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A feasibility study of Neoadjuvant chemoradiation in locally advanced carcinoma rectum on tumor down staging and sphincter preservation

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Abstract
Purpose: To evaluate the rate of sphincter preservation, tumor regression, local control and acute toxicities of Neoadjuvant chemoradiation for locally advanced distal rectal carcinoma.
Method: Patients with clinical T_3 / T_4 cancer of distal rectum were taken into the study to receive Combined Neoadjuvant chemoradiation followed by surgical resection. All the patients were given inj. Leucovorin (30 mg/m^2) and inj. 5-FU (325 mg/m^2) D_1 concurrently with radiation of 45 Gy/25# @ 1.8 Gy for 5 weeks. Surgery was performed 4-6 weeks after completion of chemoradiation. The primary end points of this study are tumor regression and sphincter preservation and acute normal tissue toxicities were taken into account as secondary point.
Results: A total of 15 patients have been evaluated from July 2007 to July 2008. The study shows overall resectiability rate of 86.6% and a sphincter preservation rate of 53% as 53% of patients underwent Low anterior resection (LAR) and Abdominoperineal resectioin (APR) was done in 33%. Only 13% patients were declared inoperable in whom palliative colostomy were done. Non hematological toxicities (diarrhea of grade III – 20% and skin reaction of grade II- 20%) were main complication observed during neoadjuvant chemoradiation. Grade II hematological toxicity (neutropenia) reported only in one patient. With a median follow up period of 6 months no loco regional failure has been seen. One patient has failed distantly presenting with lung metastasis without any local failure.
Conclusion: Concurrent preoperative chemoradiation for locally advanced carcinoma rectum is associated with improved tumor respectability which results in improved sphincter preservation, local control and is relatively safe, effective and well tolerated.

Keywords: Rectal carcinoma, adenocarcinoma, neoadjuvant chemoradiation, sphincter preservation, LAR, APR

Introduction
Cancer of the rectum is less frequent than colon cancer, accounting for 5% of all malignant tumors and ranks as the 5th most common cancer in adults with a male predominance of 30-50% higher than in women [1, 2]. Management of patients with rectal cancer remains a challenge for GI surgeons. At presentation about 15-30% patients present in locally advanced stage and 15-20% in metastatic stage. Ca rectum is often curable when localized to the bowel. Radical resection represents the first option and results in cure in approximately 50% of patients yet the rate of local failure in pelvis following surgery increases with increasing stage of the disease ranging between 20-70% [4, 5].
The standard approach (>3 fields, computerised plan and customised blocking; 45–55 Gy, delivered in 4–6 weeks followed by surgery 6–8 weeks later) has the potential objective of inducing down-staging in locally advanced tumors and permitting radical surgery with preservation of sphincter function [11-12]. Based on a series of experiences the optimal time of surgery is about 4–6 weeks after radiotherapy for obtaining the maximum therapeutic effect with lower postoperative complications. The NCI consensus conference in USA in 1990 recommended postop chemoradiation for patients with stage II and III ca rectum as standard treatment. The standard adjuvant therapy for transmural (T_3) and/or node positive rectal cancers is the combination of pelvic radiation with 5-FU based chemotherapy, which significantly improves both local control and overall survival compared with surgery alone and surgery with radiotherapy.

As a sole adjuvant modality, preoperative radiation provides loco-regional control of approx 90% for stage I-II tumors and overall freedom from relapse of approx 65-70% [16].

The potential advantages of neoadjuvant chemoradiation are to reduce the risk of local recurrence, down staging the primary tumor that possibly enhance curative (R_0) resection in locally advanced T_4 rectal cancers, sterilization of tumor cells prior to the surgery, smaller treatment fields/ volumes with less irradiation of small bowel and therefore less acute toxicity and increase the rate of sphincter preservation for tumors located in distal rectum [21-23].

Currently preoperative chemoradiation with 5-FU based chemotherapy is considered treatment of choice for stage II_B/ III rectal cancers and when the goal of preoperative therapy is Sphincter preservation, conventional doses and techniques of radiation are recommended. These include multiple field techniques to a total dose of 45-50 Gy @ 180 cGy per fraction. Surgery should be performed 4-7 weeks following the completion of chemoradiation. This conventional design allows the recovery from the acute side effects of radiation adequate time for tumor down staging [37].

The management of rectal cancer has thus evolved from surgery alone to neoadjuvant management and holds promise for the future.

All these studies concluded that this combination approach achieved down staging of locally advanced tumors and sphincter preservation in the significant number of patients, and that overall survival was at least, better to those reported with aggressive surgical approaches.

Aims & Objectives

To study impact of Neoadjuvant chemoradiation with 5-Fluorouracil and Leucovorin in treatment of Ca rectum with respect to tumor down staging and local control and sphincter preservation and acute toxicities encountered

Materials and Methods

Twenty previously untreated patients of Ca rectum attending SURGERY and RADIOTHERAPY OPD during July 2007 to July 2008 were selected for this descriptive study, subjected to the following selection criteria: Histopathologically proven Adenocarcinoma rectum, tumor distal border located > 4 cm of anal verge, absence of metastatic spread on CT Scan, WBC count $\geq$ 4000/ mm^3, Total Platelet Count $\geq$100,000/mm, Bilirubin, SGOT, SGPT and Creatinine $\leq$ 1.5 times the upper limit of normal, Karnofsky Performance Score (KPS) (Appendix B) $\geq$ 70. Patients with duke A & D or with any other malignancies or having prior history of any Chemotherapy or Radiotherapy or of Colorectal surgery or with distant metastasis were excluded. Preoperative Combination chemotherapy (CCT) was consisted of inj. Leucovorin (LCV) 30mg/m^2 and 5-Flurouracil (5-FU) 325mg/m^2. The Leucovorin was administered by IV infusion for 30 minute and 20 minute later was followed by inj. 5-Fluorouracil IV bolus. Radiation was given within 4-6 hours of chemotherapy. Chemotherapy was given concurrently with radiation weekly for five weeks.

Megavoltage External beam (6 MV-15 MV) with AP/PA pelvic field or Box techniques (AP-PA & Left and Right lateral fields) according to the patient's suitability was used. All fields were treated each day.

All the patients were prepared by giving oral, rectal and IV contrast. A rectal marker was placed on the anal verge to ascertain the distal extent of the tumor. All the patients were asked to evacuate the urinary bladder and to drink at least 2 litres of water and not to urinate thereafter prior to planning as well as before the delivery of radiation. Planning CT scans were taken after fiducial markings over the abdomen of the patients. Tumor was plotted on the TPS and radiation portals were defined. For the AP/PA field, superior border was placed at the L_5-S_1 junction and the inferior border at 3-5 cm distal to primary tumor or at the inferior margin of the Obturator foramen, whichever was the most inferior. The lateral borders were kept 1.5 cm lateral to widest bony margin of the two pelvic side walls. In order to encompass iliac node chain, the lateral borders of the posterior portal were 1.5 cm outside the true bony pelvis. The lateral field encompassed the sacrum and coccyx with a 1 cm margin posteriorly and the anterior margin of lateral field kept at the posterior margin of pubis symphysis for T3 tumors or at the tip of pubic symphysis for T4 tumors (femoral head anteriorly to include the Obturator nodes) and Multi Leaf Collimators (MLC) were used to spare posterior soft tissue and small bowel in anterior and lateral fields (Fig 5, 6). Calculation was done and verified on the Eclipse TPS. All the patients were treated in prone position with full urinary bladder on a 'BELLY BOARD'. We delivered total dose of 45 Gy in 25# @180 cGy over 5 weeks by LINEAR ACCELERATOR. All the patients were thoroughly examined weekly for acute toxicity during preoperative combined modality therapy and in follow up 2-3 weeks after completion of this treatment with Complete blood counts at each visit. If clinically indicated other blood tests or X-ray were obtained and acute treatment related toxicity were noted weekly and graded by using Common Terminology Criteria for Adverse Events (CTCAE v 3.0).

Patients were evaluated for surgery 4-5 weeks following completion of combined modality therapy. The operative procedures were: Low anterior resection (LAR), Low anterior resection/coloanal anastomosis and Abdominoperineal resection (APR) using sharp dissection according to the principal of Total Mesorectal Excision (TME) and palliative colostomy for unresectable disease. All patients with Low anterior resection had protective diversion ileostomy which was reversed 2-3 months after surgery.

After completion of treatment patients were evaluated clinically every 4 weeks for the first 6 months and every 2 months for the next 6 months. At each visit patients were examined clinically and Ultrasonography abdomen-pelvis, Chest X-ray and Liver function test obtained every 3 months. A Chest X-ray and colonoscopy obtained 3 monthly for first 1 year. Patients were advised for 3 monthly CEA.

Patients Characteristics

The age of patients ranged from 23 to 70 years with median of 38 years. There were sixteen male patients and four female patients in the study group (Fig.1). History of smoking was present in 5 patients (25%). The median Karnofsky Performance Status (KPS) was 80, ranged from 70-90. Patients specific variable are depicted in Table 1.

Table 1

Patients number	20	
Sex	Male	16
	Female	4
Age	Median	38
	Range	23-70
KPS		70-90
Family history	Present	2
Co-morbidities	Absent	
Addiction history	Present	5

Clinical Presentation

All the patients were symptomatic for a mean duration of 9 months before attending the institute. Most of the patients presented with bleeding P/R (95%). Other presenting symptoms were altered bowel habits, pain perianal region, generalized weakness, abdominal pain, loss of appetite and weight loss. Most of the patients had presented with more than one symptom. Table 2 represents the common symptoms of the patients at the time of diagnosis.

Table 2: (Total no. of patients= 20)

Symptoms	No. of patients	Mean Duration (months)
Bleeding P/R (or blood in stool)	19 (95%)	7
Altered bowel habbit	6 (30%)	6
Pain perianal region	5 (25%)	4
Increased frequency of stool	7(35%)	8
Abdominal discomfort/ pain	15(75%)	3
Generalized weakness	10(50%)	6
Loss of appetite/ Loss of weight	6(30%)	6
P/R Mucus discharge/ pruritus ani	6(30%)	4

Disease Characteristic

All twenty patients had adenocarcinoma. Out of twenty patients three patients had low grade tumor, ten patients had high grade tumor and grade not specified in two patients. Out of twenty patients, fourteen patients (70%) were T3N1M0 and three patients (15%) were T4N1M0 (fig.2). So 90% patients belong to the stage IIIB and there was one patient in stage IIA and in stage IIIC. Clinical Scoring was calculated taking into account the tumor location from anal verge, tethering, circumferential extent and obstructive pattern. Mean tumor distal location was 4.72 cm from the anal verge. All the patients were clinically and radiologically assessed by the surgeon and declared locally advanced disease and APR (Abdominoperineal resection) was predicted in all the patients. Pre treatment disease characteristic depicted in Table: 3

Table 3

Histology		Clinical Scoring		Stage Pre CRT	
Adenocarcinoma	20	**0**	2	T3 N0M0	1
Low grade	3	**1**	10	T3 N1M0	14
High grade	10	**2**	8	T3N2M0	1
NOS	2			T4N1M0	3
				T4N2M0	1

Treatment

External beam radiotherapy was delivered by linear accelerator in all patients. 3DCRT planned and external radiation dose of 45 Gy/25#/5wks was delivered to whole pelvis by Four-field technique. Inj. 5-FU was used concurrently with external beam radiation with dose of 325mg/m^2/day and given on D1 weekly. Inj. Leucovorin with dose of 30 mg/m^2/day was given as biomodulator prior to the infusion of 5-FU. All patients were monitored during this entire period of treatment and completed planned treatment with manageable minor toxicities.

After five weeks of chemoradiation all the patients were assessed by the same surgeon for the feasibility of sphincter preserving surgery clinically and radiologically. Majority of patients showed good response to chemoradiation. Resectability rate increased to 90%. Out of 20 patients 13 (65%) underwent LAR (Low anterior resection) and 5 (25%) patients underwent APR. Only two patients showed poor response to chemoradiation and declared inoperable due to fixity of tumor in the pelvis and considered for Palliative colostomy.

Histopathological study showed Pathological complete response (pCR) of 55% (11/20). Nine patients with LAR showed complete pathological response while only two showed pCR in APR group. Diversion colostomy was reversed in patients who underwent LAR in 6-8 weeks who showed complete response and in case of partially responded patients it was reversed 4 weeks after completion of adjuvant therapy.

Postoperatively seven patients who underwent definitive surgery with partial response were given 5-FU and Leucovorin at full therapeutic doses biweekly for 12 cycles. The single patient who developed lung metastasis 6 months postop was given Oxaliplatin, 5-FU and Leucovorin 6 cycles 3 weekly.

Acute toxicities were graded according to NCI CTCAE Vs 03 table. Major toxicities were gastrointestinal and dermatological. Grade I and II nausea was seen in 10 patients and 5 patients respectively and grade III in only one patient. Grade I and II vomiting seen in 6 and 2 patients. Grade III vomiting was seen in only one patient which were controlled by administration of oral antiemetic agents. Similarly, grade I and grade II diarrhea was seen in 11 and 6 patients respectively. Three patients had grade III. Diarrhea managed with loperamide tablet and ORS. Grade I skin reaction was seen in 16 patients. Only one patient experienced grade III skin reaction in the last two days of chemoradiation which was managed with Gentian violet paint. Acute grade I and II hematological toxicity in terms of anemia was seen in 2 and 1 patients respectively. One of the patients showing grade II leucopenia was managed conservatively. Only one patient showed grade I thrombocytopenia without any bleeding symptoms which was spontaneously recovered in few days. Grade I and II increased frequency of micturition was seen in 4 and 3 patients respectively. No patients developed hematuria or acute renal toxicity during treatment and follow up. There was no interruption treatment due to toxicity. Table 4 depicts the common toxicities.

Table 4: Acute radiation reaction

Acute toxicities	Gr I	Gr II	Gr III	Treatment
Nausea	10 (50%)	5 (25%)	1 (5%)	
Vomiting	6 (30%)	2 (10%)	1 (5%)	Oral antiemetics
Diarrhoea	11 (55%)	6 (30%)	3 (15%)	ORS, Lomotil, Oral fluids
Skin reaction	16 (80%)	3 (15%)	1 (5%)	GVP for Gr III reaction
Anaemia	2 (10%)	1 (5%)	0	
Neutropenia	0	1 (5%)	0	Neutropenic precaution
Thrombocytpenia	1 (5%)	0	0	
Increased frequency urine	4 (20%)	3 (15%)		Tab. Urispas, Oral fluids

Disease Control

The follow up period ranged from 6 to 26 months with a median duration of 9 months. The initial response to treatment was assessed at 4 weeks after completion of treatment and subsequently at each follow up. The pattern of failure was analyzed after seeing the disease status at the time of last follow up. Clinically all the patients who underwent definitive surgery after completion of chemoradiation were disease free at the time of last follow up except one who developed lung metastasis in 6 months postop and had risk factors for distant metastasis.

Table 5: (Disease status at last follow up)

Disease status	Study Group
NED	17/20
Local failure	2/20
Distant metastasis	1

Survival

Local control, colostomy free survival, distant metastasis survival, disease free survival and overall survival were computed using Kaplan Meier survival analysis on SPSS 12. The local control at two year is 90% with a mean period of 24 months (Fig: 1).

Colostomy free survival (CFS) at 2 months is 70%. Actuarial Colostomy free survival at one year is 65%. Mean Colostomy free survival is 13 (Fig: 2). Disease free survival (DFS) is 85% at one year with a mean of 17 months (Fig: 3). Distant metastasis survival is 95% at one year with a mean 18 months and with respect to LVE, is 66% at 11 months with a mean period of 10 months.

Overall survival at 2 years is 95% with a mean of 25 months.

Overall survival was computed from the date of registration to the date of last follow-up or the date of death. Disease free survivals for stage, age were analyzed and none was statistically significant.

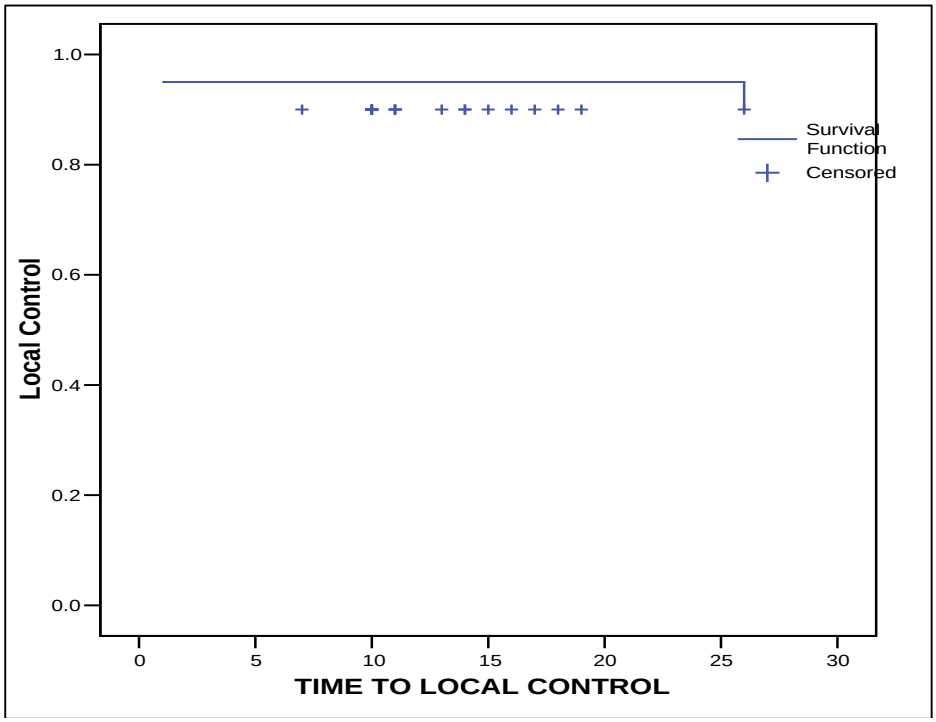

Fig 1: Local control (LC)

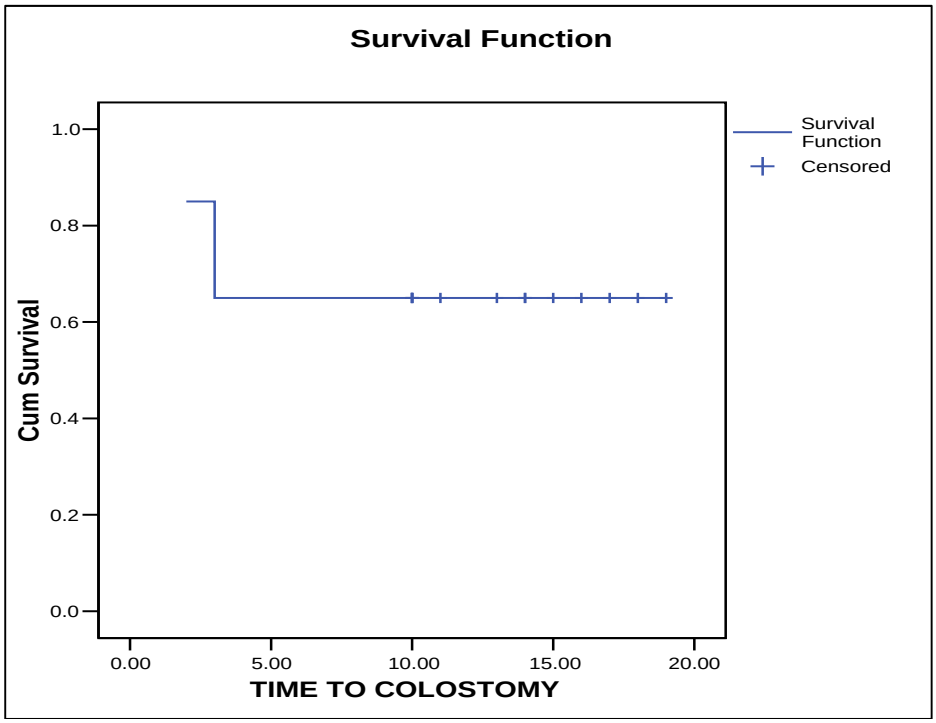

Fig 2: Colostomy free survival (CFS)

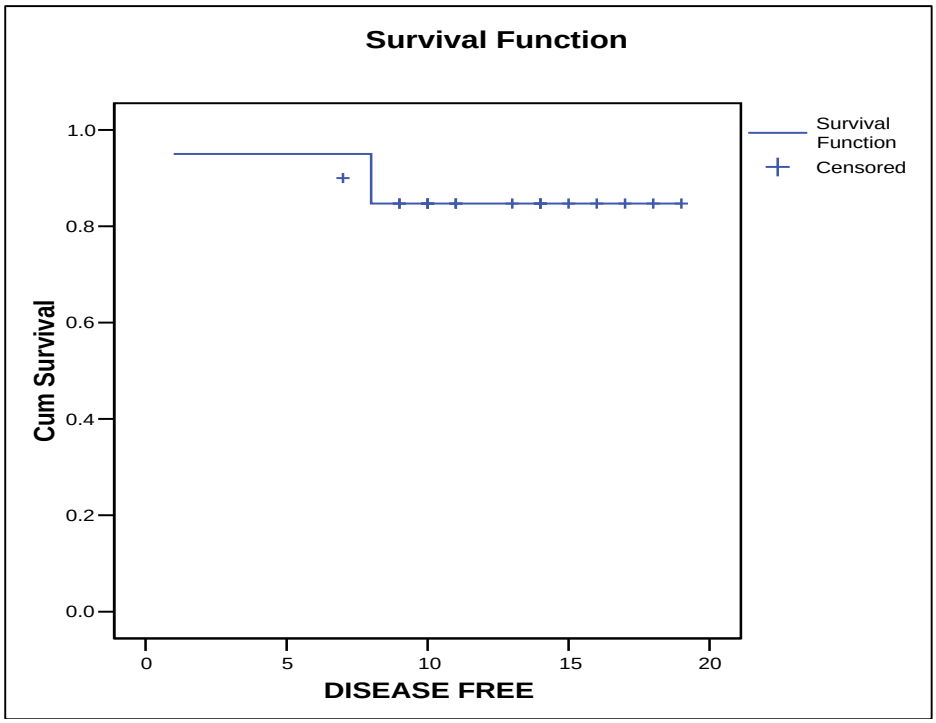

Fig 3: Disease free survival (DFS)

Discussion

Traditionally, treatment for advanced rectal carcinomas using radical surgery alone has been accompanied by poor survival and high local recurrence rates. The use of chemotherapy and radiation therapy in the adjuvant management of rectal carcinoma has been found to increase disease-free survival and decrease local recurrences. This report details the use of neoadjuvant chemotherapy and radiation therapy in a series of patients with locally advanced rectal carcinomas. Preoperative radiotherapy has been examined in a number of trials. Theoretically, there are several potential advantages of delivering radiotherapy preoperatively:

1) The radiation is delivered to well-vascularized and well-oxygenated tumor; 2) the implantation of viable tumor cells, either locally or through vascular channels as the tumor is manipulated during surgery, can be minimized; and 3) radiation injury to the small bowel decreased because the small bowel is free and not adhered to the pelvis. Preoperative radiotherapy has been explored in a number of

retrospective and prospective trials [6, 8]. All of these studies demonstrated considerable improvement in both survival and local control when compared with historic controls. Seven randomized prospective trials also have been reported [7]. Unfortunately, five of the seven delivered a dose of radiotherapy, which is quite low by modern standards. Accordingly, all five were negative studies. However, two more recent studies from Europe were performed with more appropriate doses of radiotherapy [10, 11] The European Organization for Research in the Treatment of Cancer randomized 466 patients with rectal cancer to receive either surgery alone or preoperative therapy plus surgery[8]. When considering only the 341 patients found to have localized disease at the time of surgery, the local recurrence rates in the radiated group was 15% compared with 30% in the control group (p = 0.003). Survival was improved from 60% to 70% for patients receiving preoperative therapy (p =0.08). The Stockholm study randomized 849 patients and examined results in 679 without metastatic disease[11]. There was a significant reduction in radiated patients in both local recurrence and death due to rectal cancer. In both of these studies, stage A and B, disease were included in the analyses, and it is conceivable that the results would have been better if these were excluded. In a recent Swedish report, preoperative radiation therapy was compared with postoperative radiotherapy in a randomized multicenter trial [19]. Although the dose of preoperative group was lower than that given to postoperative group (25.5 Gy vs. 60 Gy, respectively), the local control rate was significantly better in the preoperative group compared with the postoperative group (12% local failure vs. 21% in those with curative resection; p = 0.02). There was no difference in survival between the groups. To date, no randomized series has concluded that preoperative radiation therapy as a single adjuvant has a significant survival benefit.

Two previous reports of preoperative chemoradiation therapy in the treatment of rectal carcinoma did not report data on their postoperative complication type and frequency [3, 14]. In this series, 10 of 20 (50%) patients had no evidence of tumor in their resected specimens, and overall, 7 of 18 of the patients had positive lymph nodes. The percentage exceeds the rates quoted in studies using preoperative radiation therapy alone [29-31]. Comparable results have been found in our study which shows a pCR rate of 55% and down staging of tumor (p= 0.006) has been obtained which is statistically significant. Minsky reported a slightly lower rate of 20%

sterile specimens after preoperative 5-FU and leucovorin, with 30% having positive nodes. In our series, all of the tumors except in two patients appeared to have decreased in size after the course of therapy. These were based on pre therapy CT, physical examination, and biopsy compared with post-therapy histopathological study and sigmoidoscopy. Beynon *et al*. have shown that endoscopic rectal ultrasound is more accurate than computed tomography in predicting depth of invasion [33]. It is possible that preoperative staging methods used in our series allowed the inclusion of less advanced disease; this may have accounted for a higher rate of sterile specimens. To reduce this possibility, endoscopic ultrasound should be included in study as a more accurate means to stage rectal carcinoma preoperatively [34]. Pre- and post-therapy staging with endoscopic ultrasound was examined by Meterissian *et al*. In their series, there was a 30% complete response after 5-FU and radiation therapy, which compared favorably to our series. 40% (8/20) of patients received abdominoperineal resection, 50% received (10 of 20) lower anterior resection, and 10% (2) had palliative colostomy. In our series 65% (13/20) patients underwent LAR, 25% (5/20) underwent APR and only two patients were declared inoperable and considered for palliative colostomy (PC). As mentioned previously, there was no attempt in this preliminary study to reduce the magnitude of the operative procedure. The operation performed was selected based on the tumor size and location before the administration of the neoadjuvant protocol. The high rate of tumor downstaging (50% sterile specimens) however, suggests that less radical surgery may be possible. In a recent retrospective review, Paty *et al*. examined the treatment of rectal cancer by low anterior resection with coloanal anastomosis [35]. This study determined that pelvic recurrence was not associated with short distal margin, but rather correlated with T stage (T3 vs. T 1-2), positive microscopic margins, perineural and blood vessel invasion, tumor grade, and mesenteric implants; pelvic recurrence was independent of tumor size and N stage.

Thus, the ability to perform sphincter-sparing surgery depends primarily on control of the tumor. The ability to downstage tumors, as our protocol has demonstrated, suggests that less radical surgery could be performed without compromising local control. We currently are investigating the role of sphincter-preserving surgery in selected patients after chemoradiation downstaging. This therapeutic regimen has provided enhanced local control, decreased metastases and increased survival, and supports the continued investigation of preoperative chemotherapy and radiation therapy for the management of advance rectal cancers. The data, however, should be interpreted with caution, because a prospective randomized trial is needed to determine the ultimate impact of complete response and decreased pelvic node involvement on local control, survival, and the ability to perform sphincter-sparing surgery. Furthermore, optimization of preoperative chemotherapeutic regimes may enhance sterile specimen rates. Already, a 55% incidence of sterile pathologic specimens and a low rate of positive lymph nodes in a group with advanced lesions strongly suggest that significant tumor down staging is occurring with neoadjuvant therapy; this may allow less radical surgery, and hopefully, will lead to increased rate of sphincter preservation in the future.

Conclusion

This observational study was undertaken to evaluate the efficacy and toxicity of concurrent chemoradiation in locally advanced carcinoma rectum. To conclude, Neoadjuvant chemoradiation is effective, feasible and without any increase in acute morbidity. There is definite trend towards increased respectability rates with complete pathological response in this group of patients. However, to validate the findings of our study and for determining long term benefits of neoadjuvant chemoradiation in sphincter preservation, colostomy free survival and improvement in overall survival, longer follow up and more sample size is required.

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