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Evaluation of the Safety Profile of Concurrent Chemoradiation with Cisplatin versus Capecitabine of the Patients through Observation of the Toxicities in Locally Advanced Carcinoma Cervix

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Abstract

Background: Uterine cervical cancer is the second most common female malignancy in the world. And in Bangladesh, this is the most common malignancy among the female population. Concurrent chemoradiation plays an important role in the treatment of locoregionally advanced carcinoma uterine cervix. The success of treatment depends on a careful balance between megavoltage external beam radiotherapy and high dose rate intracavitary brachytherapy that optimizes the dose to the tumor. Aim of the study: The aim of the study was to compare the complete and partial responses of CCRT with capecitabine against CCRT with cisplatin. **Methods:** This was a prospective analytical study conducted at the Department of Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January 2014 to February 2015. A total of 60 patients with clinically and histologically diagnosed locally advanced squamous cell carcinoma cervix were selected for this study. The participants were equally divided into two groups based on treatment method. Arm-A group was treated with cisplatin, while the Arm-B group was treated with capecitabine. The treatment duration for each participant of both groups was 8 weeks from the start of chemoradiation. **Result:** In this study, the majority of the participants were from the age range of 46-55 years, and the mean age of the participants was 47 years. In total, over 80% of the participants were married before the age of 21. It was observed that out of 30 cases in each arm the overall response (complete and partial) in both groups were more or less equal. The complete response of Arm-A group was 22 (73.33 %) and Arm- B was 25 (83.33 %). Regarding toxicity, common toxicities associated with concurrent chemoradiation were more or less the same, and no severe unwanted reaction was noted in most patients. Reversible vomiting (grade 3) 13.3%, nephrotoxicity 20%, neurotoxicity 3.33% patients of Arm- A, only 16.6 % reversible grade 2 hand-foot syndrome seen in patients of Arm-B, which means the use of concurrent chemoradiation with capecitabine is equally effective and a well-tolerated option for patients of locoregionally advanced carcinoma uterine cervix. **Conclusion:** Capecitabine-based concurrent chemotherapy was arithmetically proven in achieving complete response better than cisplatin-based CCRT. Acute toxicities were observed in this study and there was a statistically significant difference in vomiting and nephrotoxicity. There were no nephrotoxic patients seen in capecitabine-based concurrent chemoradiation in the period of toxicity evaluation. considering effectiveness, safety profile, convenience the capecitabine-based concurrent chemoradiotherapy is the better treatment option than cisplatin-based concurrent chemoradiotherapy for treatment of locally advanced carcinoma of the uterine cervix.

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INTRODUCTION

In the present world, cancer is an emerging health problem all over the globe. Among the cancers that affect the female population of many developing countries, cancer of the uterine cervix is the most common and has become the leading cause of female mortality due to cancer in developing countries. Carcinoma of the uterine cervix, commonly referred to as cervical cancer, occurs in the cells of the cervix, the lower part of the uterus connected to the vagina. The incidence of cervical cancer is higher in women belonging to low socioeconomic status, leading to very high incidence rates in developing and developed countries, compared to the developed countries.[1] In the year 2012, cervical cancer accounted for almost 528,000 new cancer cases and 266,000 cancer deaths globally, over half of which were from the Asian region.[2] Although the world health organization (WHO) provided a comprehensive cervical cancer control and prevention guidebook for both the governments and healthcare providers, Bangladesh, along with many other developed countries, still face high incidence and mortality rates due to cervical cancer. This might be a result of the late detection of cancer in such countries. In Bangladesh, the leading cancer in women is cervical cancer, and over 80% of cervical cancer presents at an advanced age, with high mortality rates. Innovation in cervical cancer treatment is primary in addressing current and possible future needs of patients. Despite the worldwide implementation of prevention and early detection strategies like pap-smear testing, Human Papilloma Virus (HPV) testing, and vaccines, almost 30% of the newly diagnosed cases still fall into the locally advanced diseases category. This indicates the tumor spreading outside the uterine cervix. In cervical cancer, there is a transitional zone, the squamocolumnar junction. The squamocolumnar junction (SCJ) is defined as the junction between the squamous epithelium and the columnar epithelium. Its location on the cervix is variable. Most cervical cancers are caused by different strains of the human papillomavirus (HPV), a sexually transmitted infection. When the body is exposed to HPV, the immune system usually protects the virus from causing harm. However, in a tiny proportion of people, the virus persists for years, contributing to the process by which certain cervical cells develop into cancer cells.[3] The viral infection of the cervix may lead to tumors in the uterine cervix. Over 90% of the tumors of the uterine cervix are squamous cell carcinoma, and about 7-10% are classified as adenocarcinoma.[4] The method of treatment for cervical carcinoma can vary depending on tumor size, histology, stage, risk factors and complications of surgery or radiation therapy, or even patient preferences.[5] Invasive cervical cancer may be treated by surgery, radiotherapy, or in some cases, a combination of both, regardless of chemotherapy. Concurrent chemotherapy should be

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considered over radiation alone in the treatment of early stages of cervical cancer with poor prognosis, as chemotherapy is not used as a primary line of treatment for cervical cancer.[6] There have been many controversial studies on the effectiveness of radical radiotherapy and radical surgery as a treatment method for early cervical cancer stages, but the results of both arguments have remained inconclusive.[4] Concurrent Chemoradiotherapy (CCRT) is a primary choice for the International Federation of Gynecology and Obstetrics (FIGO) stage IIB, IIIA, IIIB, and IVA cervical cancer, and is an excellent alternative to surgery for selected patients with stage IA, IB, or IIA diseases.[7] The present study was initiated with the goal of comparing the response of CCRT with cisplatin and CCRT with capecitabine in the treatment of stage IIB-IVA of cervical cancer.

Objective

General Objective

- To evaluate the efficacy and safety profile of CCRT with capecitabine in locally advanced cervical cancer

Specific Objectives

- To compare the safety profile and efficacy of CCRT with cisplatin and CCRT with capecitabine

MATERIAL AND METHODS

This was a prospective analytical study conducted at the Department of Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January 2014 to February 2015. A total of 60 patients with clinically and histologically diagnosed locally advanced squamous cell carcinoma cervix were selected for this study. The participants were selected from multiple oncology departments that were selected previously. The 60 participants were then divided into 2 groups, "Arm-A" and "Arm-B", with 30 patients in each group. Arm-A patients were treated with CCRT with cisplatin, and ARM-B patients were treated with CCRT with capecitabine. Complete clinical history, performance status, physical examination, location, and type of lesion were recorded prior to the start of treatment. After the selection of patients from different institutes among those selected from radiotherapy treatment, written informed consent was taken from each of the participants. Clinical staging was done according to FIGO staging, the duration of the CCRT was 8 weeks starting from the first day of treatment. Arm-A patients received inj. Cisplatin 40mg/m2 with 1 liter of normal solution on both arms each week, and patients of Arm-B received Tab. Capecitabine 825 mg/m2 twice per day. Improvement of Quality of life was assessed by ECOG (Eastern Cooperative Oncology Group) performance scale. Prior to the commencement of the study, the research protocol was approved by the Institutional Review Board and concerned department.

Inclusion Criteria

- Only female population
- Patients who had given consent to participate in the study.
- All patients diagnosed with locally advanced cervical cancer (FIGO stage IIB-IVA)
- Patients between the age range of 18-65 years.

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Exclusion Criteria

- Mentally ill.
- Pregnant or lactating women
- Prior records of chemotherapy, radiotherapy, or surgery
- Patients with uncontrolled infection
- Patients with a life expectancy of <6 months
- Patients refusing to continue treatment or follow-up.

RESULTS

Among the participants of both groups, the maximum number of patients were from the age group of 46-55 years, 56.70% from Arm-A, and 60% from Arm-B. The age of the participants aged from 26-65 years and no significant age difference was observed between the groups. The majority of the patients from both groups (83.4% in Arm-A, 80% in Arm-B) were married before the age of 21. Only 13.3% from Arm-A and 16.7% from Arm-B were married between the age of 21-30, and 1 participant from each group was married after the age of 30. The majority of the patients from both groups (60% from Arm-A, 56.7% from Arm-B) had used oral contraceptive pills for longer than 5 years. This was the most prominent risk factor. Smoking also had a high prevalence as a risk factor for both groups, and unhealthy personal hygiene was recorded in both groups in smaller numbers, as a risk factor. Most of the patients from both groups belonged to Stage IIB and Stage IIIB according to the FIGO stage of the disease. 60% from Arm-A and 63.3% from Arm-B were in stage IIB, and 26.7% from Arm-A and 30% from Arm-B were in stage IIIB. Post-coital bleeding was present in the majority of patients from both groups. 83.33% from Arm-A and 80% from Arm-B had post-coital bleeding. Vaginal discharge was the most common clinical presentation, presenting in 90% of Arm-A and 93.33% of Arm-B participants. Some other common clinical presentations were Anemia (73.33% in Arm-A, 76.67% in Arm B), Intermenstrual Bleeding (66.67% in Arm-A, 60% in Arm-B), and loss of appetite (63.33% in Arm-A, 60% in Arm-B). Per-vaginal examination revealed P/V bleeding, growth, and discharge, all with high ratios, in both Arm-A and Arm-B. Per-Speculum examination findings revealed similar results also with high ratios in both groups. Bimanual & Per Rectal Examination revealed the growth was present in 100% of cases, Involvement of parametrium was present in 86.67% of Arm-A and 83.33% of Arm-B cases, Fixation of growth with the pelvic wall was present in 30% of Arm-A and 40% of Arm-B cases. Rectum involvement was observed in only 1 patient (3.33%) of Arm-A and none from Arm-B. Table 6 shows the response of various signs and symptoms and their relative percentage post-treatment. It was observed that post-coital bleeding, intermenstrual bleeding, and rectal pain had a 100% positive response in all present cases from both groups. Vaginal discharge cases were present in 90% in Arm-A, and 93.3% in Arm-B. Among them, 70.4% of Arm-A, and 85.7% of Arm-B vaginal discharge cases, saw a positive response. The difference between pre-treatment and post-treatment cases of vaginal discharge was not statistically significant. The statistical association was made in Vaginal Discharge, Pelvic pain, Dysuria, Loss of Appetite, and Anemia symptom cases, and statistical significance ($p<0.05$) was only observed in pelvic pain, dysuria, and anemia cases. Table 7 showed the distribution of patients according to FIGO stage of the disease

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and their response type to treatment. A total of 35 patients (Arm-A=17, Arm-B=18) were from stage IIB, 5 patients (Arm-A=3, Arm-B=2) were from Stage IIIA, total of 19 patients (Arm-A=9, Arm-B=10) were from stage IIIB and 1 patient of Arm-A was from stage IVA. In total, 73.3% of Arm-A participants and 83.3% of Arm-B participants showed complete response to the treatment, 23.3% of Arm-A and 16.7% of Arm-B participants showed partial response, while only 1 patient of Arm-A, Stage IIIB showed no response to treatment, and was recognized as a progressive disease. No statistical significance was observed between the treatment type and response type, but arithmetically it was observed that Arm-B patients had a better response than Arm-A (Complete response in 73.3% of Arm-A and 83.3% of Arm-B). Table 8 observed the different toxicity levels of common toxicities of both groups. In Arm-A, 80%, and in Arm-B, 100% had grade 0 nephrotoxicity, which was statistically significant. In Arm-A, Grade-1 vomiting was present in 46.7%, Grade-2 vomiting in 26.7%, Grade-3 and Grade-0 vomiting in 13.3% of participants. In Arm-B, Grade-1 vomiting was present in 53.3% and Grade-0 vomiting in 33.3%. This difference was also statistically significant. At the follow-up pap-smear test 6 month after the CCRT treatment, 76.7% in Arm-A and 83.3% in Arm-B tested negative for cancer, while 23.3% from Arm-A and 16.7% from Arm-B tested positive.

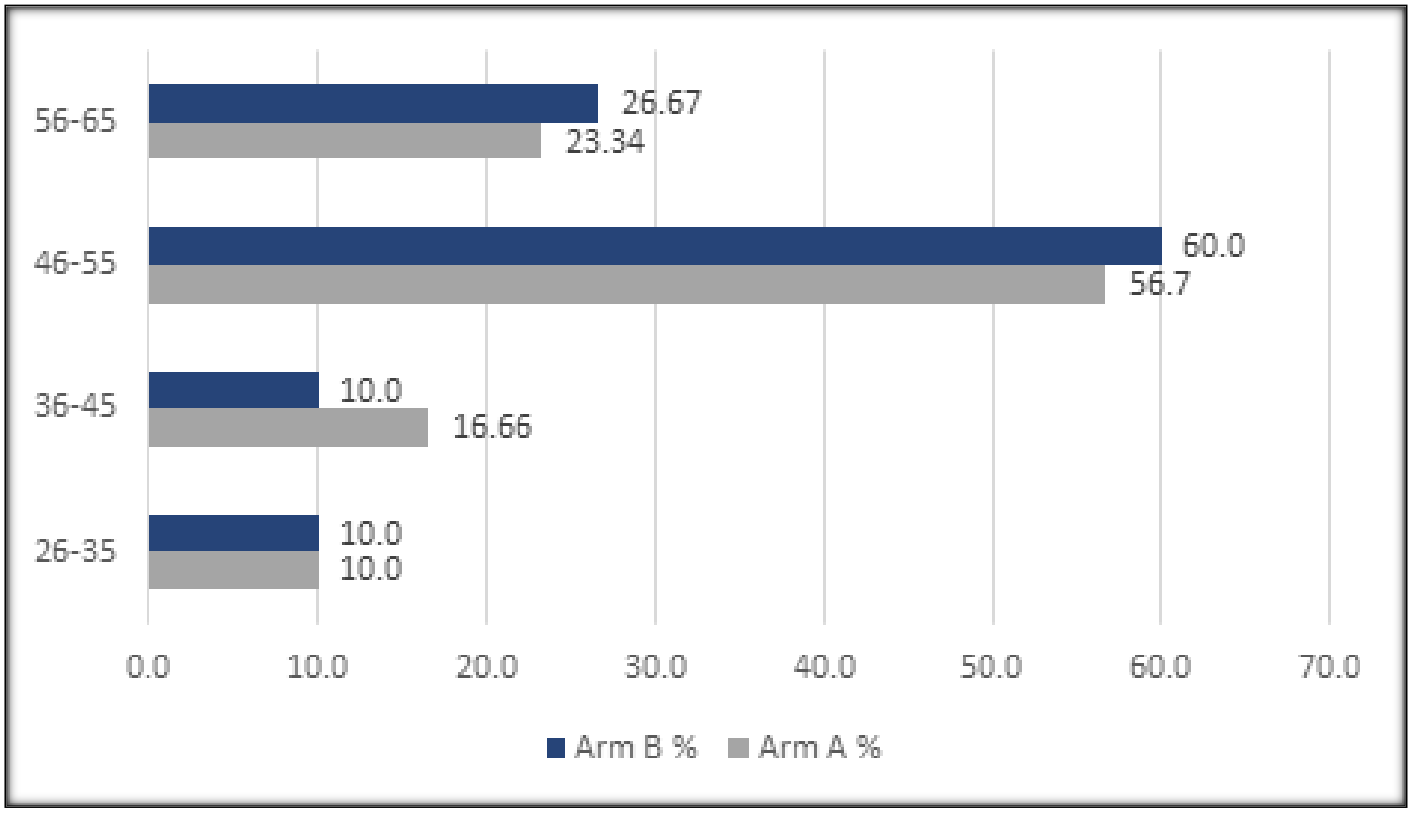

Figure 1: Age distribution of the participants (n=60)

Table 1: Distribution of participants by age of marriage (n=60)

Age of marriage	Arm A	Arm B

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	n	%	n	%
≤20	25	83.4	24	80
21-30	4	13.3	5	16.7
≥31	1	3.3	1	3.3

Table 2: Distribution of participants by risk factors (n=60)

Risk Factors	Arm A		Arm B	
	n	%	n	%
OCP	18	60	17	56.7
Smoking	10	33.3	12	40
Unhealthy personal Hygiene	8	26.7	5	16.7

*OCP= Oral Contraceptive Pill

Table 3: Distribution of participants by FIGO staging (n=60)

FIGO Stage	Arm A		Arm B	
	n	%	n	%
Stage IIB	18	60	19	63.3
Stage IIIA	3	10	2	6.7
Stage IIIB	8	26.7	9	30
Stage IV	1	1	0	0

Table 4: Distribution of participants by clinical presentations (n=60)

Clinical Presentation	Arm A		Arm B	
	n	%	n	%
Post Coital Bleeding	25	83.33%	24	80.00%
Intermenstrual Bleeding	20	66.67%	18	60.00%
vaginal Discharge	27	90.00%	28	93.33%
Pelvic Pain	13	43.33%	15	50.00%
Dysuria	13	43.33%	14	46.67%
Rectal Pain	1	3.33%	0	0.00%
Loss of Appetite	19	63.33%	18	60.00%
Anemia	22	73.33%	23	76.67%

Table 5: Distribution of participants by examination findings (n=60)

Examination Findings	Arm A		Arm B	
	n	%	n	%
Per Vaginal Findings				
P/V Bleeding	28	93.33%	27	90.00%
Growth	30	100.00%	29	96.67%
P/V Discharge	27	90.00%	28	93.33%
Per-Speculum Examination Findings				
Growth	30	100.00%	29	96.67%

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P/V Discharge	30	100.00%	30	100.00%
P/V Bleeding	28	93.33%	27	90.00%
Bimanual & Per Rectal Examination				
Growth Present	30	100.00%	30	100.00%
Involvement of parametrium	26	86.67%	25	83.33%
Fixation of growth with pelvic wall	9	30.00%	12	40.00%
Involvement of rectum	1	3.33%	0	0.00%

Table 6: Distribution of participants according to response of signs and symptoms (n=60)

Total Patients n=60 Arm A (n=30) & Arm B (n=30)	**Pre-Treatment**	**Post-treatment**	**Positive Response**	**P-Value**
Post Coital Bleeding				
Arm A	25 (83.3)	0 (0)	25 (100)	
Arm B	24 (80.0)	0 (0)	24 (100)	
Intermenstrual Bleeding				
Arm A	20 (66.7)	0 (0)	20 (100)	
Arm B	18 (60.0)	0 (0)	18 (100)	
Vaginal Discharge				
Arm A	27 (90.0)	8 (29.6)	19 (70.4)	0.168
Arm B	28 (93.3)	4 (14.3)	24 (85.7)	
Pelvic Pain				
Arm A	13 (43.3)	5 (38.5)	8 (61.5)	0.008*
Arm B	15 (50.0)	0 (0)	15 (100)	
Dysuria				
Arm A	13 (43.3)	8 (61.5)	5 (38.5)	<0.001*
Arm B	14 (46.7)	0 (0)	14 (100)	
Rectal Pain				
Arm A	1 (3.3)	0 (0)	1 (100)	
Arm B	0 (0)	0 (0)	0 (0)	
Loss of Appetite				
Arm A	19 (63.3)	11 (57.9)	8 (42.1)	0.886
Arm B	18 (60.0)	10 (55.6)	8 (44.4)	
Anemia				
Arm A	22 (73.3)	9 (40.9)	13 (59.1)	0.035*
Arm B	23 (76.7)	3 (13)	20 (87.0)	

Table 7: Distribution of participants according to types of response to treatment and staging

Response Type **Total Patients n=60 Arm A (n=30) & Arm B (n=30)**	**Complete Response**	**Partial Response**	**Progressive Disease**	**P-Value**
Stage IIB (n=35)				
Arm-A (n=17)	15 (88.2)	2 (11.8)	0 (0)	N.A
Arm-B (n=18)	16 (88.9)	2 (11.1)	0 (0)	

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Stage IIIA (n=5)				
Arm-A (n=3)	2 (66.7)	1 (33.3)	0 (0)	
Arm-B (n=2)	1 (50)	1 (50)	0 (0)	
Stage IIIB (n=19)				
Arm-A (n=9)	5 (55.6)	3 (33.3)	1 (11.1)	
Arm-B (n=10)	8 (80)	2 (20)	0 (0)	
Stage IVA (n=1)				
Arm-A (n=1)	0 (0)	1 (100)	0 (0)	
Arm-B (n=0)	0 (0)	0 (0)	0 (0)	
Total (n=60)				
Arm-A (n=30)	22 (73.3)	7 (23.3)	1 (3.3)	0.361
Arm-B (n=30)	25 (83.3)	5 (16.7)	0 (0)	

Table 8: Distribution of participants by toxicity assessments (n=60)

Total Patients n=60 Arm A (n=30) & Arm B (n=30)	**Arm A**		**Arm B**		**P-Value**
Toxicity Assessments	**n**	**%**	**n**	**%**	
Nausea					
Grade-0	16	53.3%	15	50.0%	0.958
Grade-1	9	30.0%	10	33.3%	
Grade-2	5	16.7%	5	16.7%	
Vomiting					
Grade-0	4	13.3%	10	33.3%	0.045
Grade-1	14	46.7%	16	53.3%	
Grade-2	8	26.7%	4	13.3%	
Grade-3	4	13.3%	0	0.0%	
Diarrhea					
Grade-0	18	60.0%	14	46.7%	0.265
Grade-1	12	40.0%	14	46.7%	
Grade-2	0	0.0%	2	6.7%	
Skin Reaction					
Grade-0	2	6.7%	1	3.3%	0.762
Grade-1	10	33.3%	12	40.0%	
Grade-2	18	60.0%	17	56.7%	
Anemia					
Grade-1	18	60.0%	20	66.7%	0.592
Grade-2	12	40.0%	10	33.3%	
Leucopenia					
Grade-1	13	43.3%	14	46.7%	0.795
Grade-2	17	56.7%	16	53.3%	
Bladder Toxicity					
Grade-0	10	33.3%	8	26.7%	0.548
Grade-1	12	40.0%	10	33.3%	
Grade-2	8	26.7%	12	40.0%	

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Rectal Toxicity					
Grade-0	9	30.0%	10	33.3%	0.853
Grade-1	11	36.7%	12	40.0%	
Grade-2	10	33.3%	8	26.7%	
Hand-Foot Syndrome					
Grade-0	30	100.0%	25	83.3%	0.065
Grade-1	0	0.0%	4	13.3%	
Grade-2	0	0.0%	1	3.3%	
Nephrotoxicity					
Grade-0	24	80.0%	30	100.0%	0.036
Grade-1	5	16.7%	0	0.0%	
Grade-2	1	3.3%	0	0.0%	
Neurotoxicity					
Grade-0	29	96.7%	30	100.0%	
Grade-1	1	3.3%	0	0.0%	

Table 9: Distribution of participants by pap-smear test at 6 months follow up (n=60)

Pap Smear test at follow-up	**Arm A**		**Arm B**	
	n	**%**	**n**	**%**
Negative	23	76.7%	25	83.3%
Positive	7	23.3%	5	16.7%

DISCUSSION

Gynecologic cancers were the first malignancies treated with radiation, more than a century ago. The current strategy for treating cancers of the uterine cervix is tailored to the clinical and pathologic stages of the disease. The early stage of the disease can be treated surgically if resection can be accomplished without substantial tissue disruption. Postoperative radiotherapy is reserved for cases in which histopathological analysis of the removed specimen reveals features suggesting a high risk of local recurrence.[8] The present study was conducted to see the difference of results in two treatment methods used in two groups. In Arm-A group, participants were treated with CCRT with cisplatin, and in Arm-B group, participants were treated with CCRT with capecitabine. In the present study, the maximum number of patients from both groups were from the age group of 46-55 years, with the mean age of the participants being 47 years. The peak age observed in our study was 46-55 years, and a decline was noticed in the following age group. This was different from the findings of an Indian study, where the peak age of the disease was 55-59 years.[9] This difference might be a result of all the participants of the Indian study being in the late stages of their cancer. Over 80% of patients from both groups were married earlier before the age of 21. Early age of marriage was also observed in other studies, where it was recognized as a significant risk factor.[10,11] In this study, the most common risk factors for the participants of both groups were oral contraceptive pills and cigarette smoking. Unhealthy personal hygiene was also recognized as a risk factor, which had a

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slightly higher prevalence in the Arm-A group compared to the Arm-B group. OCP was used for longer than more than 5 years by the participants, which was considered a significant risk factor. This hypothesis was supported by a case-control study, showing a high prevalence of cervical cancer with prolonged use of OCP.[12] The majority of patients from both of Arm-A and Arm-B presented with post-coital bleeding (Arm-A 83.3% and Arm-B 80.0%), intermenstrual bleeding (Arm-A 66.7% and Arm-11 60.0%), and excessive per vaginal watery discharge (Arm-A 90.0% and Arm-B 93.3%) and anemia (Arm-A 73.3% and Arm-B 76.7%). Some patients presented with loss of appetite, urinary problems. pelvic pain and rectal discomfort. Per vaginal examination, findings showed in this study that there were per vaginal bleeding, vaginal discharge, and growth. These findings were also observed in per speculum examination. Bimanual examination per rectal examination revealed the involvement of parametrium and fixation of the pelvic floor and rectal involvement. Although patients presented with per vaginal bleeding had no more bleeding after treatment, some patients had persistent vaginal water discharge even after treatment. On the basis of staging and response to treatment, it was observed that 73.3% of Arm-A and 83.3% of Arm-B had a complete response, and patients from FIGO stage IIB and IIIA had a much better complete response and very few partial response cases, compared to other stages with late presentations. Partial response was observed in 23.3% of Arm-A and 16.7% of Arm-B patients, and the only progressive disease case was from the Arm-A group. Although no statistically significant difference was observed, it was arithmetically proven that Arm-B patients treated with capecitabine had higher complete response rates compared to Arm-A patients. This was in line with the findings of other studies.[13,14,15] Toxicity assessment showed that toxicity from vomiting and nephrotoxicity, none of the other toxicity categories were statistically significant. At a 6-month follow-up by a pap-smear test, it was observed that 76.7% of Arm-A patients tested negative, while 83.3% of Arm-B tested negative for cancer. This supports the theory that capecitabine-based chemotherapy is an active and very well tolerated treatment for locally advanced cervical cancer.

Limitations of The Study

The study was conducted in a single hospital with a small sample size selected from multiple local hospitals. So, the results may not represent the whole community. The short time period was not enough to conduct a quality study.

CONCLUSIONS

Capecitabine-based concurrent chemotherapy was arithmetically proven in achieving complete response better than cisplatin-based CCRT. Acute toxicities were observed in this study and there was a statistically significant difference in vomiting and nephrotoxicity. There were no nephrotoxic patients seen in capecitabine-based concurrent chemoradiation in the period of toxicity evaluation. considering effectiveness, safety profile, convenience the capecitabine-based concurrent chemoradiotherapy is the better treatment option than cisplatin-based concurrent chemoradiotherapy for treatment of locally advanced carcinoma of the uterine cervix.

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