

Regarding Clinical Response, Neoadjuvant Chemoradiation is More Effective than Neoadjuvant Radiation alone in the Treatment of Advanced Stage (Stage II and III) of Rectal Carcinoma

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Abstract: Colorectal cancer is one of the leading cause of cancer death in male women in the world. Though surgery is the mainstay of treatment but there is a potential and important role of adjuvant therapies in the management of advanced rectal cancer. Neoadjuvant chemoradiation has been shown significantly decrease the local tumour size as well as local recurrence and become an standard option in the management of advanced stage of rectal cancer. An observational prospective hospital based study was done to compare the clinical response and acute adverse effects of neoadjuvant chemoradiation with that of standard treatment. A total of 90 eligible patients with histopathologically proven adenocarcinoma and radiologically staged stage II and stage III rectal cancer, were enrolled in this study. 45 patients in arm A was treated with 45 Gy in 25 fractions combined with inj. 5-FU 225mg/m² daily during RT. And on the other hand 45 patients in arm B received 45 Gy in 25 fractions only. Comparing the clinical response by symptom relief and decrease of tumour size between these two arms. Out of 90 enrolled patients, 61.67% were male and 38.33% were female. Mean age was 43.65±10.24 years. Majority of the patients (60%) were in stage III rectal carcinoma. Regarding improvement of clinical symptoms Arm A showed more response than Arm B. Observed treatment related toxicities were acceptable in both Arm. **Conclusion:** The neoadjuvant chemoradiation with 45 Gy in 25 fractions combined with inj. 5-FU 225mg/m² showed improved clinical response and more local control compared with neoadjuvant radiation alone (45 Gy in 25 fraction)

Keywords: Advanced stage (Stage II and III) rectal carcinoma, Gy-Radiation Unit 5FU- Fluorouracil (Anti Cancer Drug)

1. Introduction

Colorectal carcinoma is one of the most common cancers worldwide. The incidence of colorectal carcinoma is high. One third of colorectal tumours arise in the rectum, more commonly in men^{1,19}. Rectal cancer is defined as cancer arising below the peritoneal reflection, up to approximately 12 to 15 cm from the anal verge².

Worldwide colorectal cancer is most commonly diagnosed cancer in males (new cases 663600) and ranked second in female (new cases 529800) cancer patients, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008³. According to the GLOBOCAN 2008, in the developing countries the numbers of new cases of colorectal carcinoma in male are 274000, which is ranked 4th most common and in female are 232400, which is ranked 5th most common cancer. Colorectal cancer is the second most common cancer in UK in term of incidence and mortality¹. American cancer society found that 142570 people were diagnosed with colorectal cancer and 51379 died of disease in 2010. About 72% of those colorectal carcinomas arise in the colon, and the remaining 28% arise in the rectum².

The management of rectal cancer in advanced stage (stage II and stage III) requires a multidisciplinary approach^{16,18}. Although surgery is the mainstay of treatment but there is potential and important role of adjuvant therapies. Neoadjuvant radiotherapy has been shown to significantly decrease the local recurrence rate. The theoretical superiority of preoperative versus postoperative combined modality therapy has been confirmed by the German rectal cancer trial⁴. The European Organization of Research and Treatment has shown a significant reduction in the local recurrence rate with preoperative radiotherapy in stage II and stage III rectal cancer⁵. To improve tumor response, preoperative Radiotherapy (RT) has been combined with systemic chemotherapy. There is a strong radiobiological rationale to combine RT with chemotherapy. Combined chemoradiation (CRT) for rectal cancer was introduced in the adjuvant setting and subsequently in unresectable disease, where significant downsizing and down staging was observed in many patients⁵. There have been several randomize between preoperative/ neoadjuvant CRT versus preoperative RT. According to several trials like Boullis-Wassif study⁶, EORTC 22921 Trial⁷, FFCO 9203 Trial (Fc'dc'ration dc Francophone dc Cance'rologie Digestive)⁸ and The Polish Trial⁹. Showed potential of both modalities of treatment and also show the superiority of neoadjuvant

chemoradiation in the field of local control. Though the toxicities is more during chemradiation than radiation alone. But different study and analysis has showed that the toxicities are in acceptable limit¹⁰.

This study showed that more improvement of loco-regional control and clinical symptoms in rectal cancer patients of Bangladesh who were treated with chemoradiation rather than radiation alone in neoadjuvant setting.

2. Material and Methods

An observational prospective hospital based study was done in the period of Jan 2015 to Dec 2015 in Bangabandhu Sheikh Mujib Medical University and National Institute of Cancer Research and Hospital to compare the clinical response and toxicities of neoadjuvant chemoradiation versus radiation alone in the treatment of advanced stage of rectal carcinoma. Two-arms were formed, Arm-A and Arm-B. 45 patients were enrolled in each arm. All patients in both arms received external beam radiation with 45 Gy in 25 daily fractions over five weeks. Patients in Arm-A also received inj. 5-FU 225mg/m² daily during RT. Patients were selected on the basis of histopathologically proven rectal carcinoma. On the basis of colonoscopy report and contrast enhanced CT scan of whole abdomen with special attention to locoregional lymphadenopathy and locoregional organs involvement, staging of disease done. Only the advanced stage (stage II and stage III) of the diseased patients were included in the study, who were in the performance status of less than III.

3. Results

Table 1: Distribution of patients by risk factors and age group

	ARM-A		ARM-B		Total	
	No. of Pt.	(%)	No. of Pt.	(%)	No. of Pt.	(%)
Risk Factors						
Smoking habit	25	55.55	24	53.33	49	54.44
Family history	3	6.67	2	4.44	5	5.55
Age Group (years)						
21-30	4	8.88	3	6.67	7	7.77
31-40	10	22.22	11	24.44	21	23.33
41-50	20	44.44	21	46.66	41	45.55
51-60	10	22.22	9	20	19	21.11
61-70	1	2.22	1	2.22	2	2.22

Table 2: Comparison of clinical response according to clinical symptoms in both arms

Clinical symptoms	Treatment group	Pre-treatment		Post treatment		Response %
		N	%	n	%	
Per rectal bleeding	Arm A	39	86.67	0	0	100
	Arm B	36	80	3	6.67	91.67
Alteration of bowel habit	Arm A	21	46.67	9	20	57.14
	Arm B	23	51.11	17	37.78	26.08
Tenesmus	Arm A	12	26.67	2	4.44	83.33
	Arm B	10	21.74	6	13.33	40
Mucoid discharge	Arm A	10	21.74	5	11.11	50
	Arm B	12	26.67	8	30	33.33
Anaemia	Arm A	27	60	18	40	33.33
	Arm B	24	53.33	16	35.56	33.33

Table 3: Distribution of patients according to stage, response & Arm

Stage	Treatment group	Number of patient according to stage		Complete response		Partial response	
		No	%	No	%	No	%
II	Arm A	16	35.56	07	43.75	09	56.25
	Arm B	19	42.22	05	26.31	14	73.68
III	Arm A	29	64.44	05	17.24	24	82.75
	Arm B	26	57.78	02	07.69	24	92.30

Table 4: Distribution of patients by treatment response

Treatment group	Complete response no (%)	Partial response no (%)	X2 value	P value
Arm-A	12(26.66)	33(73.33)	4.444	0.042
Arm-B	06(13.33)	39(86.67)		

(Data were analyzed by using Chi-square test)

Arm-A (n=30): Chemo-radiation

Arm-B (n=30): Radiation alone.

4. Discussion

Two-arms were formed, Arm-A and Arm-B. 45 patients were enrolled in each arm. All patients in both arms received external beam radiation with 45 Gy in 25 fractions over five weeks and inj. 5- FU 225mg/m² daily during RT¹¹.

In this study the peak age incidence of rectal cancer in both arms was found in the age group of 41 - 50 years. The mean age of patients with stage II and stage III rectal cancer here in this study was 43.65±10.24 years. Mean age of patients with rectal cancer is 42.3+10.17 years and 45 + 10.47 years respectively in Arm A and Arm B, which is consistent with the findings of Talukder et al. (2009)¹² who showed that peak incidence occurs at the age of 35 - 44 years.

In this study the number of male and female patients was 57(63.33%) and 33 (36.66%) respectively with the ratio of 1.72:1 indicating male predominance which is relevant to the study¹² who showed male and female ratio 1.7:1. Regarding sex distribution, number of male patients was found greater than female patients in both arm respectively 60% in the Arm A and 63.33% in the Arm B.

About the socio economic condition this study showed that 54 (60%) were in lower class, 20 (22.22%) were in middle class and 16 (17.77%) were in upper class. In this study it had been observed that majority of patients were below SSC level 35 (58%), which might have been a cause of low awareness about the malignancy and its effect.

In this study it was found that total 49 (54.44%) were smoker and this data associate that there is a relation between smoking and rectal cancer, which also support the studies¹³. But the association between family history and rectal cancer cannot be established probably due to lack of cancer awareness and illiteracy.

In this study most patients presented with the complaints had per rectal bleeding (83.33%). In Arm A among 45 patients, 39 (86.67%) had per rectal bleeding, 21 (46.67%) had alteration of bowel habit, 12(26.67%) had tenesmus, 11 (24.44%) had mucoid discharge. 21 (46.67%) had weight

loss and 27 (60%) had anaemia. In Arm B among 45 patients, 36 (80%) had per rectal bleeding, 22 (48.88%) had alteration of bowel habit, 11 (24.44%) had tenesmus, 12 (26.67%) had mucoid discharge, 25 (55.55%) had weight loss and 24 (53.33%) had anaemia. These findings in clinical features had concordance with the findings by Bomford & Kunkler and Suryanarayana^{14, 15}.

Clinical response was observed in both Arm A and Arm B after the treatment and compared with initial clinical presentations. Regarding per rectal bleeding response was almost same (100% vs 91.67%) in both arms. But regarding other symptoms or clinical presentation, response is more dominant in Arm A. Such as in alteration of bowel habit response was 57.14% in Arm A and 26.67% in Arm B, in tenesmus response was 87.5% in Arm A and 42.85% in Arm B and in mucoid discharge 57.1% in Arm A and 37.5% in Arm B. So, it was observed that clinical symptoms improved in both arms of treatment modalities but more in chemoradiation arm which is similar to the study of Chao et al.¹⁶

All the patients in this study were with KPS >70, among them about 68.33% patient were found of KPS 80. In Arm A, before starting the treatment, 05 patients were, found with KPS 90 where in Arm B 06 patients were found with the same performance status. After completion of the RT improvement was noticed in the performance status with 30 patients in Arm A and 16 patients in Arm B with KPS 90. It was observed that performance status was more improved in the chemoradiation arm and thereby, improved quality of life.

In this study showed that in Arm A complete response was observed in 12 (26.67%) and partial response in 33 (73.33%) patients. On the other hand in Arm B complete response was observed in 6 (13.33%) and partial response in 39 (86.67%) patients. While complete response was analyzed by using Chi-square test P value was found 0.042, which is statistically significant. The complete response was calculated and compared according to the stage of disease at diagnosis it was found that stage II disease responded more in both modalities of treatment. It showed that in Arm A 16 (35.55%) patients were in stage II disease, among them complete response was observed in 07 (43.75%) and in Arm B 19 (42.22%) patients were in stage II disease, among them complete response was observed in 05 (26.31%). Overall complete response in stage II disease is 35.03%, whereas complete response in stage III disease is 12.26%.

In this study loco regional control i.e. overall response of patients treated with chemoradiation was 26.67% in comparison to radiation alone in which loco regional control was 13.33%. Suryanarayana et al (2004)¹⁵ in a comparative study have shown loco regional control was 32% of patient chemo-radiation and 17% in radiotherapy alone. The study results were very near to each other. National treatment guidelines, such as NCCN guideline also suggested neoadjuvant chemoradiation in stage II and stage III rectal cancer.

Regarding toxicities no reaction was noted in most patients. Most common toxic effect was diarrhoea, which was more

in Arm A than in Arm B. And one case of grade IV diarrhea was reported in the patient of Arm A¹⁶. Nausea and vomiting were more common in Arm A than Arm B. Other toxicities were also observed more in Arm A than Arm B, but there was no significant difference⁷. Haematological side effects were also noticed but were in acceptable range and no significant difference in both arms.

After careful consideration of the above facts, it is evident that the patients who had neoadjuvant chemoradiation with 5-FU had better treatment response in comparison to patients who received radiation alone.

5. Conclusion

This prospective observational study was done to find out the efficacy of treatment and efficacy was assessed according to RECIST criteria as complete response, partial response, stable disease and progressive disease and loco-regional control was assessed pre-treatment and post treatment tumour size. Other clinical improvements were also assessed and compared between two treatment arms. Toxicities that occurred in both treatment arms also recorded and compared. It can be concluded that neoadjuvant chemoradiation showed high loco-regional control and more clinical response than neoadjuvant radiation alone in the treatment of advanced stage (stage II and stage III) rectal cancer.

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