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OriginalArticle

Outcome of Adjuvant Concurrent Chemo-Radiation in Operated Locally Advanced Rectal Cancer

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Abstract

Background: *Rectal cancer is one of the most common cancers in Kashmir, India. The clinical course of patients treated with surgery alone has been characterized by a high death rate and also by the pain and disability associated with pelvic recurrence of the tumor. Adjuvant radiation combined with chemotherapy has been studied for prevention of such recurrences. We treat more than 200 rectal cancer patients annually at our center. Most of the patients registered at our center are those who have been already subjected to surgery at the peripheral hospitals. We studied role of 5-fluorouracil (5-FU) and calcium leucovorin concurrently with radiotherapy in Dukes' stage B2 and C and toxicities thereof in the adjuvant setting.* ***Objective****: To assess the outcome of concurrent chemoradiation in operated locally advanced treated cancer patients.* ***Materials and Methods****: In operated Dukes' B2 and C rectal cancer patients, we conducted a prospective non-randomized study comprising of 40 patients between 2012 and 2014. Patients were treated with two hours protracted infusion of calcium leucovorin 500 mg/m^2 on day 1 followed by 5-fluorouracil 500 mg/m^2 on days 1 to 5 and repeated four weekly for total of six cycles. Radiotherapy of 45 Gray in 20 fractions was delivered concurrently with chemotherapy for first two cycles.* ***Results****: Combination of chemotherapy and radiotherapy in a concurrent setting appears to be more efficient in reducing local recurrence rates and improving survival than either modality alone. Toxicities with this schedule were mostly gastrointestinal mucositis, but no treatment interruption was needed.* ***Conclusion****: A combination of 5-fluorouracil and radiotherapy can be administered in operated locally advanced rectal cancer patients.*

Key words*: Rectal cancer; 5-fluorouracil; Adjuvant; External beam radiotherapy*

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Introduction

Rectal cancers have a high local recurrence rate ranging from 2.6 to 47%, even after curative resection.[1] Tumor recurrence has been seen to correlate with stage, the number of metastatic lymph nodes, meso-rectal tumor spread, mucinous histology, lympho-vascular invasion and the distance of distal margins of resection.[2] Rectal tumors resected with close margins are especially prone to recur locally. Approximately 8% of Dukes' (A), 25-30% of Dukes' (B) and nearly 50% of Dukes' (C) develop pelvic recurrence after surgical resection.[3] The incidence of local recurrence of tumors with negative nodes and only microscopic extension through wall is

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17% and it increases to 54% in tumors adherent to or invading adjacent organs and structures.[4] The areas of greatest risk for tumor recurrence are the pre-sacral space, pelvic side walls and soft tissue anterior to rectum. Addition of adjuvant radiation has significantly decreased loco-regional recurrences but local failures are still posing a big challenge to the oncologists. Chemotherapy combined with radiation as a radiosensitizer has been studied at many centers. It is also being increasingly used to facilitate a sphincter saving procedure in low-lying cancers. An optimal combination of chemo-radiotherapy for rectal cancer does not exist. A critical review of the literature shows that the superiority of chemo-radiation over radiation alone is weak or lacking. There is a great need for more conclusive study designs and a more rational explanation of drug-radiation interaction prior to clinical testing.[5] At our center we have been treating large number of patients with locally advanced rectal cancers with adjuvant chemotherapy and radiotherapy in a sequential manner but so far have not studied concurrent chemoradiation in our setting. To our knowledge, this study is the first of its kind in Jammu & Kashmir state of India.

Materials and Methods

Between 2012 and 2014, forty operated Dukes' B2 and C rectal cancer patients were recruited in this prospective nonrandomized study. All the patients studied in this trial had histological documentation of adenocarcinoma with computed tomography (CT) scan of abdomen and chest ruling out any lung or liver metastasis. All patients underwent a potentially curative resection with no gross or microscopic evidence of any residual disease (R0 resection). Concurrent treatment was started within six weeks after surgery conducted after a valid consent. The study was reviewed and approved by the ethical committee of our institution. Patients were started on two hours protracted infusion of calcium leucovorin 500 mg/m^2 on day one followed by 5-fluorouracil 500 mg/m^2 as a protracted infusion for two hours. 5-fluorouracil was instituted for 5 days a week. The chemotherapy was continued for a total of six cycles at an interval of four weeks. Radiation therapy was delivered by Cobalt-60 teletherapy unit by standard parallel opposed portals to a mid plane dose of 45 Grays for 4 weeks (five fractions per week). 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.[6] 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, serial serum CEA levels, chest radiography and yearly magnetic resonance imaging of abdomen and pelvis.

Results

Only 40 patients were eligible as per the predefined inclusion criteria which included pathological stages American Joint Committee on Cancer (AJCC) IIB and III, Eastern Cooperative Oncology Group (ECOG) performance score of less than or equal to 2, normal hemogram, liver function tests, kidney function tests, surgery done within six weeks, written informed consent from the patient, no significant associated comorbidity, no evidence of distant metastasis as defined by a CT scan of chest and abdomen, and patients not having received prior chemotherapy or radiotherapy. Majority of the patients (52.5%) were aged less than or equal to 50 years with a male preponderance (male to female ratio of 1.35:1) (Table I). Most common presenting symptoms of patients were bleeding per rectum (80%) and constipation (45%). Thirty one (77%) patients had growth located more than 5 cm above the anal verge. Low anterior resection was performed in 20 (50%) patients and abdominoperineal resection was done in 17 (42%). Transrectal excision was performed in only 3 (7%) cases.

Table I: Patient characteristics (N=40)

Age	⩽ 50	21
	> 50	19
Sex	Males	23
	Females	17
Stage (AJCC)	II B	6
	III A	10
	III B	19
	III C	5
Surgical intervention	LAR	20
	APR	17
	Transrectal	3
Types of lesions on DRE	Stenotic	12
	Polypoid	21
	Ulcerative	7
HPE differentiation	WD	27
	MD	10
	PD	3

Since all patients were operated, accurate histopathological staging was available along with histopathological differentiation. Most of the patients (28, 70%) had well differentiated cancers on histology. Moderately differentiated and poorly differentiated tumors were found in 10 (25%) and 2 (5%) patients respectively. Staging was done as per AJCC. Thirty four (85%) patients were having node positive disease (stage III), 6 (15%) patients had stage II disease (Table I). In nine (23%) patients disease was within 5 cm of anal verge, and in the rest 31 (77%) the disease was high up. Low anterior resection was the procedure performed in 20 (50%) cases, abdominoperineal resection (APR) in 17 (42.5%) and transrectal excision in 3 (7.5%) patients.

Treatment was well tolerated by majority of patients. In 5 patients treatment was interrupted because of toxicity (3, lower GI; 2, cardiac). Six patients required dose modification. Lower gastrointestinal toxicity (Table II) in the form of diarrhea was the commonest toxicity related symptom which was managed conservatively by antidiarrheals, antispasmodics and steroids. During chemo-radiotherapy, asymptomatic bradycardia was unexpectedly found in 15 (37.5%), while 2 patients developed chest pain. All these patients were followed with extensive cardiac monitoring including troponin T test and echocardiography to rule out any myocardial ischemia or cardiac dysfunction. In all patients bradycardia was reversible after chemotherapy was stopped and thus the treatment schedule was completed without any interruption. In all patients, 12 events of febrile neutropenia after chemotherapy were recorded. All these patients were admitted in indoor hospital wards and were managed successfully with antibiotics and other supportive measures.

Table II: Toxicity with the treatment schedule

	Toxicity	Number	%
Mucosal toxicity	Mucositis grade 3	5	12.5
	Mucositis grade 4	3	7.5
Cardiac toxicity	Asymptomatic bradycardia	15	37.5
	Chest pain	2	5
Hematological toxicity	Febrile neutropenia	12	37.8
	Anemia	12	54.1
	Thrombocytopenia	03	8.1
Cutaneous toxicity	Skin pigmentation	04	10.8
	Onycholysis	03	8.1
	None	30	81.1

During a follow-up of 3 years 22 (55%) patients have been disease free, 12 patients (30%) relapsed (locoregional, 7 and distant, 5). Out of these, 4 patients recurred at local anastomotic site or perirectal area and 3 recurred in regional nodal areas. Lung (2 cases) and liver (2 cases) were the only sites of relapse among distant sites. In one patient, recurrence was found at both nodes and liver. After completion of treatment, 6 patients were lost to follow-up and could not be traced for evaluation.

Table III: Survival data (3-year follow-up)

Parameters		Number
Relapse free		22
Relapse (12)	Local	4
	Nodal	3
	Lung	2
	Liver	2
	Liver and Nodal	1
Died		8
Disease related		6
Disease unrelated		2
Lost to follow–up		6

During follow-up, eight (20%) patients were recorded dead in our study. Six (15%) patients died of disease (2; locoregional, 3; distant failure; 1; local and distant metastasis) and one patient of the complications of diabetes mellitus type 2. Nodal metastasis was a significant predictor of both locoregional as well as distant failures.

Discussion

The management of rectal cancer has evolved from surgery alone to surgery with adjuvant and neoadjuvant treatment to present-day targeted therapies. Significant advances have been made in the study of rectal cancer over the last two decades and a more thorough understanding of the molecular basis of this disease, coupled with the development of new therapeutic approaches has dramatically altered the way in which patients are managed.[7] Although, surgery is the treatment of choice for rectal cancer, local recurrence is common even after apparently curative resection.[8] Clinical approach at adjuvant therapy for rectal cancer began more than 35 years ago and has involved numerous trials enrolling several thousand patients treated with

cytotoxic drugs, non-specific immune stimulants to various combination thereof.[9] Addition of chemotherapy to radiation is intended to decrease local recurrence and meanwhile control distant relapses. In North Central Cancer Treatment Group (NCCTG) trial[10], there was a 46% reduction in the pelvic recurrence, a 37% reduction in distant tumor spread and 29% reduction in patient deaths and the study confirmed the benefit achieved with chemotherapy when combined with irradiation. In our study after a follow-up of 3 years, 22 (55%) patients were disease-free which is comparable to most studies using concurrent adjuvant chemoradiation. In 12 patients, relapse was recorded (Table III) and most recurrences were locoregional (locoregional, 7; distant, 4 and locoregional with distant metastasis or spread, 1). None of the patients in the study group had undergone total mesorectal excision which could be the possible explanation for comparatively higher loco-regional failure rate.

A study was conducted by Conell & co-workers in 1986 to determine the outcome of protracted venous infusion (PVI) of 5-fluorouracil concurrent with radiation vis-à-vis bolus 5-fluorouracil and radiation with a median follow-up of 46 months of 686 patients with Dukes' B and C stage operated rectal carcinoma patients, those who received PVI during pelvic radiation had significantly increased time to relapse (p=0.01) and improved survival (p=0.005).[11] Although radiation therapy decreased local recurrence in one half of patients, it was the addition of 5-fluorouracil based chemotherapy that further decreased local recurrence to approximately 10–12% and is the agent responsible for increasing overall 5 years survival rates by about 10–15%.[12]

In a randomized trial involving 144 cases in Norway, patients were randomized to postoperative radiation plus bolus 5-fluorouracil (500 mg/m^2) day 1–2 of week 1, 2 and 3 of radiation versus surgery alone. Despite the fact that 5-fluorouracil was delivered with a radiosensitizing dose rather than dose adequate to treat systemic disease this combined modality therapy regimen significantly decreased local recurrence by 18% (p=0.001) and improved 5-year survival by 14%.[13] Although the results with limited doses of 5-fluorouracil are encouraging, additional experience with this approach is needed before modifying standard regimen.

In a Gastrointestinal Tumor Study Group (GITSG) trial, 227 patients with stage B2 and C rectal cancers were randomly allocated to receive: (i) no postoperative treatment, (ii) chemotherapy alone, (iii) pelvic radiotherapy or (iv) combined chemotherapy and radiation. After a median follow-up in excess of 10 years, the combined modality was found superior to surgery alone in terms of disease-free survival (65% versus 45%; p=0.006) and overall survival (45% versus 26%; p=0.04).[14] Although patients given combined modality had a greater likelihood of remaining free of recurrence than those treated with radiation alone or chemotherapy alone, these differences were not statistically significant.

The superiority of chemo-radiotherapy over radiation alone was confirmed in a subsequent study by the North Central Cancer Treatment Group which randomly assigned 240 patients with stages B2 or C rectal carcinoma to receive either postoperative radiotherapy alone (45Gy) or combined chemotherapy and radiation. After a median follow-up in excess of seven years the combined modality therapy was clearly superior, reducing the overall probability of recurrence rate by 46%, the likelihood of developing distant metastasis by 37% (P=0.04) and the mortality rate by 29% (p=0.003).[14]

Post-operative chemo-radiotherapy was the recommended standard therapy for patients with locally advanced rectal cancer.[15] In a randomized study conducted by Sauer and co-workers to assess the overall regimen vis-a-vis pre-operative and post-operative adjuvant treatment in rectal cancer, 421 patients were randomly assigned to receive pre-operative chemo-radiotherapy and 402 patients to receive post-operative chemo-radiotherapy. The overall 5-year survival rates were 76% and 74% respectively; cumulative incidence of local relapse was 6 percent for patients assigned to pre-operative chemo-radiotherapy and 13% in post-operative chemo-radiotherapy group. Grade III and IV acute toxic effects occurred in 27 patients in the pre-operative treatment group as compared with 40% of the patients in the post-operative treatment group; the corresponding rates of long term toxic effect were 14% and 24% respectively (p=0.0001). Pre-operative chemo-radiotherapy as compared with post-operative chemo-radiotherapy improved local control and was associated with reduced toxicity but did not improve overall survival.[16]

A study was conducted by E Krook et al[10] to optimize the contribution of chemotherapy, decrease the local recurrence and improve survival with adjuvant radiation alone. Two hundred and four patients (with rectal cancer that was either locally advanced or metastatic to regional nodes) were randomly assigned to post-operative radiation alone or to radiation plus 5-fluorouracil – both were preceded and followed by a cycle of systematic therapy with 5-fluorouracil plus methylchloro-ethylcyclohexylnitrosourea (MeCCNU). After a median follow-up of more than seven years, the combined modality treatment had overall recurrence rate reduced by 34%, local recurrence was reduced by 46% and distant metastasis by 37%. In addition, combined therapy reduced the rate of cancer related deaths by 36%. Its acute toxic effects included nausea, vomiting, diarrhea, loss of appetite whereas delayed treatment related reactions like small bowel obstruction requiring surgery occurred in 6.7% of all patients receiving radiation and the frequencies of their complications were comparable in both treatment groups. The combination of post-operative therapy with radiation plus a 5-fluorouracil based regimen significantly and substantially improves the results in rectal carcinoma patients as compared to post-operative radiation alone.[10]

A randomized study was conducted by Fisher et al[15] to assess the benefits of adjuvant chemotherapy and radiotherapy in operated rectal cancer patients. Patients were randomized to receive any of three measures– radiotherapy, chemotherapy or no further treatment. Their average time of study was 64.1 months. The chemotherapy groups when compared with the group treated by surgery alone demonstrated an overall improvement in disease-free survival (p=0.006) and in overall survival (p=0.08). When the group receiving post-operative radiation was compared to the group treated only by surgery, there was an overall reduction in locoregional recurrence from 25% to 16%. No significant benefit in overall disease-free survival or survival from the use of radiation was demonstrated. In conclusion, the study demonstrated a benefit of adding adjuvant chemotherapy in the treatment of operated rectal cancer; post-operative radiation therapy although reduced the incidence of locoregional recurrence but it failed to affect overall disease-free survival.[15]

In yet another study Mimsky and co-workers compared the combined chemo-radiotherapy regimens of two separate parallel phase I trials to determine if combined pelvic radiotherapy, 5-fluorouracil and high dose leucovorin had less toxicity when delivered pre-operatively versus post-operatively in patients with rectal cancer. In this study patients with unresectable disease received pre-operative radiotherapy plus 5-fluorouracil and leucovorin followed by surgery and post-operative leucovorin and 5-fluorouracil. Patients with resectable disease received identical doses, techniques and schedules of radiotherapy and leucovorin and 5-fluorouracil except that the treatment was delivered post-operatively. Although more patients in the pre–operative group (75% versus 32%; p=0.02) received the higher doses level of 5-fluorouracil (250 mg/m^2), significantly fewer experienced acute grade 3–4 toxicity (13% versus 48%; p=0.045). There was no grade 3–4 myelosuppression in either group. The two grade 3 toxicities in the pre-operative group were gastrointestinal. The grade 3 toxicities in the post-operative group included severe gastrointestinal and genitourinary symptoms;[4] patients had grade 4 toxicity. Due to the high incidence of grade 3 and 4 toxicities reported in the post-operative combined modality group exploration of preoperative modality was suggested.[17]

In a randomized phase III trial by Sauer and co-workers to assess the efficacy of pre-operative versus post-operative radio-chemotherapy as regards to toxicity and post-operative morbidity patients with locally advanced operable rectal cancer were randomly assigned to pre- or postoperative radio-chemotherapy. The toxicity profile in both the groups was comparable. Post-operative complication rates were similar in both arms with 12% (post-operative radio-chemotherapy) and 13% (pre-operative radio-chemotherapy). The results of this trial were reported to be satisfactory and neo-adjuvant radio-chemotherapy was well tolerated and there was no higher risk as far as post-operative morbidity was concerned.[18]

From the findings of our study we can conclude that as a reference treatment a combination of 5-fluorouracil and radiotherapy can be advocated in locally advanced rectal cancer patients who have been subjected to surgery; but the mode of administration of 5-FU whether bolus or protracted infusion warrants further study.

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