

## Original Article

# Outcome of Adjuvant Chemo-Radiation in Operated Locally Advanced Rectal Cancer in a Tertiary Hospital in Bangladesh

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### Abstract:

Rectal cancer is the one the common cancer in Faridpur, Bangladesh. The clinical course of patient treated with surgery alone has been characterized by a high death rate and also by the pain and disability associate with pelvic recurrence of the tumor. Adjuvant chemotherapy combined with radiation has been studied for prevention of such reoccurrence. Most of the patients at our center are those who have already been in subjected to surgery in this hospital or other private hospital in this district or other district hospital. We studied role of Oxaliplatin and Capcitabine with Radiotherapy in AJCC stage IIB to IIIC locally advanced rectal cancer and toxicities in adjuvant settings. This study was done to assess the outcome of adjuvant chemoradiation in operated locally advanced treated cancer patients. A total of 30 patients were included in between June 2016 to June 2019 in non-randomized clinical trial. About 66.6% of the patient underwent low anterior resection and 33.3% had abdominoperineal resection. Patients were treated postoperatively with Oxaliplatin and capcitabine. Radiotherapy of 45 Gy in 20 fractions were delivered in concurrently with Capcitabine 825 mg/m<sup>2</sup> from day 1 to day 5 of Radiotherapy at National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, median follow-up was 3 years. At 3 years overall survival of operated patient was 66.3% with no disease relapse. Toxicities of this schedule were mostly Anemia and Gastrointestinal mucocitis but without treatment interruption. Combination of adjuvant chemotherapy and radiotherapy is effective modality in reducing local tumour recurrence and improves survival.

**Key words:** Adjuvant chemoradiation, Locally advanced rectal cancer, Improved outcome.

### Introduction:

Rectal cancer is one of the most common cancers in Bangladesh<sup>1</sup>. Its accounts for 8<sup>th</sup> leading male and 9<sup>th</sup> female cancer among patient attending in National Institute of Cancer Research and Hospital, Mohakhali, Dhaka from 2011 to 2013<sup>1</sup>. The incidence of rectal cancer is increasing in Bangladesh day by day due to food habit (high intake of red meat, high fat and low fiber intake), sedentary life style, smoking, family history, rectal polyp etc<sup>2,3</sup>. In United States Colorectal

cancer is the 4<sup>th</sup> most common cause of cancer and 2<sup>nd</sup> leading cause of cancer related deaths<sup>2</sup>. The rectal cancer is mainly treated by radical surgical resection but due to increase in local failure rates in the pelvis ranging between 20-70% it has led clinicians to increase the use of chemo-radiation either preoperative or postoperatively to improve local control and overall survival<sup>3</sup>. Rectal cancers have high local recurrence rate ranging from 2.6 to 47 %, even after curative resection<sup>4</sup>.

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Tumor recurrence has been seen to correlate with stage, the number of metastatic lymph nodes, meso-rectal tumor spread, histology, lympho-vascular invasion and distance of the distal resection margins of resection<sup>4</sup>.

Rectal cancers resected with close margins are especially prone to recur locally due to close proximity of rectum to pelvic structures and absence of serosa surrounding the rectum. Approximately 8% of stage I, 25% of stage II and nearly 50% of stage III rectal cancer develop pelvic recurrence after surgical resection<sup>5</sup>. The incidence of local recurrence of tumours with negative nodes and microscopic extension through wall is 17% and increases to 54% when adhere to adjacent structure and organs<sup>6</sup>. Greatest risks of recurrence are the presacral space, pelvic side walls and soft tissue anterior to rectum. Adjuvant radiation has significantly decreases loco-regional recurrences but local failure is still a challenge to oncologists. Adjuvant chemotherapy is universally recommended for stage II and stage III rectal cancer. Chemotherapy combined with radiation as radio sensitizer has been studied in many centers. Minimizing the risk of local recurrence is especially important in rectal cancer due to morbidity that can result from a local recurrence, such as pain, bleeding and obstruction. Even with expert TME (Total Mesorectal Excision) the rate of distant metastasis was 18% in stage II patients and 37% in stage III patients<sup>7</sup>. Adjuvant chemotherapy and radiation therapy have demonstrated improvement in disease free survival (DFS) and overall survival (OS) of patient which has been discussed here. It is also being increasingly used to facilitate as sphincter preserving procedure in low-lying cancers. A critical review of literature shows that chemo-radiation is better than radiation alone. There is great need for more conclusive study designs and a more rational explanation of drug-radiation interaction prior to clinical testing<sup>8</sup>. At our center we are treating patients with locally advanced rectal cancer with chemotherapy and radiotherapy in a sequential way. In this study advantage of adjuvant chemotherapy and radiotherapy being studied in locally advanced carcinoma of rectum in a tertiary level district hospital in Bangladesh.

### Materials and Methods:

This non-randomized clinical trial was carried out from June 2016 to June 2019 at Bangabandhu Sheikh Mujib Medical College Hospital (BSMMCH). A total of 30 patients with American Joint Committee on Cancer (AJCC) stage IIB and IIIC of operated histologically proved adenocarcinoma patients were included in this study. All the patients studied in this trial had computed tomography (CT) scan Chest and abdomen to rule out any liver or lung metastasis. Patients with distant metastasis, synchronous growth, second malignancy, age 60 > years and psychiatric illness were excluded from the study. Chemotherapy was started after 3 weeks of surgery with a valid consent. Chemotherapy was total

of six cycles with three weeks interval with Oxaliplatin 130 mg/m<sup>2</sup> and Capecitabine 1000 mg/m<sup>2</sup> per orally b.i.d from Days1-14. Radiotherapy was delivered by LINAC/Cobalt-60 machine in parallel opposed field in midline dose of 45 grays in 4 weeks. Radiotherapy was delivered at National Institute of Cancer Research and Hospital, Mohakhali concurrently with Capecitabine 825mg/m<sup>2</sup> from day1 to day 5 of radiotherapy as radio sensitizer. Superior border of the field was at the junction of L5-S1 and inferior border 3 cm below the lower limit of the primary tumour or at the lower border of the obturator foramen. Lateral border 1.5 cm lateral to widest bony margin of the two pelvic bones. During entire period of chemo-radiation patients were assessed for treatment toxicities. All treatment related toxicities were defined as per Radiotherapy and Oncology Group (RTOG) toxicity criteria. The patients were reviewed monthly after completion of treatment for one year and three monthly thereafter. They were followed with clinical examination including digital rectal examination, sigmoidoscopy and colonoscopic examination, serial CEA levels, CT scan of the Chest/CT scan (few cases with X-ray chest and Ultrasonography of the Abdomen) of the Abdomen. The collected data of this study were edited, coded and processed for computer entry. The clean and edited data were analyzed using Statistical Package for Social Sciences (SPSS), software, version-23.0 and presented as tables and figures.

### Results:

Among total 30 patients, majority (50%) were aged less than or equal to 50 years with a male predominance (80%). About 13 of them (43.33 %) were lower middle class, and 8 of them were middle class (26.67 %) and rest 9 (30%) were poor patient (Table I).

**Table I:** Distribution of patients according to socio-demographic characteristics (n=30).

Demographic character	Number (%)	
Age (Year)	30-40	7 (23)
	41-50	15 (50)
	>50	8 (27)
	<b>Total</b>	<b>30 (100)</b>
Socio-economic Status	Poor	9 (30)
	Lower middle class	13 (43.33)
	Middle class	8 (26.67)
	<b>Total</b>	<b>30 (100)</b>
Gender	Male	24 (80)
	Female	6 (20)
	<b>Total</b>	<b>30 (100)</b>

Most common presenting symptoms were per rectal bleeding 53.33% and constipation (40%). Twenty two (73.33%) patients had growth located more than 5 cm from the anal verge. Staging was done as per AJCC. Twenty seven (90%) patients were node positive disease (stage III), three (10%) had stage II disease. Since every patient were operated histopathology and staging was available along with histopathological differentiation. Most patient had well differentiated 20 (67%), 7(23%) was moderately differentiated, 3(10%) were poorly differentiated carcinoma. (Table II).

**Table II:** Distribution of patients according to histopathological types & staging (n=30).

Types of Stage		Number of Patients (%)
Stage(AJCC)	IIB	3 (10)
	IIIA	9 (30)
	IIIB	15 (50)
	IIIC	3 (10)
		<b>30 (100)</b>
Histopathological Types		
HPE	Well Differentiated	20 (67)
	Moderately Differentiated	7 (23)
	Poorly Differentiated	3 (10)
<b>Total</b>		<b>30 (100)</b>

Low anterior resection was performed in twenty (66.6) and abdominoperineal resection was done in 10 (33.3%) of the patient. On digital rectal examination 15 (50%) had polypoid lesion, 9 (30%) had stenotic and 6 (20%) had ulcerative lesion (Table III).

**Table III:** Types of lesion on DRE and surgical intervention (n=30)

	Type of lesion & Type of Surgery	Number of patients (%)
Types of lesion on DRE	Stenotic	9(30%)
	Polypoid	15(50%)
	Ulcerative	6(20%)
Surgical Intervention	Low Anterior Resection	20(67%)
	Abdominoperineal Resection	10(33%)

Majority of the patients well tolerated treatment. Only in 4 patient treatments was interrupted because of toxicity (3 lower GI; 1 cardiac). 5 Patients required dose

modification. Lower gastrointestinal toxicity was mainly in the form of diarrhea and tenesmus and was managed conservatively by antidiarrheals, antispasmodics and steroids.6 patients had remote complication of radiation induced proctocolitis and managed accordingly. During whole period of chemo-radiation 12(40%) patients had asymptomatic bradycardia and 1 patient had chest pain. Cardiac monitoring was done by troponin T test and Echocardiography was done to rule out any myocardial ischemia or cardiac dysfunction. In all patient bradycardia was reversible after chemotherapy was stopped and treatment schedule was completed without any interruption. Nine patients had febrile neutropenia during chemotherapy. All patients were admitted in indoor during chemotherapy and were managed accordingly with supportive and other symptomatic care (Table IV).

**Table IV:** Distribution of patients according to toxicity to the treatment schedule (n=30).

Toxicity	Number of patients (%)	
Mucosal toxicity	Mucositis grade 3	4 (13.3%)
	Mucositis grade 4	3 (10%)
Cardiac toxicity	Asymptomatic bradycardia	12 (40%)
	Chest pain	01 (3%)
Haematological toxicity	Febrile neutropenia	09 (30%)
	Anemia	09 (63.3%)
	Thrombocytopenia	02 (6.7%)
Cutaneous toxicity	Skin pigmentation	03 (10%)
	Onycholysis	02 (6.7%)
	None	24 (83.3 %)

During follow-up of 3 years 19(63,3%) patients were disease free, 3 patients (10 %) relapsed locally at anastomotic site or perirectal area and 2 had recurred regional nodal areas. After completion of treatment

**Table V:** Distribution of Patients according to outcome (n=30).

Parameter	Number of patients	Percentage
Relapse Free	19	63.3
	Local	3
	Nodal	2
Relapse	Lung	0
	Liver	1
Died	Disease Related	1
	Disease Unrelated	2
Loss of follow up	2	6.7
<b>Total</b>	<b>30</b>	<b>100</b>

2(6.7 %) patient were out of follow-up. One patient had found recurrence at both nodes and in the liver. During follow up 1 patient had died due to disease related cause and 2 died due to complication of type 2 diabetic mellitus and other co morbid condition (Table V).

## Discussion

Surgery alone, surgery with adjuvant, neoadjuvant treatment and targeted therapies are present day's treatment for rectal cancer. Over last two decades significant advances have been made in the study with molecular basis of the disease coupled with development of new therapeutic approaches. It has dramatically changed the approach of treatment plan<sup>9</sup>. Although surgery is main treatment of rectal cancer, local recurrence is common ever after curative resection<sup>8</sup>. Clinical approach at adjuvant therapy for rectal cancer began more than 40 years ago and numerous trials of several thousand patients treated with cytotoxic drugs, on-specific immunotherapy of various combination<sup>10</sup>. Addition to chemotherapy radiotherapy is intended to decrease local recurrence and distal metastasis. In North Central Cancer Treatment Group (NCCTG) trial<sup>11</sup>, there was a 46 % reduction in pelvic recurrence and 37% reduction in distant spread and 29% reduction of patient death and the study also confirmed the benefit of chemotherapy when combined with radiation. In this study after 3 years follow-up 19 patients (63.3%) were disease free which is comparable to most studies with concurrent adjuvant chemo-radiation. Relapses were recorded in 5 patients. Most recurrence were loco regional 5 (16.6 %) and 1 distant metastasis. In a randomized trial of 144 cases in Norway, patients were randomized to postoperative radiation plus bolus 5-fluorouracil (500 mg/m<sup>2</sup>) in day 1-2 of a week's 1, 2,3 of radiation versus surgery alone. 5- fluorouracil was delivered with a radiosensitizer dose rather than to systemic disease with combined modality regimen significantly decreases local recurrence by 18% (p=0.001) and improved survival by 14%<sup>12</sup>. In our study follow-up was only three years but we used more recent modifying chemotherapeutic agent of standard dose. Additional experience with large sample size and long-term follow up is needed.

In a Gastrointestinal Tumour Study Group (GITSG) trial, 227 patients with stage B2 (AJCC IIB) and C (AJCC IIIA) rectal cancer patient randomly studied to 1. No postoperative treatment, 2. Chemotherapy alone, 3. Radiotherapy or 4. Combined chemotherapy with radiation. After 10 years median follow-up combined modality was found superior to alone in terms of disease free survival (65% versus 45%;p=0.006 and overall

survival (45% versus 26%;p=0.04)<sup>13</sup>. Because of limited facilities of treatment with limited sample size, limited time of follow-up (only 3 years) we had also comparable disease free survival of 63.3%. Patient treated with combined modality had more recurrence free than that radiation alone or chemotherapy alone. Post-operative chemo-radiotherapy was recommended standard therapy for patient with locally advanced rectal cancer in a randomized study conducted by saucer and co-workers to assess response in preoperative and postoperative adjuvant treatment in rectal cancer<sup>14</sup>. Total 402 patients received postoperative chemo-radiotherapy. The 5 years survival was rates were 76%. In our 3 years of follow-up 63.3% were disease free which is comparable to that study. The combination of postoperative therapy with radiation plus a 5-fluorouacil based regime significantly and substantially improves the result in rectal carcinoma patient as compared to that post-operative radiation alone<sup>15</sup>. Fisher et al<sup>16</sup>, conducted a randomized study to assess the benefits of adjuvant chemotherapy and radiotherapy in operated rectal cancer patients. Patients were randomized in three measures; radiotherapy, chemotherapy and no further treatment. Their average time of study was 64.1 months. Chemotherapy groups when compared with group treated with surgery alone demonstrated an overall improvement in disease free survival (p=0.006). When the group receiving post-operative radiation was compared to group treated only by surgery, there was an overall reduction in loco-regional recurrence from 25% to 16%. No significant benefit in overall disease free survival or overall survival from the use of only radiation. The study proved a benefit of adding adjuvant therapy in the treatment of operated rectal cancer. Postoperative radiation therapy although reduce the incidence of loco-regional recurrence but it failed to affect overall disease free survival<sup>16</sup>.

## Conclusion:

Patient with stage II and stage III rectal cancer is beneficial from a multidisciplinary approach. Adjuvant chemotherapy and radiotherapy is beneficial in reducing local recurrence and improving survival in locally advanced rectal cancer. This study was a single center study with a small sample size for a shorten study period. So, the results of this study may not be effective until conducting a multicenter study with a large sample size. Therefore, a multicenter study is recommended to justify the exact scenario of rectal cancer and its treatment outcome in Bangladesh with Adjuvant Chemo-Radiation. However except for anemia, toxicities of adjuvant chemo-radiation were tolerable and adjuvant therapy was absolutely beneficial.

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