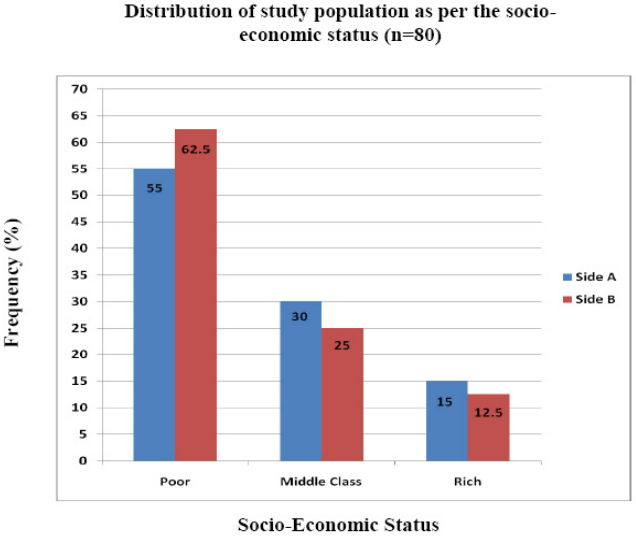

Figure 2 Distribution of study population according to socio=economic status (on the basis of monthly income) (n=80), n=Number of the study population.

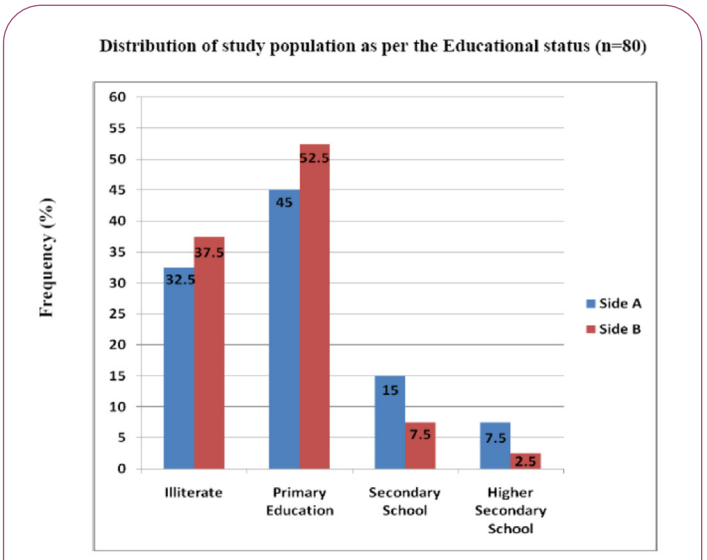

Figure 3 Distribution of study population according to educational status (n=80), n=Number of study population.

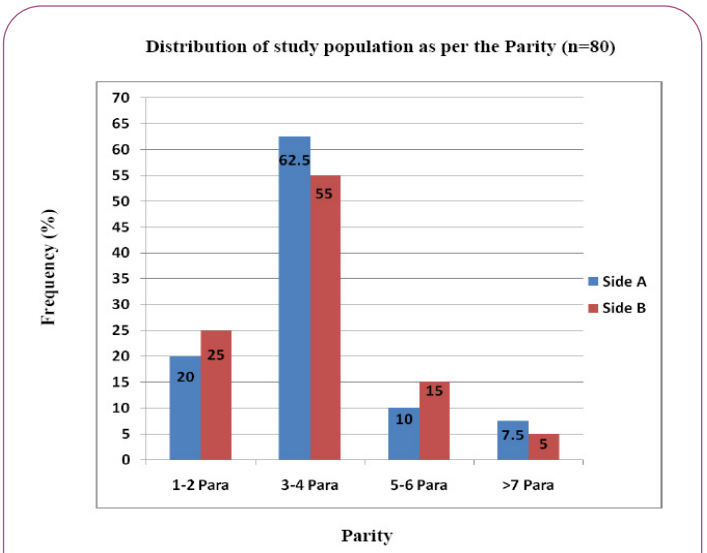

Figure 4 Distribution of study population according to parity (n=80), n=Number of the study population.

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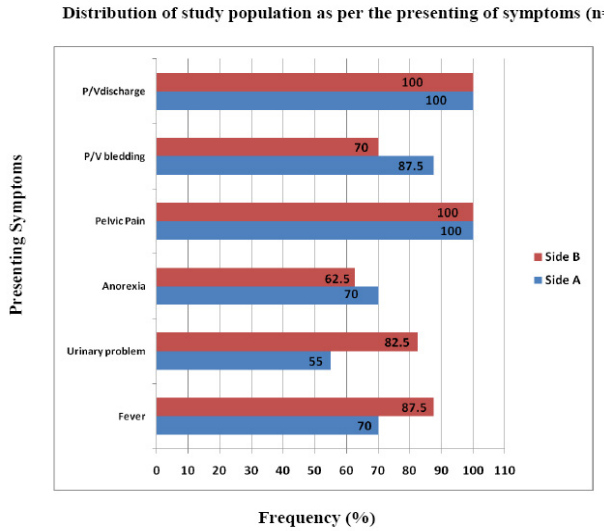

Figure 5 Distribution of study population according to the presence of symptoms (n=80), n=Number of the study population.

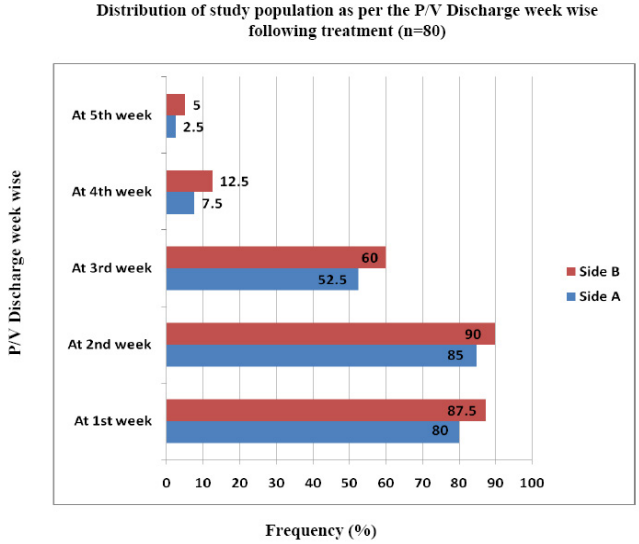

Figure 7 Distribution of study population according to P/V discharge following treatment (n=80), n=Number of the study population.

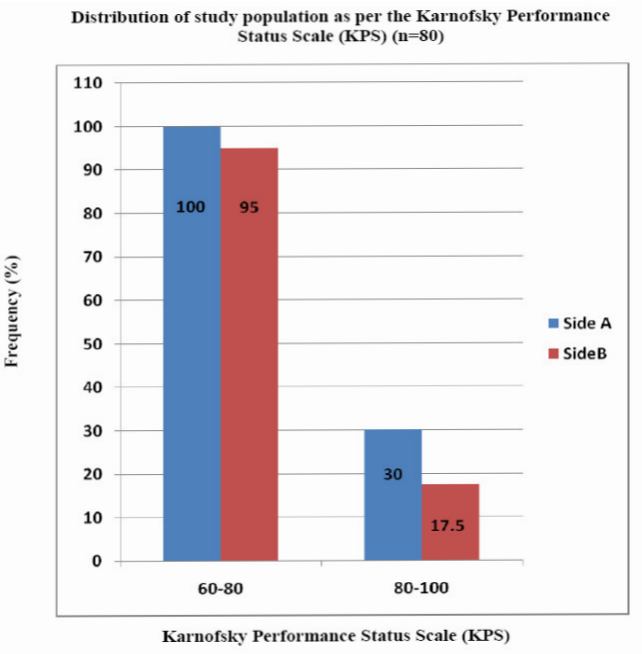

Figure 6 Distribution of study population according to Karnofsky Performance Status Scale (KPS) (n=80), n=Number of the study population.

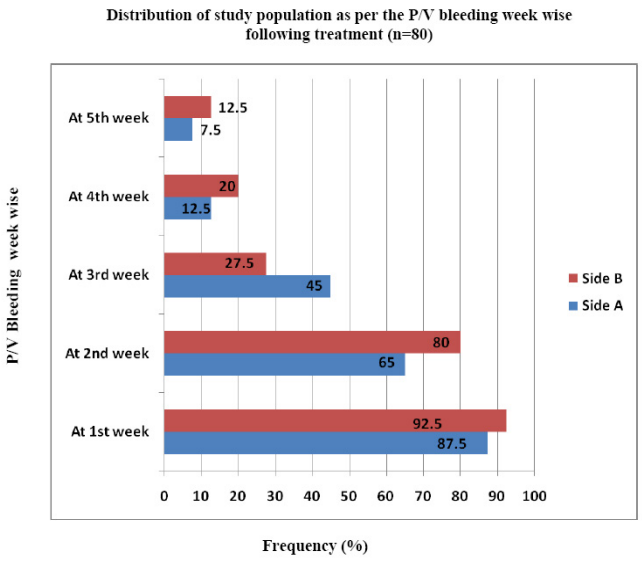

Figure 8 Distribution of study population according to P/V bleeding following treatment (n=80), n=Number of the study population.

In this study in had been observed that Karnofsky Performance Status Scale (KPS) score in both sides 60-80 in most of the study population **(Figure 6)**.

Bar chart showed discharge mildly increases in 2nd week of treatment then decline gradually **(Figure 7)**.

The bar chart showed P/V bleeding decline gradually following treatment **(Figure 8)**.

The bar chart showed pelvic pain decline gradually following treatment **(Figure 9)**.

Bar chart showed fever decline gradually following treatment **(Figure 10)**.

A significant symptomatic improvement was found in Side A, after treatment than Side B (**Figures 7-10)**. Overall treatment-related toxicity was more in Side A than Side B. In Grade-I nausea/vomiting and skin reaction in Grade-II were more in Side A. Leukopenia and anemia II also more in Side A Grade-I and II respectively. Data were analyzed by using the Chi-Square Test and the result was not significant in nausea/vomiting and skin reaction and significant in leukopenia at p<0.05 **(Table 2)**.

Table 2 Showed the distribution of study population according

to treatment-related toxicity. Overall treatment-related toxicity was more in Side A than Side B. In Grade-I nausea/vomiting and skin reaction in Grade-II were more in arm-A. Leukopenia and anemia II also more in Side A Grade-I and II respectively. Data were analyzed by using Chi-square Test and the result was not significant in nausea/vomiting and skin reaction and significant in leukopenia at p<0.05.

Categorization of the study population had done according to the Karnofsky Performance Status Scale (KPS) into 3 groups in both arms at the time of diagnosis and after treatment to see the symptomatic improvement. A significant improvement was found in Side A after treatment. Data were analyzed by using Chi-Square Test and the result was significant in Side A at p<0.05 **(Table 3)**. **Table 3** showed the distribution of the study population according to KPS performance status. Categorization had done according to Karnofsky Performance Status Scale (KPS) into 3 Groups in both sides at the time of diagnosis and after treatment to see the symptomatic improvement. A significant improvement was found in Side A after treatment. Data were analyzed by using Chi-Square Test and the result was significant in Side A at p<0.05.

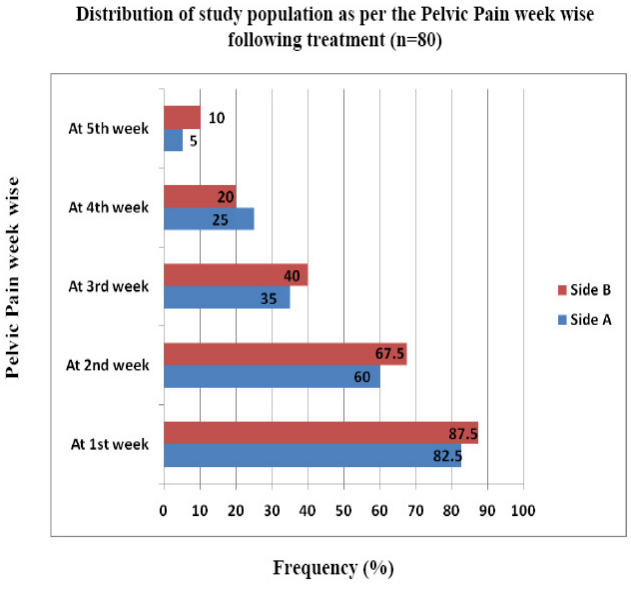

Figure 9 Distribution of study population according to pelvic pain following treatment (n=80), n=Number of the study population.

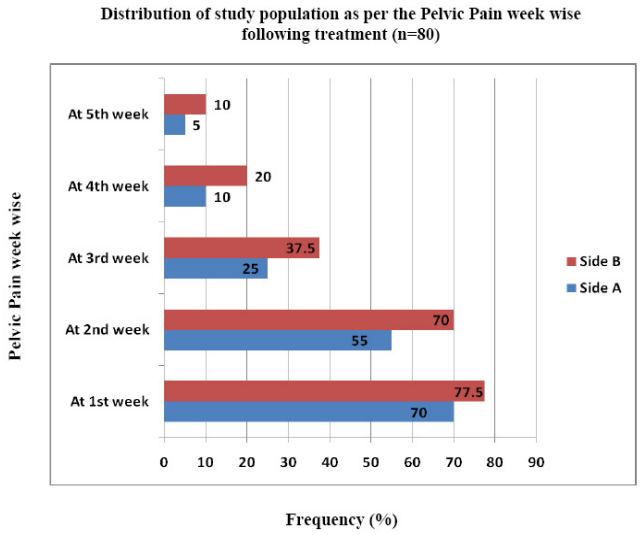

Figure 10 Distribution of study population according to fever following treatment (n=80), n=Number of the study population.

Table 2: Distribution of study population according to treatment-related toxicity (n=80), n=Number of the study population, S=Significant, NS=Non-Significant.

Toxicity	Side A		Side B		p-value
	No. of patient (n=40)	Percent (%)	No. of patient (n=40)	Percent (%)	
Nausea/Vomiting					
Grade-0	8	20	14	35	0.0399 S
Grade-I	28	70	20	50	
Grade-II	4	10	6	15	
Skin reaction					
Grade-0	0	0	2	6.7	0.0554 NS
Grade-I	5	16.7	7	23.3	
Grade-II	25	83.3	21	70	
Leukopenia					
Grade-0	10	33.3	20	66.7	0.00016 S
Grade-I	18	60	6	20	
Grade-II	2	6.7	4	13.3	
Anemia					
Grade-0	0	0	0	0	0.0260 S
Grade-I	10	33.3	18	60	
Grade-II	20	66.7	12	40	

Table 3: Distribution of study population according to Karnofsky Performance Status Scale (KPS) (n=80), n=Number of the study population, S=Significant, NS=Non-Significant

Performance Status	Arm-A (n=40)			Arm-B (n=40)		
KPS	Pre-treatment (%)	Post-treatment (%)	p-value	Pre-treatment (%)	Post-treatment (%)	p-value
0	10 (25.0%)	20 (50.0%)	0.00418 S	08 (20.0%)	16 (40.0%)	0.0219 S
1	23 (57.5%)	14 (35.0%)		28 (70.0%)	22 (55.0%)	
2	07 (17.5%)	06 (15.0%)		04 (10.0%)	02 (5.0%)	

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Discussion

It was an empirical study done on patients with carcinoma cervix attained at the Radiation Oncology Department of NICRH and EMCH during the study period. The pick age incidence of cervical cancer had found. The majority of the patients in this study were in age groups of 40-50 years on both sides (37.5% and 42.5% respectively). Bellow 30% of the cases were found in between 30-40 years in both sides and lesser number cases found in the age groups 20-30 years. A study by showed 51.1% of cases had got chemo-radiation in between 41-50 years. So these observations were in conformity with that of the present study [17]. Most of the populations on both sides were in the poor group followed by the middle class. Studied had found that patients with low socioeconomic conditions were at a higher risk of in-hospital mortality due to cervical cancer [18]. In this study more than 30% of patients were belonged to illiterate, 45% to 50% had primary education and bellow 5 patients have found to have HSC in both sides. The previous study found that quite a greater number of the interviewees who received chemo-radiation, 68.3% were literates, whereas the other 31.7% were illiterates. That was not largely different from reports of our studies [19]. In agreement with studies conducted in Bangladesh, our study also revealed than 25 (62.5%) of the study population had given birth to 3-4 children in Side-A and 22 (55%) in Side B. Almost all the study population had presented with P/V watery discharge with pelvic pain and about 70% to 87% patient presented with P/V bleeding, approximately 80% fever and 70% anorexia. It had been observed that Karnofsky Performance Status Scale (KPS) score on both sides was 60-80 in most of the study population. These clinical findings were almost similar to previous studies [20]. A significant symptomatic improvement was found in Side A after treatment than side-B which was similar to observations made in several other studies [21,22]. Overall treatment-related toxicity was more in Side A than Side B. In Grade-I nausea/vomiting and skin reaction in Grade-II were more in Side A. Leukopenia and anemia II also more in Side A Grade-I and II respectively. Studies abroad have also demonstrated increased cytotoxicity when cisplatin was combined with radiation therapy [7]. One GOG (Gynecologic Oncology Group) trial with weekly cisplatin combination radiation in IIB-IIB cervical cancer showed 5 years survival rate [8,23,24]. Among the drugs used for chemotherapy in advanced CC, Cisplatin was one of the most effective agents [25]. Thus, Cisplatin was primarily selected as one of the drugs tested in trials investigating CCRT. Among early researches comparing Cisplatin-based concurrent chemoradiotherapy (DDP-CCRT) with RI, results with apparent discrepancies were reported. Four studies reported positive results, with a maximum risk reduction of 49% for estimated 4-year Overall Survival (OS), which supported the superiority of DDP-CCRT [8,14]. However, no significant benefits in favor of DDP-CCRT concerning survival outcomes and toxicity profiles were revealed in two other studies [15]. These differences might be attributed to different study designs, subjects enrolled, control settings, regimens used, and duration of follow-up. A meta-analysis summarized these pilot studies, which presented positive results and comments recognizing improved outcomes achieved by DDP-CCRT, as well as evident toxic effects possibly enhanced by treatment combination [25]. However, the results of the meta-analysis showed that interventions for control groups were not totally consistent among the included studies [8,14,15]. Without considering surgical treatment performed in two studies as part of the local interventions for both experimental and control arm [26,27], exclusive RT were set as control in four studies; [14,15], however in another two studies [8], hydroxyurea, a widely used cytotoxic agent with antitumor-activity-targeting a variety of malignancies, was combined with RT as control group treatment. Afterward, several similar studies comparing DDP-CCRT with RI alone were conducted, with different results reported [16,24,28,29]. Although more than 2 decades have passed since the initial application of DDP-CCRT in treating high-risk CC patients, during which time new agents and modalities have been developed, tested, and utilized, DDP remains in the first-line drug list for this specific population. Most recently, an RCT conducted in Brazil again evaluated the difference in treatment effects between DDP-CCRT and exclusive RT in advanced CC, using patients with International Federation of Gynecology and Obstetrics (FIGO) Stage III disease as the targeted population [24]. With accumulated and updated data from relevant studies available for a new pooled analysis, we performed this study with a refined design and analytical methods to provide more definitive evidence for clinical guidance. A significant improvement was found in Side A after treatment according to Karnofsky Performance Status Scale (KPS). Almost similar types of results were found in a previous study [23]. From the result of present findings as well as the findings obtained by a number of studies, it is conceivable that concurrent chemo-radiotherapy is more effective than radiotherapy only in advanced cervical cancer.

Conclusion

On the basis of the discussion of the conclusion is made to improve the quality of patients suffering from inoperable carcinoma cervix and severe pain in Bangladesh. In the recent past carcinoma, the cervix is cardinal cancer among the women in Bangladesh. This empirical study was carried out to compare the responsiveness of improvement and acute complications following treatment of carcinoma cervix with concurrent chemo-radiotherapy against radiotherapy only. In conclusion, the use of concurrent chemotherapy with radiotherapy is effective for responsive improvement and feasible with acceptable toxicity for advanced cancer of the uterine cervix. It is recommended to conduct more clinical trials with a more intensive dose of chemotherapy or a combination of two or three agents.

Recommendation

Given the findings of the present study and discussion thereof, the following recommendations are laid down to reach a rational decision:

1. This present study was done on a relatively small sample, a large-scale study to be conducted to make the findings of the study generalize to reference population
2. This study may not reflect the exact situation of the disease in the community but its proximity to reality cannot be underestimated

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3. Further studies are recommended to determine the efficacy of concurrent chemo-radiotherapy

Limitations

The study was conducted for both academic and clinical purposes in a short period of time, a small sample size with limited resources and facilities, in spite of maximum effort by the researcher. It was conducted in a selected hospital. So the study population might not represent the whole community. The sample was taken purposively. So there may be a chance of bias that can influence the results. So it may not be adequate to represent the total population and large sample size would have given a better result.

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