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Original Article

Adding Low Dose Chemotherapy to Preoperative Radiotherapy in Locally Advanced Rectal Cancer: Retrospective Analysis of an Institutional Experience

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ABSTRACT

Objective: Analysis was done to assess the implications and effectivity of adding chemotherapy to preoperative radiotherapy in locally advanced rectal cancer. It was priority to observe any change in resectibility with combined treatment. **Methods:** Twenty five patients were randomized to undergo neoadjuvant chemoradiation and were compared head on with only radiation group for locally advanced rectal cancer patients in CNCI, Kolkata. **Results:** Of the 25 patients in the chemoradiation arm, 20 patients (80%) were potentially resectable. In the radiation only group the number was 16 (64%). [p=0.35] Curative resection with negative margins was possible in 17 patients (68%) in the combined modality arm, as opposed to 13 patients (52%) in the other arm. [p=0.39] The failure rates in the radiation group were higher. [p= 0.49] Median Overall Survival was higher in chemoradiation group (14 months vs. 11 months) as well as median Disease free survival (14 months vs. 12 months) (p = 0.99) in comparison to only radiation group. **Conclusion:** As a beginner's experience, it was very encouraging to observe the positive trend of the study and effectively this study allowed us to further proceed with different dose and schedule modulation of chemotherapy and radiotherapy to build up a definitive protocol for locally advanced Rectal cancer in our institute.
Key words: Chemotherapy, Radiation, Rectal cancer.

INTRODUCTION

Cancer of the rectum forms an integral part of the more widely used term "Colorectal Cancer" (CRC) in medical literature. In general, colorectal cancer is the third most common cancer in men globally and second in women. Worldwide nearly 8,00,000 new cases of colorectal cancer are believed to occur each year, which accounts for approximately 10% of all incident cancers. Mortality from colorectal cancer is estimated at nearly 4,50,000 per year.[1] Generally speaking, colorectal cancer incidence and mortality rates are greatest in developed western countries.[1-4]

The primary treatment modality of rectal cancer, irrespective of stage, is surgery, with radiotherapy and chemotherapy used either in adjuvant setting, neo adjuvant settings or for palliation. Radiotherapy as a neo adjuvant option can be used as a primary modality in T2 onwards tumor. There are certain prognostic factors which influence the natural progress of the disease are as Stage of the Disease, Histology Grade, Histology Type, location of the Tumor, Resection Margin Status, Blood or Lymphatic Vessel Invasion, Pre-operative CEA level, Molecular Markers, Tumor Border , Obstruction and perforation. Locally advanced rectal cancer comprises of stages II and III rectal cancers according to the current TNM staging system. That means all node-negative T3 and T4 tumors as well as all node-positive non-metastatic tumors are included within this category.

Radiotherapy has been used to decrease the local failure rates. Loco-regional failure is further decreased by the use of concurrent 5-FU based chemotherapy,[5-7] as has been proven in various trials.

Surgical procedure adapted depends primarily upon the site of the tumor. Lesions in the upper third of rectum are managed with a low anterior resection, with restoration of intestinal continuity and preservation of a continent sphincter apparatus. For tumors located in the mid and lower rectum, abdominoperineal resection (APR) has been the most common surgical procedure.[8] Nowadays Total Mesorectal Excision (TME) has emerged as a major surgical procedure for management of middle and lower third rectal cancers.[9-12] Whatever may be the procedure, the goal while performing a resection for rectal cancer is to preserve intestinal continuity and the sphincter mechanism whenever possible, while still maximizing tumor control.

Radiotherapy in rectal cancer can be administered either pre or post-operatively. For theoretical reasons it is believed that radiation therapy delivered pre-operatively can decrease the toxicity of therapy, compared to post-op RT. It also has the potential advan-

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tage of tumor downstaging. Moreover, acute surgical morbidities are not substantially increased with the use of pre-operative irradiation.

Until recently all chemotherapy for colorectal carcinoma has been based on 5-fluorouracil (5-FU). Other drugs with known activity in rectal cancer are Capecitabine, Irinotecan, Oxaliplatin etc. 5-FU is a anti metabolite and is cell-cycle specific, with activity in the S-phase. 5-FU is actually a prodrug which, after intracellular phosphorylation, produces its active metabolites which in turn exert their anti-neoplastic activity through inhibition of DNA synthesis and function, as well as alteration in RNA processing and/or translation . This drug is used either along or with leucovorin. In either case it is used in radiosensitisng dose. The drug has been used both as bolus administration and continuous protracted infusion. Common toxicities include gastrointestinal (GI), hematologic, stomatitis and hand/foot syndrome. The primary end-point of this study was to observe the resectability of the tumor along with toxicities, compliance and survival to the patients coming to our institute.

MATERIALS AND METHODS

Biopsy proven rectal cancer patients were evaluated for this study in multidisciplinary tumor board of Chittaranjan National Cancer Institute from September 2006 to December 2007. Patients were first staged clinically and radiologically according to the TNM staging system on the basis of Digital Rectal Examination (DRE), whole abdomen CT Scan, Chest X-ray. It was followed by routine complete blood counts, biochemistries, serum CEA level and colonoscopy.

Criteria for inoperability and declaring the case as locally advanced included tumor invasion into pelvic sidewalls or sacrum, where a complete surgical resection might be impossible; or invasion of bladder or prostate (in case of males), where a more extensive surgical resection could be done, but often at the expense of major morbidity or functional loss. The patients who were confirmed to have unrespectable locally advanced disease and ECOG performance status 0-2 were randomized in the study with informed consent into two arms.

Treatment Protocol

Patients received External Beam Radiotherapy (EBRT) to the whole pelvis to a dose of 45Gy, delivered in 25# over 5 weeks. Teletherapy was delivered through anteroposterior-posteroanterior (AP-PA) fields in a Telecobalt (^{60}Co) machine. The superior border of the fields was at the level of L_5-S_1 vertebral junction; inferior border according to the extent and location of the disease, usually 3 cm. below the tumor or at the inferior aspect of the obturator foramina, whichever was lower and lateral borders 2 cm lateral to the pelvic sidewalls (True Pelvis). If Inter-field Distance (IFD) for AP-PA fields was more than 18 cm. a four-field 'BOX' technique was used, with the addition of two lateral fields. The superior and inferior borders were same as for the AP-PA fields. The anterior border was at least 4 cm. anterior to the rectum, as determined by rectal contrast placed at simulation. Posterior border was placed to encompass the entire sacrum posteriorly. Patients received RT from Monday to Friday of each week. Any gap in treatment due to obvious reasons, were taken into consideration and appropriate dose adjustments (Gap Correction) were made accordingly.

Concomitant chemotherapy was administered Inj. 5-FU by IV bolus route in a dose of 325 mg./m^2 along with inj.Leucovorine 20mg/m^2, in two cycles, during the first and fifth weeks of treatment (i.e. along with 1st to 5th # and 21st to 25th # of RT). In control Arm, patients were treated with only EBRT to the whole pelvis to a dose of 45 Gy, delivered in 25# over 5 weeks.

Treatment was continued as long as Hb. level remained above 8 g/dl. and TLC above 4000/cmm. Radiotherapy was withheld if there was extreme skin ulceration or wet desquamation or there were severe GI toxicities. 5-FU was discontinued in case of low platelet count (< 100000/cmm.), low Hb. or low TLC or if LFT and/or KFT values were beyond normal range. Four weeks after completion of radiotherapy all patients were assessed for resectability of the tumor. Those who got operated, received 4 cycles of post-operative chemotherapy with Inj. 5-FU (500 mg. /m^2 IV bolus on days 1 to 5) and Inj. Leucovorin (20 mg/m^2 IV bolus on days 1 to 5); 28 days cycle. Patients who remained unresectable were offered palliative treatment.

Statistical Analysis

Chi-square test and also Corrected Chi-square test was done to find out the statistical correlation between the two arms. Also test of proportion (Z-test) was used to compare the proportions. For plotting the disease-free survival (DFS) and overall survival (OS) for the two arms, Kaplan-Meier survival curve was obtained. In case of disappearance of the disease confirmed at 12 weeks after completion of adjuvant treatment, the cases were included in complete response (CR) category whereas the cases who had at least 50% decrease in tumor size were included in partial response (PR) category. Progressive disease (PD) was defined as 25% increase in tumor size over a persistent disease.

RESULTS

A total of 51 patients of locally advanced and primarily unresectable carcinoma of rectum were enrolled in which one patient in the study group expired while undergoing treatment, after receiving 7 fractions of RT. The rest of the patients all completed therapy in due course.

The mean age of the patients in the study group was 40.96 years and 45.8 years was in the control group. [p= 0.22] Majority of the patients in either group were male [p=0.74] and Hindu. [p= 0.74] Seven patients in the study group and 4 patients in the control group were addicted to alcohol. [p= 0.5] No patients in either group had any family history of rectal cancer. Majority of the patients belonged to Stage III [p= 0.59] and all of them were having adenocarcinoma of Rectum. The average distance of the tumors from the anal verge was 5.6 cm. and 5.56 cm in the study and control group. [p=0.93]

The median pre-treatment CEA levels were 6.85ng/ml in the study arm, as opposed to 5.47 ng. / ml in the control arm. The pre-treatment performance status and blood investigations were comparable in both groups. [p= 0.29] All patients were treated on the Telecobalt (^{60}Co) machine with AP-PA parallel opposed pelvic fields. Only 3 patients (one in the study group and two in the control group) were planned with four-field 'BOX' technique. The total duration of therapy was calculated from the day of first fraction to the day of last fraction of EBRT. The median duration of therapy was 36 days in the study arm and 35 days in the control arm. Treatment was interrupted in 12 patients (48%) in the study group and 9 patients (36%) in the control group. [p=0.57] In majority of the patients the interruption did not exceed 10 days. [p= 0.78] Table 1

Acute Toxicities During Therapy

The most commonly encountered acute toxicity was drop in the Hemoglobin level. [p= 0.4]. Three patients in the study group experienced Grade 3-4 anemia where no incidence of even Grade 3 anemia was in the control group. Compared to anemia, leucopenia was observed in much less frequency. [p= 0.42] Diarrhea was observed in both the study and the control groups. A grade 2 diarrhea was found to be more common in the study arm. There was no incidence of Grade 3 diarrhea in the control arm, but four patients in the study arm experienced Grade 3 diarrhea. [p= 0.0097] Grade 2 and 3 stomatitis was observed in twelve and three patients respectively in the study group. [p= 0.0001] Skin toxicity mainly presented as erythema, dry desquamation or wet desquamation.

Table 1: Interruption in Treatment.

Arm Days	1 to 5	6 to 10	11 to 20	21 to 30	Total
Study	5	5	1	1	12
Control	3	5	1	0	9
Total	8	10	2	1	21

Table 2: Table of Acute Toxicities.

Toxicity	Arm	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Study	54%	8%	8%	12%
	Control	48%	8%	12%	0%
Leucopenia	Study	12%	8%	8%	-
	Control	19%	4%	0%	-
Diarrhea	Study	58%	23%	15%	-
	Control	60%	8%	0%	-
Stomatitis	Study	42%	46%	12%	-
	Control	36%	0%	0%	-
Skin Reaction	Study	65%	15%	-	-
	Control	76%	20%	-	-
Dysuria	Study	42%	15%	8%	-
	Control	56%	12%	4%	-

Table 3: Late Toxicities.

Toxicity	Study			Control		
	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total
Bladder Dysfunction	1(4%)	1(4%)	2(8%)	1(4%)	1(4%)	2(8%)
Rectal Injury	1(4%)	0(0%)	1(4%)	0(0%)	0(0%)	0(0%)
Soft Tissue Injury	0(0%)	0(0%)	0(0%)	1(4%)	0(0%)	1(4%)
Neuropathy	1(4%)	0(0%)	1(4%)	1(4%)	0(0%)	1(4%)
Small Bowel Injury	1(4%)	1(4%)	2(8%)	1(4%)	0(0%)	1(4%)

[p= 0.24]. Dysuria was encountered during treatment with no significance. [p= 0.79] Table 2.

Late morbidities of therapy included bladder dysfunction, rectal injury, soft tissue injury, neuropathy and small bowel injury. The overall incidence of late morbidities were 24% in the study arm compared to 20% in the control arm. [p=1.0] Table 3.

Post-Treatment Evaluation and Follow-Up

Resectability of the tumor was evaluated clinically and radiologically 4 weeks after completion of pre-operative treatments. Of the 25 patients in the study arm 20 patients (80%) were potentially resectable. In the control group the number was 16 (64%). [p=0.35] Not all patients deemed resectable actually underwent curative resection. Some of them were found to be still unresectable at the operation table and only a colostomy could be done. Curative resection with negative margins was possible in 17 patients (68%) in the study arm, as opposed to 13 patients (52%) in the control arm. [p=0.39]

The median follow-up period was 13 months for the study group and 9 months for the control group. A total of seven patients (three in the study arm and four in the control arm) expired during this period of follow-up. At the last follow-up 13 patients in the study arm and 7 patients in the control arm were free of disease. There were 3 cases of local recurrence and 1 case of combined metastases with local recurrence in the study arm. The corresponding values in the control arm were 4 and 1 respectively. The failure rates in the control arm were higher. [p= 0.49] Table 4

Table 4: Disease Status at last follow-up.

Disease Status	Study	Control	Total
No Disease	13	7	20
Persistent Disease	8	12	20
Local Recurrence(LR)	3	4	7
Metastases(M)	0	1	1
Both (LR+M)	1	1	2
Total	25	25	50

The Median Overall Survival was 14 months in the study arm and 11 months in the control arm. (p = 0.29) Disease-free Survival (DFS) was calculated only for the 30 patients across the two treatment arms, in which curative resection with negative margins was possible. The Median Disease-free Survival was 14 months in the study group and 12 months in the control group. (p = 0.99)

DISCUSSION

The standard approach to these patients with unresectable rectal cancer has been pre-operative radiotherapy followed by surgery. This is based on the observation that surgery alone would leave residual tumor in the pelvis. The primary goals of pre-operative RT are to convert an unresectable cancer to a resectable status and to decrease the incidence of local failure. The use of full dose pre-operative RT converts 48% to 64% of patients to a respectable status.[13-15] The important issues concerning the use of combined modality therapy are whether the addition of chemotherapy increases the resectability, complete response and local control rates, whether there is any improvement in terms of overall and disease-free survival and whether the addition of chemotherapy is associated with significant increase in the acute toxicities.

The results of randomized trails worldwide indicate that there is definitive advantage with the use of concomitant chemoradiotherapy as opposed to radiotherapy alone in terms of resectability rate and local control, but most of them failed to show any definitive survival advantage. Acute toxicities, mainly gastrointestinal and urological, were slightly more evident when combined modality therapy was used. After post-treatment assessment, the resectability rate for the CCRT arm was 80%. These results are more or less comparable to those observed by Minsky BD *et al.*[16] (89%), Leong T *et al.*[17] (91%), Videtic GM *et al.*[18] (79.31%) or Rodel C *et al.*[19] (94%). 5-FU was used as chemotherapy in all these trails. Apart from diarrhea and stomatitis, other acute toxicities were hematological (anemia, leucopenia) and urological (dysuria). When present, stomatitis and diarrhea usually began by day 7 of each cycle of chemotherapy and resolved in one week. Radiation associated GI toxicities usually began during the fourth or fifth week of RT.

After a median follow-up period of 11 months the median disease-free survival (DFS) for the 30 patients undergoing curative resection was 14 months as opposed to 12 months for the control arm. The median overall survival (OS) for the study and the control groups were 14 months and 11 months respectively, which are quite comparable with the rates obtained by various other studies. Table 5

Table 5: Comparison of different studies.

Study	TNM Stage	N	Treatment Modality	Resectability	CR	Grade 3+ Acute Toxicities	DFS	OS
Minsky *et al.*[16]	III	20	EBRT (50.4 Gy) + concomitant bolus 5-FU and leucovorin	89%	21%	Diarrhea-17% Dysuria-7% Mucositis-8% Erythema-8%	64% at 3 years	69% at 3 years
Leong *et al.*[17]	III	13	EBRT (50.4 Gy) + concomitant bolus 5-FU	91%	10%	NA	NA	NA
Videtic *et al.*[18]	II, III	29	EBRT (54 Gy/ 28#) with concomitant continuous infusion 5-FU	79.31%	13%	NA	NA	NA
Rodel *et al.*[19]	II, III	31	EBRT (50.4 Gy + local boost) with concomitant continuous infusion 5-FU	94%	NA	Diarrhea-23% Dermatitis-6% Leucopenia-10%	NA	68% at 5 years

Local failure rates in the study and the control groups are 24% and 46% respectively, whereas distant failure rates are 6% and 15% respectively. Most of the recurrences in our study have occurred between 6 to 12 months of follow-up and there is a tendency of greater distant failure in the control arm as compared to the study arm where the failure was mainly loco-regional.

In the study arm the resectability and tumor response rates have been found to be somewhat lower compared to the results obtained in several similar studies. This might be explained with lower dose of radiotherapy, bolus use of 5-FU, comparatively little lower dose of to the other studies. So there had been certainly scope of improvement in the results with some modifications in the dosing and schedule of both chemotherapy and radiotherapy. As an experience to start with, it was really encouraging to establish the role of preoperative chemoradiation in locally advanced rectal cancer.

CONCLUSION

Pre-operative chemoradiotherapy has been established as an effective treatment options that can be used in locally advanced primarily unrespectable rectal cancer, to downstage or downsize the tumors and make them resectable. The combined modality treatment certainly results in improved resectability and local control rates when compared with pre-operative radiotherapy alone. The local and distant failure rates have been also lower in the chemoradiotherapy group. There is a trend towards improved disease-free and overall survival with the CCRT.

So with the acceptable toxicities and promising results inspired us to set up the protocol for neoadjuvant cheoradiation for locally advanced rectal cancer which was further warranted with bigger patient sample, modulated chemotherapy regimens and longer duration of follow-up.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CCRT: Concurrent chemoradiotherapy; **5FU:** 5 Fluro Uracil; **EBRT:** External Beam Radiotherapy; **#:** Fraction; **CEA:** Carcino Embryonic Antigen; **60Co:** Cobalt 60; **CR:** Complete Response; **PD:** Progressive Disease OS= Overall Survival; **LFT:** Liver Function Test; **TLC:** Total Leucocyte Count.

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