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Original Article

Concurrent 2-D Versus 3d-Crt Chemoradiotherapy in Locally Advanced Squamous Cell Carcinoma of Uterine Cervix

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Farhana Khanam[1], ANM Mainul Islam[2], Shah Md. Fazlay Rabby Khan[3], Shirajush Salekin[4], Afsana Sharmin Anika[5], Md. Abdullah Al Maruf[6]

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ABSTRACT

Introduction: *Concurrent chemoradiotherapy is the standard treatment of locally advanced carcinoma of uterine cervix. Traditionally, External Beam Radiotherapy (EBRT) is given by two-dimensional radiotherapy in which surrounding normal tissue gets more radiation and causes significant toxicities. To overcome these toxicities EBRT is given by three-dimensional conformal radiotherapy technique.* ***Objective:*** *To compare the effectiveness and toxicities of treatment with concurrent three-dimensional conformal radiotherapy and concurrent two-dimensional radiotherapy in locally advanced squamous cell carcinoma of uterine cervix.* ***Methods and Materials:*** *This quasi-experimental study was conducted from January 2018 to June 2019. A total number of 60 patients of locally advanced squamous cell carcinoma of uterine cervix allocated equally in Arm A and Arm B. Patients of Arm A received 3D-CRT concurrent chemoradiotherapy and those of the Arm B received 2D-RT concurrent chemoradiotherapy followed by Intracavitary radiotherapy for both Arms. Every patient was assessed weekly during radiotherapy and then at 6^{th}, 12^{th} and 24^{th} weeks after radiotherapy.* ***Results:*** *At six months after completion of radiotherapy, 29 (96.7%) and 26 (86.7%) patients of Arm A and B had complete response respectively ($p \geq 0.05$). Among acute toxicities, significant (Grade 3) gastrointestinal toxicities were seen in Arm B ($P<0.05$). Grade 3 dermatological toxicity were observed in 1 (3.3%) and 6 (20%) patients of the Arm A and B respectively ($p<0.05$).* ***Conclusion:*** ***T****he patients of 3D-CRT arm showed better response arithmetically. Also, there was an observable significant reduction of toxicities in the 3D-CRT arm.*

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1. *Medical officer, Department of Radiotherapy, Sher-E-Bangla Medical College Hospital, Barishal*
2. *Assistant professor, Department of Radiotherapy, Sher-E-Bangla Medical College, Barishal*
3. *Junior consultant, Ortho Surgery, Sadar Hospital, Jhalokathi*
4. *Indoor medical officer, Department of Radiotherapy, Sher-E-Bangla Medical College Hospital, Barishal*
5. *Specialist, Radiation Oncology, Labaid Cancer and Super speciality Hospital, Dhaka*
6. *Medical officer, Upazilla Health Complex, Mehendiganj, Barishal*

Key words: *Concurrent chemoradiotherapy, EBRT, 2D-RT, 3D-CRT, ICRT*

INTRODUCTION

Uterine cervical cancer is the 8th most common cancer with an estimated 569847 new cases in 2020 worldwide. In Bangladesh, new cases of cervical cancer were 8,068 (5.4 %) it ranked 5th (5.4%) among the whole cancer patients and the 2nd (12%) most common cancer among female [1]. In Bangladesh and many other developing countries, unfortunately the incidence and mortality rates of carcinoma uterine cervix remains high, predominantly due to late detection. Majority of patients usually present at an advanced stage with a high mortality rate [2]**.** In advanced stage of disease treatment related morbidity remain significant challenges in treating carcinoma uterine cervix. Standard treatment of locally advanced squamous cell carcinoma of the uterine cervix is concurrent chemoradiotherapy and brachytherapy [3]. Radiotherapy plays a major role in the management of locally advanced cervical cancer both EBRT and ICRT are used, often in combination with chemotherapy. Radiotherapy is always a trade off between the dose that can be delivered to malignant tissue and the dose that can be tolerated by healthy tissue. To achieve local control, and subsequently patient cure very high doses have to be delivered to patients with locally advance cervical cancer. Traditionally this treatment has been rather toxic and it has been reported up to 20-25% of patients experience adverse effect [4]**.** Although the traditionally used conventional radiotherapy fields (4 field box technique) based on bony anatomy have resulted in fairly good loco-regional controls, but the geographic miss of the clinical target volume may often result in increased risk of failures and the large target volumes were treated results in substantial increase in gastrointestinal (GI), genitourinary (GU) and haematological toxicity [5] .These toxicities can lead to unplanned treatment breaks and long overall treatment time that may negatively influences the outcome. Conventional radiotherapy has also some limitation like: inadequacy of the standard fields for large volume coverage, under dosing in lymph node regions, the rate of missed therapeutic margins (common site in rectum) and the rate of incomplete coverage of the uterine fundus. On the contrary 'three dimensional conformal radiotherapy (3D-CRT)' not only minimizes the risk of a geographical miss but has also shown to result in reduced coverage (20% reduction in the risk of a geographical miss) and significantly reduces the volume of radiation exposed to normal structures such as bowel, bladder, and bone marrow [6] . Due to this limitations, the optimum radiation dose can't be delivered by conventional radiotherapy in most of the cases. So conformal techniques can be overcome this limilations by using 3D-CRT where optimum tumoricidal dose can be given as well as providing less dose to the surrounding normal tissue and critical structures due to the conformity of the radiation beams [7] . Radiation induced toxicity is more when used with two dimensional method but it is less and acceptable in three dimensional method. To reduce the toxicities, using Three-dimensional conformal radiotherapy (3D-CRT) is more preferable and less toxic to treat the patients of locally advanced squamous cell carcinoma of the uterine cervix than that of concurrent 2D-RT.

METHODS AND MATERIALS

This was a quasi-experimental study conducted in the department of clinical oncology Bangabandhu Sheikh Mujib Medical University (BSMMU), Radiation Oncology department of National Institute of Cancer Research and Hospital (NICRH) and Ahsania Mission Cancer and General

Hospital (AMCGH) from January 2018 to June 2019. The inclusion criteria was biopsy proven locally advanced squamous cell carcinoma of cervix, The International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IVA with Eastern Cooperative Oncology Group (ECOG) performance score 0-2. Selected 60 patients were divided into two Arms (A&B) .For Both Arms **r**adiotherapy was delivered in the form of EBRT followed by three insertions of ICRT to patient of both arms (Arm-A & Arm-B) with weekly cisplatin 40mg/m^2 given 2 hour prior radiotherapy throughout the course of EBRT**.** Adequate hydration policy was maintained for Cisplatin. Patients of this arm A was treated by three dimensional concurrent chemoradiotherapy (3D-CRT) technique. For Arm B patients was treated by two dimensional conventional concurrent chemoradiotherapy (2D-RT) technique.

After completion of treatment patients were carefully evaluated with clinical examination and relevant investigations at week 6th following treatment. They were advised to attend for second follow up at 12th weeks after first follow up. At each follow up clinical examination, ultrasonogram of whole abdomen and associated laboratory investigations were done and effects of RT (treatment response), relief of symptom, and toxicities due to radiotherapy were assessed.The final response was documented at twenty fourth week (six month) after completion of treatment by clinical examination, ultrasonogram of whole abdomen and computed tomography (CT) scan/ MRI of the abdomen (when needed). Designation of complete response, partial response, stable disease, or progressive disease was based on standard WHO criteria. Toxicities were assessed as per The European Organization for Research and Treatment of Cancer (EORTC) 1995**.** All the relevant data were compiled on a master chart for the patients of both Arm-A and B and then statistical analysis was done according to the objective of the study. Differences between two means were assessed by T-test. All the outcomes were compared by chi square test. Fisher's exact test was done when more than 20% of cells in cross table had expected frequency <5.A p-value of <0.05 in two tailed test was considered as statistically significant.

RESULTS

From April 2018 to December 2018, a total number of 60 patients with locally advanced squamous cell carcinoma of uterine cervix (FIGO stage IIB to IVA) were included in this study. The mean age of patients in Arm A was 51.4±8.2 years and for the Arm B it was 48.7±7.5 years. These differences were not statistically significant as p-value was 0.195. Overall mean age was 50±7.9. Age range was 39-70 years and 35-69 years for the Arm A and B respectively

Table 1: Age of patients in the Arm A and B

Character	**Arm A (n = 30) (years)**	**Arm B (n = 30) (years)**	**Overall (N = 60) (years)**
Mean	51.4	48.7	50
SD	±8.2	±7.5	±7.9
Range	39-70	35-69	35-70
p-value*	0.195		

SD = Standard deviation. *For both means

Patients with age more than or equal to 60 years was 23.4% in Arm A and 10.0% in Arm B. Most of the patients of both the arms were in 40-49 years. (Figure 1)

Distribution of patients according to their age range

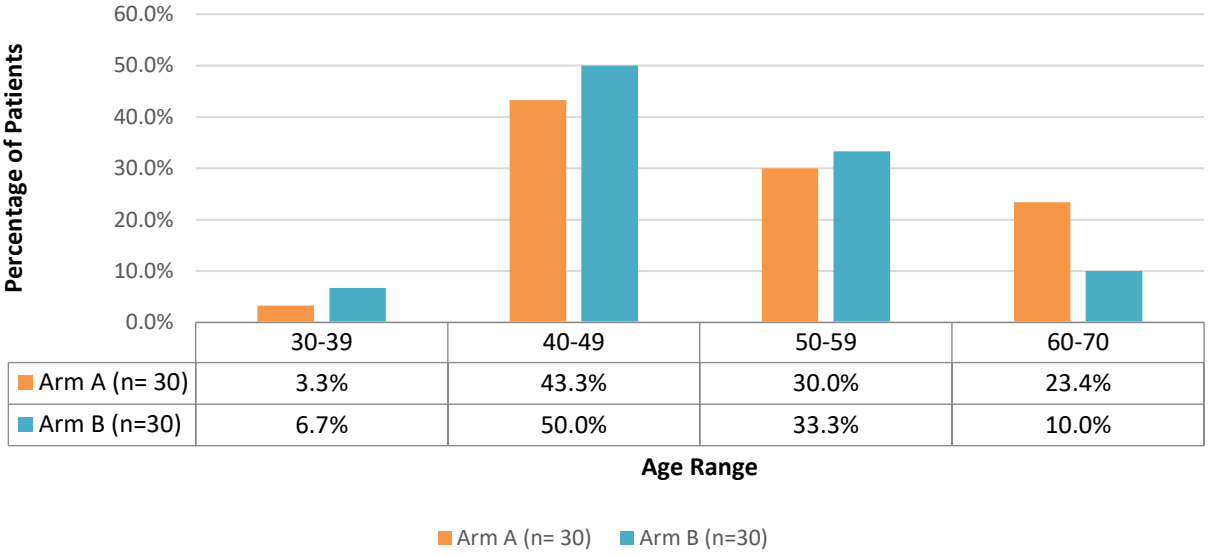

Figure 1: Graphical representation of patients according to age groups in both the arms.

In respect of post-coital, inter/ post-menopausal bleeding and excessive pervaginal whitish discharge were seen to develop in the arm A versus Arm-B as following 73.3% versus 70%, 80% versus 40%, 90% versus 96.7% respectively.

Table 2: Distribution of the patients according to clinical presentation:

Clinical presentation	**Group**				**P value**
	Arm-A (N = 30)		**Arm-B (N = 30)**		
	n	**%**	**n**	**%**	
Post Coital Bleeding	22	73.3	21	70.0	0.373
Intermenstrual Bleeding/Post menopausal bleeding	24	80.0	12	40.0	
Excessive per vaginal Discharge	27	90.0	29	96.7	
Pelvic Pain	16	53.3	23	76.7	
Urinary symptom	13	43.3	18	60.0	
Rectal Symptom	4	13.3	5	16.7	
Weight loss	14	46.7	17	56.7	

At the time of diagnosis, the stage of the disease is shown in the below graph. Most of the patients were in stage IIB in both the arms and it was 19 (63.3%) and 15 (50.0%) for the Arm-A and B respectively. There were 8 (26.7%) patients in Arm-A and 9 (30.0%) patients in Arm-B were in were in stage IIIB. Only 1(3.3%) patient found in stage IVA who was enrolled in Arm-A and 3 (10%) patients were found in Arm B.

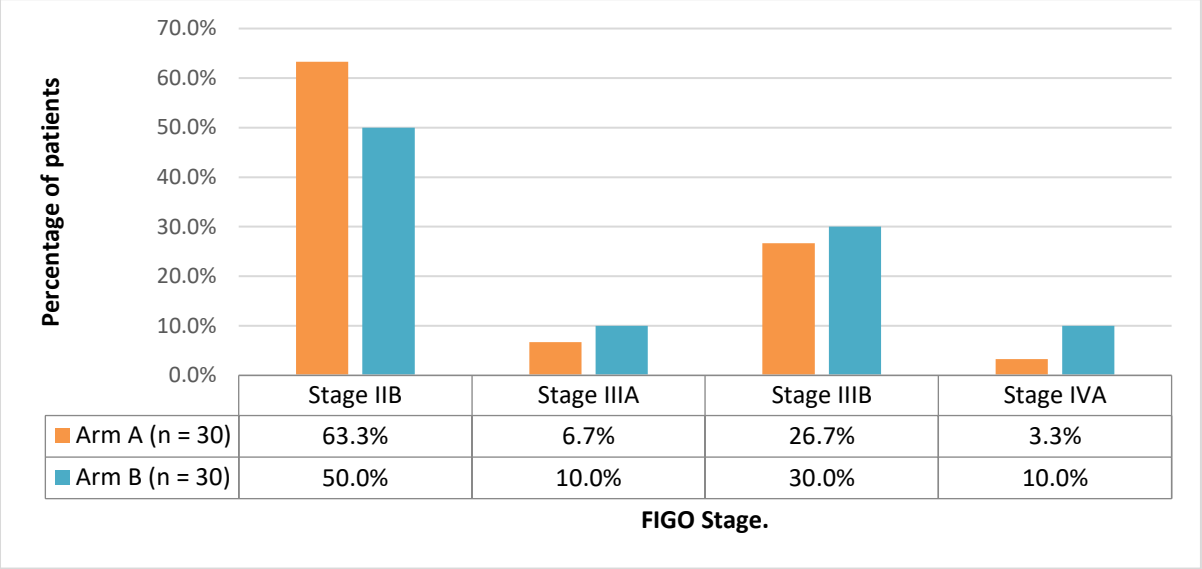

Figure 2: Graphical presentation of disease stage for the both arms

Patients distribution according to histological differentiation of tumour observed is shown in figure 3. Most of the patients of both the Arms had moderately differentiated tumour (56.7% and 66.7% in Arm A and B respectively).

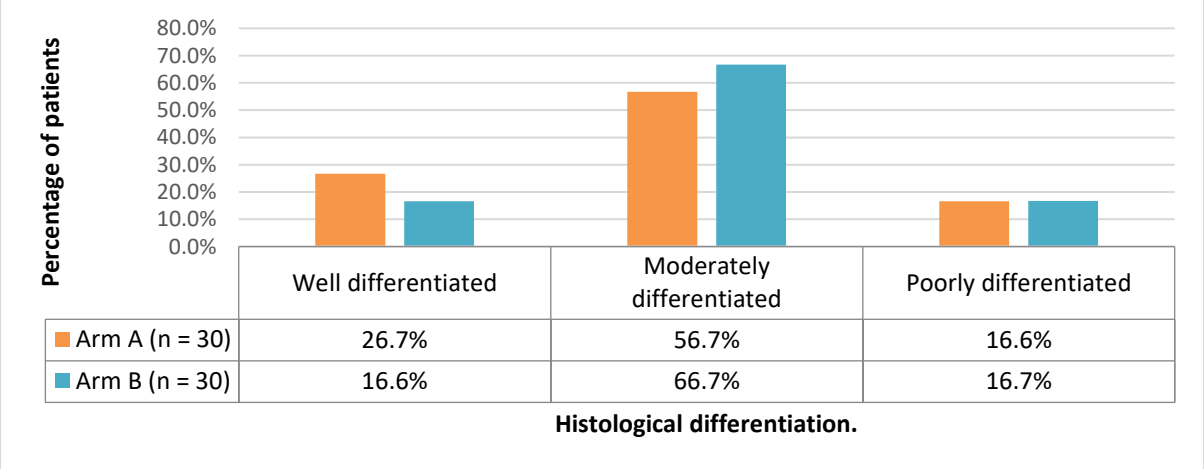

Figure 3: Graphical presentation of histological differentiation observed in the study

Table 3 shows that there were 19 (63.3%) patients of Arm-A and 15 (50%) of Arm-B with stage IIB disease. 10 (33.3%) patients from arm A & 11 (36.6%) patients of arm B were of stage III and 1 patient of arm A and 3 patients in Arm-B was stage lVA. Among them from stage IIB disease complete response observed in 19 (50%) of Arm-A and 15 (30%) of Arm-B. It was shown that patients had earlier presentation of the disease had more complete response than late presentation of the disease with treatment. There was no statistically significant difference in complete and partial response between two arms on the basis of staging (p>0.05). There was 1 patient in Arm A and 3 patient in Arm-B had progressive disease. Chi-square test was used to determine the p value.

Table 3: Evaluation of response during 3rd follows up at 24th weeks according to FIGO stage.

Response	Arm A			Arm B			chisquare	p value
CR	Stage IIB n=19	19		Stage IIB n=15	15		3.00	0.03
PR		0			0			
SD		0			0			
PD		0			0			
CR	Stage IIIA n=2	2		Stage IIIA n=3	3		4.00	0.046
PR		0			0			
SD		0			0			
PD		0			0			
CR	Stage IIIB n=8	8		Stage IIIB n=9	8		7.00	0.135
PR		0			0			
SD		0			0			
PD		0			1			
CR	Stage IVA n=1	0		Stage IVA n=3	0		4.00	0.004
PR		0			0			
SD		0			0			
PD		1			3			

CR= Complete Response, PR= Partial Response, SD=Stable disease, PD=Progressive Disease

Table 3 showing treatment response of the patients according to the FIGO stage at 24 week after completion of treatment.

Table 4 Treatment response observed during 3rd follow-up at 24 week

Response	Arm A (n = 30)		Arm B (n = 30)		X2	P value
	n	%	n	%		
CR	29	96.7	26	86.7	1.964	0.16112
PR	0	0.0	0	0.0		
SD	0	0.0	0	0.0		
PD	1	3.3	4	13.3		

Table 4 shows that there were 29 (96.7%) patients in Arm-A & 26(86.7%) patient in Arm-B had complete response. 1(3.3%) in Arm-A and 4 (13.3%) in Arm-B had progressive disease. This observation didn't show any statistical significant difference. Chi-square test was used to determine the p value (0.161).

The most observed toxicity in both the Arm A and B were gastrointestinal, dermatological. Regarding acute haematological toxicity, none of the toxicity had significant difference between the study arms. Acute nephrological toxicities were also observed in both the Arms but none were statistically significant (Table 5, 6, 7)

Table 5: Acute skin, mucosal and nephrological toxicities observed during radiotherapy

Toxicity	Arm A (n = 30)		Arm B (n = 30)		X2	P value
	n	%	n	%		
Skin						
No toxicity	7	23.3	3	10.0	11.967	0.0075
Grade 1	17	56.7	8	26.7		
Grade 2	5	16.7	13	43.3		
Grade 3	1	3.3	6	20.0		
Grade 4	0	0.0	0	0.0		
Vaginal mucositis						
Grade 1	25	83.3	22	73.3	0.508	0.475
Grade 2	5	16.6	7	23.3		
Grade 3	0	0.0	1	3.3		
Cystitis						
No toxicity	14	46.7	7	23.3	3.867	0.14467
Grade 1	13	43.3	17	56.7		
Grade 2	3	10.0	6	20.0		
Grade 3	0	0.0	0	0.0		
Grade 4	0	0.0	0	0.0		

Renal						
No toxicity	29	96.7	27	90.0	1.071	0.3006
Grade 1	1	3.3	3	10.0		
Grade 2	0	0.0	0	0.0		
Grade 3	0	0.0	0	0.0		
Grade 4	0	0.0	0	0.0		

Table 6: Acute gastrointestinal toxicities observed during and immediately after radiotherapy

Toxicity	Arm A (n = 30)		Arm B (n = 30)		X2	P value
	n	%	n	%		
Nausea						
Grade 1	24	80.0	3	10.0	33.3	0.0001
Grade 2	6	20.0	21	70.0		
Grade 3	0	0.0	6	20.0		
Grade 4	0	0.0	0	0.0		
Vomiting					0.465	0.4603
No Toxicity	10	33.3	0	0.0		
Grade 1	17	56.7	7	23.3		
Grade 2	3	10.0	17	56.7		
Grade 3	0	0.0	6	20.0		
Grade 4	0	0.0	0	0.0		
Diarrhoea						
No toxicity	16	43.3	6	20.0	0.158	0.004
Grade 1	11	36.7	10	33.3		
Grade 2	3	10.0	10	33.3		
Grade 3	0	0.0	4	13.3		
Grade 4	0	0.0	0	0.0		
Proctitis						
No toxicity	13	43.3	7	23.3	4.726	0.09415
Grade 1	12	40.0	11	36.7		
Grade 2	5	16.7	12	40.0		
Grade 3	0	0.0	0	0.0		
Grade 4	0	0.0	0	0.0		

Table 7 : Acute haematological toxicities observed during radiotherapy

Toxicity	Arm A (n = 30)		Arm B (n = 30)		X2	P value
	n	%	n	%		
Anaemia						
No toxicity	9	30.0	5	16.7	7.446	0.06
Grade 1	14	46.7	8	26.7		
Grade 2	6	20.0	12	40.0		
Grade 3	1	3.3	5	16.6		
Neutropenia					1.687	0.4302
No toxicity	14	46.7	19	63.3		
Grade 1	10	33.3	7	23.3		
Grade 2	6	20.0	4	13.3		
Grade 3	0	0.0	0	0.0		
Thrombocytopenia					0.162	0.6875
No toxicity	27	90.0	26	86.7		
Grade 1	3	10.0	4	13.3		
Grade 2	0	0.0	0	0.0		
Grade 3	0	0.0	0	0.0		

DISCUSSION

Diagnosed patients of locally advanced uterine cervical carcinoma (stage IIB to IVA) of squamous cell variety were enrolled in this study. The mean age of patient at diagnosis in this study was 51.4+8.2 years in arm A and 48.7+7.5 in arm B. The overall mean age was 50+7.9 years. Age range was 39-70 years in Arm-A and 35-69 years in Arm-B. Most of the patients had stage IIB disease in both arms, 19 (63.3%) and 15 (50%) patients in Arm A and B, respectively 8 (26.7%) patients in Arm-A and 9 (30.0%) patients in Arm-B were in Stage IIIB and there was only 1 patient from stage IVA in Arm-A and 3(10%) patients in Arm -B. This results correlates with the study Hasan et al 2018 [8]. Majority patients of both arms were presented with post coital bleeding (Arm-A 73.3% and Arm-B 70%), intermenstrual bleeding (Arm-A 80.0%, Arm-B 40%) and excessive per vaginal whitish, watery discharge (Arm-A 90% and Arm-B 96.7%) which coincides with the study Afroj et al [9]. On Pelvic examination of patients revealed bleeding, vaginal discharge and growth in both the arms. Following treatment, control of per vaginal bleeding (post coital bleeding, intermenstrual bleeding) was observed in all patients, but some of the patients had persistent per vaginal watery discharge though the amount of discharge was reduced. Some of the patients had pelvic pain, dysuria, anemia and loss of appetite even after completion of treatment.At final follow up after 6 months of treatment, clinical examination was done to see the presence of any residual disease. It was observed that 96.7% of patients showed complete response in arm A and it was 86.7% in arm B. Statistical analysis revealed, there was no significant difference but arithmetically

this is proven that the patient of Arm-A patients had better response than the Arm-B. The most prevalent acute toxicities in both the arms were haematological, nephrological, and gastrointestinal origin. Skin reaction, vaginal mucositis and small gut toxicities were also observed. Grade 2 and 3 radiation dermatitis in radiation field was seen in 5(16.7%) and 1 (3.3%) patients of Arm-A while 13 (43.3%) and 6 (20%) in Arm-B respectively. More patients developed Grade 2 and 3 acute skin toxicities in conventional radiotherapy arm compared to 3D-CRT (p-value 0.0075). The dermatological toxicity was found to be statistically significant (p value <0.05).Grade 2-3 nausea was higher in Arm-B then Arm-A. 90% of the patient in Arm-B experienced significant nausea in comparison to the patient in Arm-A (20%) and the p value is 0.001 which is statistically significant. Grade 2-3 vomiting was higher in Arm B (76.6%) than Arm A (10%). Grade 2-3 Diarrhoea was observed higher in Arm B (46.6%) than Arm A (10%). The gastrointestinal toxicity was found to be statistically significant (p value 0.004) this findings co relates with the study Mutrikah, N. et al 2017 [12]. .As grade 2 & 3 gastrointestinal and dermatological toxicities were high in two dimensional conventional chemoradiotherapy group for which a little treatment delay was present in this arm.Regarding acute haematological toxicity, anaemia was most observed toxicity in both the Arms. 14 (46.7%) and 8 (26.7%) patients of Arm A and B respectively had grade 1 anaemia. Neutropenia and Thrombocytopenia was also observed. None of the toxicity had significant difference between the study arms. Cystitis, nephrological toxicity, vaginal mucositis, proctitis and were also observed in both the Arms but none were statistically significant .From above discussions it can be said that, concurrent three dimensional conformal radiotherapy technique is associated with significant reduction in gastrointestinal (nausea, vomiting, diarrhoea) and dermatological complication compared to conventional radiotherapy technique with no significant reduction in other toxicities and tumour response. But toxicities with two dimensional (conventional) chemoradiotherapy were higher than 3D-CRT and the toxicities were well managed. Tumour response was more arithmetically though it was not statistically significant. So, at low resource and high patient burden centres, two dimensional radiotherapy technique still can be considered as effective method. In contrast, where adequate resources and facilities are available, then 3D-CRT technique may be considered.

CONCLUSION

Tumour response was not statistically significant between the patients of concurrent 3D-CRT and 2D-RT Arms. But the patients of 3D-CRT arm showed better response arithmetically. Also, there was an observable significant reduction of toxicities (gastrointestinal & dermatological) in the 3D-CRT arm.

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