NEOADJUVANT CHEMO-IRRADIATION IN UN-RESECTABLE CARCINOMA OF RECTUM

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Background: Rectal cancer is one of the most frequent gastrointestinal cancers. Conventionally surgery is the mainstay of treatment, however after surgery alone, local recurrence is high especially in locally advanced rectal cancer, i.e. tethered and fixed rectal cancer. This study was conducted to determine the role of neo-adjuvant (pre-operative) chemo-irradiation in locally advanced carcinoma of the rectum to improve resectability , local control and survival. **Methods:** Study was conducted in Radiation Oncology department of Shaukat Khanum Memorial Cancer Hospital and Research Center from May 97-Oct 99. Thirteen patients with unresectable/ locally advanced adenocarcinoma rectum received neo-adjuvant chemoirradiation, 50 Gray to pelvis by box technique on Cobalt-60 machine with concomitant 5-Flurouracil 500mg/m2 for first three and last three days followed by abdomino-perineal /low anterior resection. **Results:** Neo-adjuvant chemoirradiation resulted in resectability rate of 92% and clinical down staging in 11/13 (84%) patients and pathological complete response in 2/13 (15%) patients and a local recurrence rate of 2/13 (15.38%). Non hematological toxicity (diarrhea grade 4-15%, erythema grade3-23%, dysuria grade1-2-38%) were main problems observed during neo-adjuvant chemoirradition. **Conclusion:** Concomitant preoperative chemoirradiation for locally advanced rectal cancer is associated with considerable clinical and pathological down staging. Tumor resectability is improved with potential for improved local control and is relatively safe with acceptable morbidity.

KEY WORDS: Unresectable rectal cancer, resectibility rate, neo-adjuvant chemoirradiation

INTRODUCTION

In carcinoma of the rectum radical surgical resection remains the mainstay of treatment, yet, the rate of local failure in the pelvis following surgery increases with increasing stage of disease, ranging between 20%-70%.[1,2] This has led clinicians to increase use of chemo-irradiation either pre or post operatively in an attempt to improve local control and survival. Role of post operative (adjuvant) chemo-irradiation is well established in improving local control and survival.[3,4] Pre-operative irradiation is particularly appealing in locally advanced disease due to high local recurrence rate with surgery alone.[1] In a clinicopathological review tumor mobility was the single most important pre treatment prognostic factor for survival and disease free survival.[5] Fixation significantly reduced the probability of achieving a curative resection. The curative resection rate for tethered cancer was 44 %, and the 5 year local disease free rate was only 37%. Therefore, this subgroup of patients (tethered and fixed tumor) constitute an appropriate population for study of the efficacy of pre-operative therapy in rectal cancer. The results of comparison of pre-operative radiation with pre-operative chemo-irradiation and showed that pathological down staging increased from 42% to 58% and 1, 3, & 5 years overall survival rate improved significantly with pre-operative chemo-irradiaiton.[6]

This report summarizes our experience at the department of Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, using neoadjuvant chemo-irradiation in locally advanced rectal cancer, defined as tethered annular or stenosing with emphasis on curative resectability, acute toxicities, local control and survival.

MATERIAL AND METHODS

This study was carried out from May 1997 to October 1999 at Shaukat Khanum Memorial Cancer Hospital, Lahore. Thirteen patients with diagnosis of unresectable carcinoma rectum limited to pelvis were included in the study.

The inclusion criteria were patient with clinical partially fixed/fixed or radiologically ≥ T3 or node positive rectal carcinoma, ECOG performance status 1 or 2 (See table 1), primary histopathology of adenocarcinoma and CBC granulocyte count > 4000 / mm^3, Haemoglobin not less then 10g/dl, platelet counts > 150000/mm^3 Bilirubin < 1.5 mg/dl.

The exclusion criteria were patients with distant metastasis, terminally ill patients, patients with other histopathology e.g. squamous cell carcinoma, melanoma / sarcoma, patient with ECOG performance status 3 or 4 (See table 1) and patients with clinically or radiologically resectable disease.

Case investigation was based on history and physical examination including digital rectal examination as well as endoscopy including proctosigmoidoscopy or colonoscopy and biopsy. Complete Blood Counts (hemoglobin, total leucocyte count, differential leucocyte count, platelets), Blood Chemistry Profile including liver and renal function tests (blood urea nitrogen, serum creatinine, bilirubin, aspartate transaminase, alanine transaminase and alkaline phosphatase) and Carcinoembryonic Antigen were done. Metastatic Work-up included Chest X-ray Postero-anterior view, C. T. / M.R.I abdomen/pelvis, Bone scan and CT brain.

Table-1: Eastern cooperative oncology group (ECOG) scale

Performance	ECOG Scale
Normal activity	0
Symptomatic but ambulatory; cares for self	1
Ambulatory more than 50% of time; occasionally needs assistance	2
Ambulatory 50% or less time; nursing care needed	3
Bedridden; may need hospitalization	4

Concurrent chemotherapy consisted of 5-Flourouracil 500 mg /m^2 over first three days and last three days of radiation given by I/V push over 3-5 minutes followed by radiation within 20-30 minutes.

Adjuvant chemotherapy given three to four weeks after surgery consisted of 5 Fluorouracil 400-500mg/m2 day 1-5 and Leucovorin 20 mg per oral (P/O) day 1-3, repeated every four weeks for total of 6 cycles. National Cancer Institute common toxicity criteria was used to measure toxicities during neoadjuvant chemoirradiation and during adjuvant chemotherapy.

Mega voltage radiation therapy was used, 8 patients were treated with Co-60 and 5 patients with photons (X6 Mev) Linear Accelerator. Box technique (AP//PA, right & left lateral fields) were used (see fig. II). All patients treated each day and port films were obtained weekly. The lateral border was 1.5 cm lateral to widest bony margin of true pelvic side wall, distal border 3 cm below primary tumor or at inferior aspect of obturator foramen. Superior border was at the junction of lumbar 5 and sacral 1 (L5-S1) vertebrae, and posterior border at-least 1 cm behind bony sacrum, customized blocks were used to spare posterior muscle and tissues, and small bowel in anterior and lateral fields. Total dose was 45–50 Gy at rate of 180 – 200 cGy / day to whole pelvis. In all patients tumor was located below peritoneal reflection in ano-rectal area approximately 2-8 cm from anal verge, 12 patients underwent abdominoperineal resection, while 1 patient underwent low anterior resection. Surgery was carried out 4-8 weeks after chemo-irradiation .

After 4-8 weeks of surgery adjuvant chemotherapy was advised including 5FU 400—500mg /m^2 days 1-5 and leucovorin 20 mg per orum daily, day 1-3, for 5 cycles repeated every 4 week. Two patients refused chemotherapy after 1-2 cycles, 6 patients completed 5 cycles and 5 patients lost follow up. Patients were seen every 3 months initially for two years then 6 monthly along with carcinoembryonic antigen (CEA) and yearly colonoscopy & chest x-ray. CT scan was done when carcinoembryonic antigen (CEA) levels were elevated or on abnormal clinical

physical examination. After median follow up of 7 months, 2 patients failed locally. Disease free survival and overall survival were not included in the study due to short follow-up and required continued follow-up.

RESULTS

The results of this study are summarized in tables 2-6

Table-2: Age and sex distribution

Age (Years)	Male	Female	Total
< 20	1	0	1
21- 40	2	0	2
41-60	7	2	9
>60	1	0	1

Table-3: Distribution by ECOG performance status. (See table 1)

ECOG PS	No. of Patients
0	0/13
1	9/13
2	2/13
3	0/13
4	0/13

Clinical staging of 13 patients was Partially fixed cT3:7/13 (53%), Fixed cT4 6/13 (46%). Radiological staging was done according to TNM staging system (tables-4 and 5)

Table- 4: Radiological staging was done according to TNM staging system

TNM Stage	No. of Patients	Percentage
T3	11/13	84%
T4	2/13	15%
N1	4/13	30%

After completing concurrent chemoradiation all patients were evaluated for tumor response to treatment by surgeon and radiation oncologist and 11/13 (84%) showed clinical down staging either measured as reduction in size of tumor or by increase in mobility as shown in table 5.

Table-5: Chemo-irradiation Clinical Staging

Clinical Stage	Pre Treatment	Post Treatment
CT_1 (Freely mobile)	0/13 (0%)	0/13 (0%)
CT_2 (Mobile)	0/13 (0%)	11/13 (84.61%)
CT_3 (Tethered Mobility)	7/13 (53%)	1/13 (7.69%)
CT_4 (Fixed)	6/13 (46%)	1/13 (7.69%)

All 13 patients underwent surgery and 12/13 (92.30%) had curative resection with negative margins. Abdominoperineal resection was done in twelve patients and lower anterior resection in one patient. Post-surgical pathological down staging was done according to the TNM staging (see table 5)

Table-6: Post-surgical pathological down staging

CT4	PT0	PT1	PT2	PT3	PT4
(6/13)	0/13	0/13	2/13	3/13	1/13
CT3					
(7/13)	2/13	0/13	3/13	2/13	0/13

Clinical nodal disease was present in 4/13 (30%) while Pathological nodal disease was found in 5/13 (38.4%). Pathological complete response defined as no evidence of gross or microscopic disease documented in 2/13 (15.3%) and pathological down staging was documented in 9 locally advanced rectal cancer.

Table-7 Acute toxicities in terms of National Cancer Institute Common Toxicity Criteria

NCI Criteria Grades	Neo Adjuvant Chemo-irradiation	Adjuvant Chemo-therapy Protocol
	n/ 13	n/13
Nausea G1-2	2 (15.38%)	6 (46.15%)
Vomiting G 1-2	2 (15.38%)	6 (46.15%)
Diarrhea G 2-3	5 (38%)	6 (46.15%)
Diarrhea G4	2 (15.38%)	-
Erythema G 1-2	3 (23.07%)	-
Erythema G 3	3 (23.07%)	-

DISCUSSION

The role of adjuvant pelvic irradiation therapy in rectal cancer has been confirmed in several randomized studies.[3,4,6] Pelvic irradiation can improve local control, however a significant proportion of failures in rectal carcinoma involved distant metastases. Loco-regional treatment alone such as radiation is unlikely to have any significant impact on the survival in rectal cancers. This was the observation reported in several randomized studies comparing preoperative or postoperative radiation with surgery [7,8,9] Combined systemic chemotherapy with radiation appeared to be a logical choice in the adjuvant therapy for high-risk rectal carcinoma. The therapeutic benefit was confirmed in two randomized studies using postoperative chemotherapy and pelvic irradiation both demonstrated statistically significant improvement in disease control and survival.[3,4] Most studies compared either preoperative or postoperative irradiation to surgical controls. Only Pahlman and Glimelius designed a study comparing the two schemes of radiation therapy and it showed the superiority of preoperative radiation over postoper-ative radiation.[10] Preoperative radiation therapy is especially advantageous in un-resectable or borderline resectable tumors. It can sterilize the margins of the tumor and improve resectability.[6] The main criticism about preoperative radiation therapy are the lack of a pretreatment clinical staging system for selecting the appropriate patients, and the potential of over-treatment of early tumors which were cured by surgery alone. However, certain tumor characteristics like tumor adherence, tumor size, and tumor grade can identify the high-risk subgroups, which will benefit from preoperative radiation. The prognostic significance of tumor mobility has been demonstrated in the clinico-pathlogical review of 824 patients in the British Medical Research Council study.[5] The curative resection rate was 44% for the tethered or fixed tumors versus 80% for the mobile tumors. The 5-year local disease-free rates were 37% and 70% respectively.

In a randomized study comparing preoperative radiation with combined modality treatment 200 patients with T2/3 & resectable T4 rectal cancer were treated with either preoperative radiation alone or sequential 5FU infusion followed by 34.5 Gray. No significant differences were observed in local control or survival between these two groups.[11] However, this may be the result of sub-optimal study design, low dose of radiation employed and not allowing tumor regression before resection, thereby, masking any potential difference in preoperative radiation versus combined modality treatments. Vauthy et al compared preoperative radiation with combined modality treatment for locally advanced rectal cancers and showed, that pathological down staging increased from 42 to 58% and also that 1,3 & 5 year overall survival rates improved significantly in the combined modality group[6]. Other authors using concurrent irradiation and chemotherapy reported relatively favorable local recurrence rate of 11-

20%.[12-14] Janjan et al[15] evaluated the response to a concomitant boost given during standard chemo-irradiation for locally advanced rectal cancers. In this trial toxicity rate were comparable and improvements were seen in sphincter preservation (79% versus 59% P-0.02) and down staging (86% versus 62% P-0.003) compared to the conventional fractionation (45 Gy, 1.8 Gray / fractions).

In our study the objectives were to see resectability rate, local control and acute toxicity with preoperative chemo-irradiation. There were 13 patients with median age of 54 year, ECOG performance status of 1 & 2, and locally advanced rectal cancers. With preoperative chemo-irradiaton 92.30% had curative resection with negative margins. In one patient margins were microscopically positive, who later on developed local recurrence. This curative resectability is better than the resectability rate (44%) for tethered tumors.[5] Using comparable selection criteria, tumor adherence or fixation to an adjacent structure, curative resectability rate of 90% with preoperative 5-fluorouracil, leucovorin (200 mg/m^2/day) and 5040 cGy whole pelvic radiation therapy in unresectable rectal carcinoma was reported. This curative resection rate was superior to their historical results of 64% with preoperative irradiation alone.[16] Similarly another study reported improvement from 34% to 71% in tumor resectability when chemotherapy was added to preoperative irradiation in the treatment of unresectable adenocarcinoma of rectum[17] For preoperative irradiation alone, Mendenhall et al[18] reported a complete resection rate of 48% after 3600-6000 cGy of radiation in unresectable carcinoma. Dosoretz et al had a curative resection rate of 48% after 40-45 Gray.[19] There appears to be improvement in curative resectability, from 48-64% to 90%, when concurrent chemotherapy is added to preoperative radiation therapy.

Clinical down staging measured by reduction in size or increase in mobility showed no complete response and while 84% patients showed partial responses. Valentini et al treated patients with extra-peritoneal adenocarcinoma of the rectal with preoperative chemoirradiation and showed no complete response clinically and a partial response of 77% and no change in 23% patients.[20] Chen et al treated 24 patients with fixed rectal cancer (stage $\geq$ T3) were treated with preoperative chemo-irradiation showed a clinical down staging in 23 patients (74%).[21] In our study, high frequency of clinical down staging could be explained by less accurate methods of clinical staging employing digital rectal examination and CT/MRI scans and lack of availability of trans-rectal ultrasound.

Two patients (15%) in our series had no residual tumor found in the resected specimen (T0N0M0) and tumor shrinkage and necrosis in 9 patients (69%) who underwent resection. Only 5 patients (38%) were positive lymph nodes found. This is closer to 40-45% lymph node involvement for tethered rectal cancer in British Medical Research Council review of 824 patients.[5]

This pathological down-staging phenome-non after preoperative chemoradiation or radiation has also been reported by other authors: Minsky et al. (20% T0N0, 30% node-positive),[6, 22] Mohiuddin et al (9% T0N0, 27% node-positive),[23] Horn et al (4.4% T0N0, 18.4% node-positive),[24] Haghbin et al. (12.5% T0N0, 26.5% node-positive),[25] Alexander et al (4% T0N0, 15% node-positive),[12] Chen et al (10% T0N0, 23% node-positive)[21]. The analysis of the data in these series indicate rate of pathological complete response equal to 5-20%.

In different studies prognostic value of down-staging had been proved and its results in improved local control and survival. Marie Christine et al[26] treated 88 patients with non-metastatic T3/4 rectal cancer with pre-operative irradiation. Patients who underwent down staging ($_P$T0-T2 N0) successfully, had significantly higher cancer specific survival rates than the group without down staging, 100% & 45% at 5 years respectively (P = 0.011) and 5 year recurrence free survival rates were 94% for the group with down staging and 50% for the group without (P= 0.002). The Swedish rectal cancer trial[27] including 1168 patients, which compared surgery alone to pelvic irradiation (25 Gray in 5 fractions in 5-7 days), followed by surgery 1 week later. After a 5-year follow-up, a significant reduction of local relapse rate was observed, 27% for surgery alone versus 11% for preoperative irradiation (P < 0.001). The overall 5-year survival rates were higher in the irradiation group as compared to surgery alone, 58% & 48%, respectively (P=.004).

During our treatment no hematological toxicity was observed, while two major non-hematological toxicities (National Cancer Institute toxicity criteria) were diarrhea grade 4 (15%), diarrhea grade 2-3 (38%) and erythema (46%). In the study of Valentine et al[20] 83 patients with extra peritoneal T3 rectal

cancer were treated with pre-op chemoirradiation, using IV bolus mitomycin 10 mg/m^2 , day1 plus 24 hour continuous infusion IV 5Fluorouracil 1000 mg/m^2 , days 1- 4 and concurrent external beam radiotherapy (37.8 Gy). The incidence of acute toxicity during chemo-irradiation was low, 12 patients (14%) had grade 3-4 toxicity. There was higher incidence of grade 3 hematological toxicity (10%) while grade 3 diarrhea was recorded in 2 patients. No patient had major skin or urological acute toxicity.

In various studies, toxicity varied according to the method of 5-Fluorouracil delivery. Diarrhea had high incidence in the bolus series of Grann et al[28] and of Chari et al[29] (16% and 19% respectively). In our series grade 2-3 diarrhea occurred in 38% and grade 4 in 15% of cases when compared with the continuous infusion series of Rich et al[30] and Valentine et al[20] (1% and 2% respectively). Hematological toxicity was lowest with bolus form as in our study (0%) in contrast to higher incidence with bolus form as recorded in the series of Grann et al[28] and Chari et al[29] (12% and 14% respectively). In our study, high frequency of diarrhea was related to bolus form and high dose of 5-flououracil and, high incidence of erythema was due to low-lying tumor requiring abdomino-perineal resection and inclusion of perineum within radiation field.

With a median follow-up of 7 month, 2/13 (15.38%) patients in our study, recurred locally comparable to reported local recurrence rate of 11-20% for locally advanced carcinoma of rectum.[11-13] Follow-up was too short to comment about disease free survival and overall survival.

CONCLUSION

Concomitant preoperative chemoradiation for locally advance rectal cancer is associated with considerable clinical and pathological down staging. Tumor resectability is improved with potential for improved local control and survival and is relatively safe with acceptable morbidity.

Our recommendation is that pre-operative chemo-irradiation should be used for partially fixed or fixed carcinoma rectum to improve resectability and local control. The concurrent 5Fluorouracil dose should be lowered to 500mg to reduce non hematological toxicity.

Availability of trans-rectal ultrasound in preoperative clinical staging is excellent in detecting degree of primary tumor penetration and fair to good in detecting lymph node metastasis as well as response to therapy. However, non availability of this procedure was badly missed during this study.

ACKNOWLEDGMENT

We are thankful to God and to our supervisor Dr. Shahid Hameed and consultants Dr. Mazhar Ali Shah and Dr. Muhammad Furrukh for their directions and corrections in the paper.

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