

Patient profile and treatment outcome of rectal cancer patients treated with multimodality therapy at a regional cancer center

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Abstract

BACKGROUND: Incidence of rectal cancer has wide geographical variation. Disease pattern in developing countries is different from developed countries as majority of the patients present in advanced stage because of delayed referral and lack of uniform treatment practices. **AIMS:** Present study describes the patient profile and treatment results from a tertiary care cancer center in India. **SETTING AND DESIGN:** Tertiary care Regional cancer center. Retrospective analysis 89 patients with rectal adenocarcinoma treated between 1995 and 2002 were analyzed. **METHODS:** Patients with adenocarcinoma rectum were evaluated in a G.I. Oncology clinic and were treated using multimodality protocols involving surgery, radiotherapy and adjuvant chemotherapy. **STATISTICAL ANALYSIS:** A descriptive analysis of patient and disease profile, treatment patterns and out come was performed. Survival analysis was performed using Kaplan-Meier method. **RESULTS:** Mean age of the patients was 45.4 years and majority of them had tumor in lower third of rectum with evidence of extrarectal spread. Seventy five percent of the patients underwent curative resection with abdominoperineal resection being the commonest procedure. Forty seven percent of patients were given short course preoperative radiotherapy and the remaining received postoperative radiotherapy. Sixty four percent of patients could complete planned adjuvant chemotherapy. Operative mortality was 2% and 23% had morbidity. Local recurrence rate was 8.9%. 5-year disease free and overall survival was 54% and 58% respectively. **CONCLUSION:** Majority of rectal cancer patients present with locally advanced and low rectal growths leading to low sphincter salvage rates. Despite the advanced stage of presentation optimal oncologic results can be obtained by using a good surgical techniques in combination with adjuvant radiotherapy and chemotherapy. Short course preoperative radiotherapy seems to be more feasible in Indian context. Timely referral and uniform treatment guidelines throughout the country are needed for optimal management of rectal cancer in India.

Key Words: Autonomic nerve preservation (ANP), Rectal cancer, Short course preoperative radiotherapy, Sphincter salvage, Total mesorectal excision (TME).

Introduction

Rectal cancer is one of the most frequently diagnosed GI cancers having a high disease related mortality in the

western part of the world, although in eastern regions it is one of the low incidence cancers not ranking among the first ten.¹⁻⁵ Adenocarcinoma is the most common type of rectal malignancy responsible for more than

90% of the cases. In a country like India with a large population, despite the low incidence of rectal cancer, absolute number of cases is estimated to be high. Because of delayed diagnosis and referral from peripheral parts of the country, majority of the cases present in a locally advanced stage. In addition there also exists lack of uniform treatment practices.

Although surgery is the main stay of treatment, radiotherapy (RT) and chemotherapy (CT) play a vital role, particularly in locally advanced tumors. There have been significant changes in the nature of this multimodality management over the last two decades leading to improved disease free as well as overall survival. Important surgical issues related to local control of tumor and quality of life also have undergone considerable changes. Standardization of total mesorectal excision (TME) with autonomic nerve preservation (ANP) has resulted in better quality of life. Improvements in stapling techniques and newer preoperative CT and RT protocols have led to a higher rate of sphincter preservation.

There is a paucity of literature regarding incidence, patient profile, treatment patterns and outcome of rectal cancer in India. In this study we present the results of 89 consecutive cases of adenocarcinoma, rectum treated at a tertiary care regional cancer center.

Materials and Methods

Retrospective analysis of data of a total of 89 cases of rectal adenocarcinoma (from a prospective rectal cancer database) treated between 1995 and 2002 were analyzed. All patients were evaluated in the Gastrointestinal Oncology clinic by a team of Surgical, Medical and Radiation Oncologists and underwent treatment according to the protocols designed by the same team. Only the cases with histological evidence of adenocarcinoma (established through proctoscopic or sigmoidoscopic biopsy) were included. Apart from routine investigations, preoperative staging evaluation was done through chest X-ray, CECT of abdomen and pelvis with trans-rectal / trans-vaginal ultrasound in some cases where doubtful involvement of adjacent organs was found on CECT.

As per the protocol all the patients with Astler-Coller stage B2 and above were given postoperative RT (45 grays/25#/over 5 weeks) and adjuvant chemotherapy till 1998. During the later period all operable rectal cancer patients were treated with short course preoperative RT (25 grays / 5# / over 5 days) with a gap of 10-14 days between RT and surgery.

All patients underwent exploratory laparotomy under general anesthesia and if deemed operable, resection of tumor with total mesorectal excision and preservation of autonomic nerves was done. In patients with metastatic disease and locally advanced inoperable growth, a diversion colostomy was made when there were features of impending obstruction. Sphincter salvage was attempted in tumors of upper third (11-15 cms from anal verge) and less bulky middle third tumors (6-11 cms from anal verge). In sphincter preservation operation (anterior resection / low anterior resection) colorectal anastomosis was made either manually or with staplers (double stapling technique). For tumors in lower third of rectum (up to 5 cms from anal verge) and bulky middle third tumors, abdominoperineal resection with permanent sigmoid colostomy was done. A minimum of 1 cms distal and 5 cms proximal margin was attempted in all patients. No attempts for ultra low resection were made in view of locally advanced disease in majority of the patients. After curative surgery, all patients with Astler-Coller stage B2 and C were referred for adjuvant chemotherapy comprising 5-FU based regimes. After completion of treatment, patients were followed up in clinic every 3 months with clinical examination, chest Xray, and liver function tests and annual colonoscopy during first 2 years. Imaging investigations (CECT/ USG) were done in cases with clinical suspicion of recurrence. Follow up CEA levels were done in patients with documented preoperative levels.

The collected database was analyzed using SPSS-9 (SPSS Inc. Chicago). Disease free and overall survivals were estimated using Kaplan-Meier method.

Results

Of the 89 patients 61 were male and 28 female (M/F: 2.1). Mean age of the study population was 45.4 years, (range: 18-88 years). Patients presented usually with bleeding per rectum (88%), altered bowel habits (47%), painful defecation (32%) and abdominal pain (12%). Mean duration of symptoms was 7.3 months. On per rectal examination, growth was felt in 81% of patients with mean distance of growth from anal verge being 4.02 cms. In 88% of the cases, tumor was located in lower and middle third rectum. On imaging 54% of the patients had evidence of extra-rectal or nodal involvement. Twenty one percent of the patients had undergone some form of treatment (Surgery/CT/RT) before presenting to our center with diversion colostomy being the most common procedure.

Sixty seven patients (75.2%) underwent curative surgery

and in rest of the 22 patients exploratory laparotomy with or without a palliative colostomy was done because of evidence of either metastatic disease or extensive loco-regional spread of tumor.

Types of surgical procedures performed are shown in Table-I. Stage distribution in 64 out of 67 surgically resected patients is shown in Table-II. Three patients receiving preoperative radiotherapy had complete pathological response hence they could not be staged surgically. Only one out of 67 (1.5%) resected patients had positive tumor margin. Twelve patients (18%) with locally advanced disease required extended resection including one or a combination of the following organs - uterus, vagina, ovary, seminal vesicle, presacral fascia. Adjuvant chemotherapy was offered to 56 patients with stages B2 and above. However only 43 (64%) patients could complete planned adjuvant chemotherapy and the remaining could not receive/ complete the therapy because of poor compliance, chemotoxicity or cost factors. A total of 64 (72%) patients received radiotherapy. Forty two patients (47.2%) had received

short course preoperative RT and 22 (25%) patients had undergone postoperative RT during the initial part of study.

Postoperative mortality occurred in two patients (2.2%). Postoperative morbidity occurred in 21 (23.5%) patients. Majority of the immediate complications were wound infections, others being prolonged ileus, hemorrhage and dehiscence of the wound. Late morbidities included adhesive intestinal obstruction and paracolostomy hernia and colostomy prolapse. Two patients each (3%) had impotence and urinary incontinence in the curatively treated group.

Median follow up period was 34 (10 -104) months. A total of 13 (19.4%) curatively treated patients had relapse of disease of which 6 patients (8.9%) had local relapse while another 6 (8.9%) had systemic relapse. One patient had both local and systemic recurrence. On Kaplan-Meier analysis, median 5-year disease free survival for curatively treated population was 54% (Figure 1), while 5-year overall survival for the entire study population was 58% (Figure 2). At our last follow up, 48 patients were alive and disease free, 12

Table 1: Showing Various Surgical procedures

Procedures	Number (%)
Exploratory laparotomy with / without	22 (24.7)
Diversion colostomy	
Abdomino-perineal resection	45 (50.6)
Low anterior resection / Anterior resection (Sphincter Salvage)	15 (16.8)
Total / posterior pelvic exenteration	5 (5.6)
Total proctocolectomy	2 (2.3)

Table 2: Showing stage distribution in 64 surgically resected rectal cancer patients

Astler-Coller stage	Number (%)
Stage - A	1 (1.6)
Stage - B1	7 (10.9)
Stage - B2	29 (45.3)
Stage - C1	1 (1.6)
Stage - C2	26 (40.6)

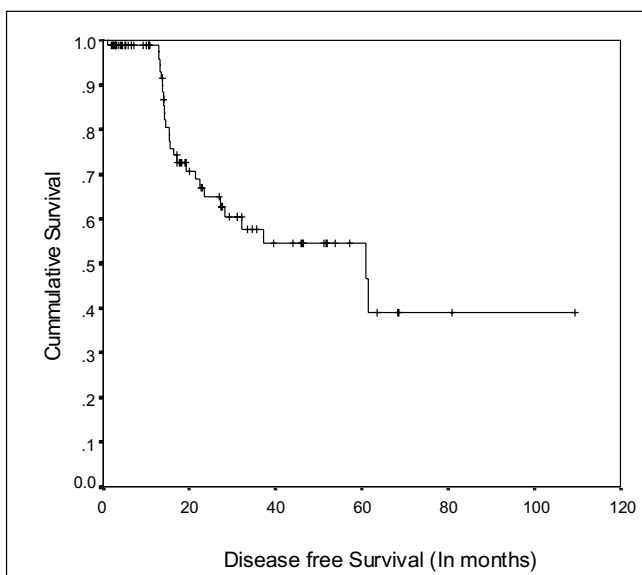


Figure 1: Figure showing disease free survival of rectal cancer patients.

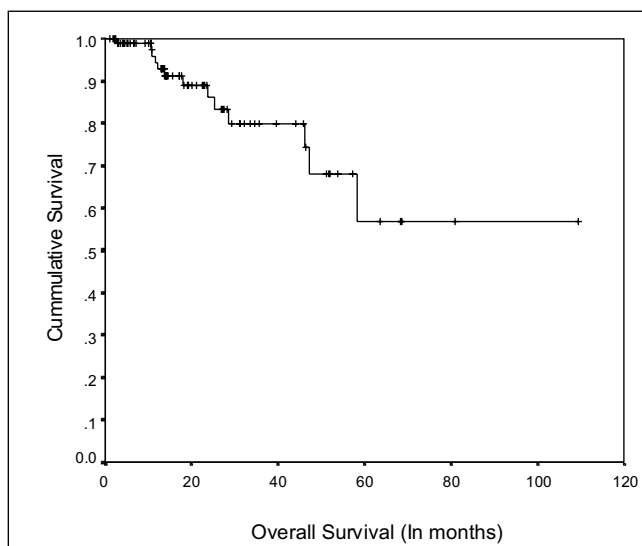


Figure 2: Figure showing the overall survival of rectal cancer patients

were alive with disease and 29 were reported to have died.

Discussion

Rectal cancer is one of the most frequently diagnosed cancers of the GI tract in the western world, ranking among the first ten as the cause of GI cancer related mortality according to SEER data in USA.¹ Incidence of rectal cancer in western countries varies between 12-14/100000 population². Incidence of rectal cancer in Asian countries is low and the reported incidence of rectal cancer in India varies from 4 to 5/100000 population.^{3,4,5} Mean age of rectal cancer patients described in western studies generally ranges between 60 to 70 years,⁵ whereas the mean age of the rectal cancer patients in this study was 45.4 years. Observational bias due to skewed distribution of Indian population might be responsible for this difference. Mean duration of the symptoms was 7.3 months; suggesting delayed primary presentation because of lack of awareness as well as delayed referral by primary and secondary level care centers. A high number of cases had locally advanced or metastatic growths signifying the lack of any screening programs as well as delayed diagnosis. Many of the patients with rectal cancer were treated as hemorrhoids before being referred to cancer center. This is in contrast to the situation in western part of the world where organized screening programmes have contributed significantly to detection of majority of the cases at an early stage. Many patients had also been treated inadequately with various modalities prior to referral, a fact stressing the requirement of uniform treatment policies for rectal cancer in different parts of the country.

The rate of sphincter preservation in this study (22.3%) is lower compared to usually reported in literature (40-70%),⁶ reflecting that most of the tumors were located in the lower part of rectum with advanced stage of presentation. To avoid a high rate of local recurrence in patients with low and bulky rectal cancers, sphincter salvage was not attempted in borderline cases in this series. Recently the role of preoperative chemo and radiotherapy in increasing the rate of sphincter preservation is being explored in some centers.⁷ However the experience with such protocols is limited and there is a need for further larger studies. In addition a significant number of patients in the current series required extended resections including, exenterations in 5.6% of patients to achieve an R0 resection.

After the introduction of concepts of total mesorectal

excision (TME) by Heald⁸ in 1979, technical aspects of radical surgery for rectal cancer have undergone significant changes with stress on sharp dissection outside endopelvic fascia under direct vision, which ensures relatively bloodless plane and a specimen with intact mesorectum and negative circumferential tumor margins. Several studies have clearly shown the vital role of TME in better local control of tumor.⁹⁻¹¹

Preservation of autonomic nerve plexus (ANP) is essential to prevent sexual impotence and bladder dysfunction. The incidence of impotence and bladder dysfunction following radical surgery for rectal cancer varies from 22-68%, although studies involving TME with ANP report comparatively lower rates.¹²⁻¹⁴ We routinely follow a policy of TME with preservation of autonomic nerves. Despite the high number of locally advanced cases, lower rate of these complications (3% each) in the current series indicates the importance of routine preservation of autonomic nerves.

Although radical surgery is the mainstay of treatment of rectal cancer, radiotherapy has become an integral part multimodality protocols to improve the loco-regional control. It can be given either preoperatively or postoperatively. Most of the centers in North America prefer postoperative RT. It has certain advantages like patients can be selected after histopathological staging is known and it is given when the tumor burden is less after surgical excision. But, it is associated with higher gastrointestinal radiation morbidity because of postoperative bowel adhesions. Many European centers prefer preoperative radiation instead of conventional postoperative radiation. The advantages of preoperative radiation are tumor down staging and sterilization of surgical margins. In addition, radiation is given to well oxygenated tumor cells resulting in a improved radiation response. But, it has disadvantages of overtreating the early tumors and possible alteration of surgical staging in good responders. Swedish rectal cancer trial involving 1168 rectal cancer patients has shown conclusively that short course pre operative radiotherapy (25 Gy/ 5Fr/ 5 days) is highly efficacious in loco-regional control of rectal cancer.¹⁵ We are following the same regime since 1998. We feel that short course regime is more suitable for Indian patients because of shorter duration of therapy leading to better compliance, good loco-regional control and acceptable morbidity.

The rate of local recurrence in this study was 8.9%, despite majority of the patients (87%) belonging to locally advanced stage. Local recurrence rates in Swedish rectal cancer trial and Dutch study were 11% and 8.6% respectively.¹⁵⁻¹⁶ These two series had relatively

more early rectal cancers in comparison to the current series. The overall recurrence rate in the current series was 19.4%. Five year median disease free survival for the curatively treated patients was 54%. Similar figures were reported internationally from other studies for stages B2 and C.¹⁵⁻¹⁷

The role of adjuvant chemotherapy in increasing the disease free as well as overall survival by 10 to 15 % over surgery alone in rectal cancer has been well proven in many studies.¹⁸⁻²⁰ However, the compliance for adjuvant chemotherapy was relatively low in the present study in view of longer duration of therapy and cost factors. There is a need to devise effective low cost short duration chemotherapy protocols for Indian patients.

In conclusion it can be said that presentation of rectal cancer in India is different from western countries with a high propensity for lower third and locally advanced tumors because of delayed referral and misdiagnosis. With careful patient selection and standardized surgical technique (TME & ANP) good results can be achieved using multimodality protocols.

References

- Greenlee RT, Hill-Hannon BM, Murray T, Thun M. Cancer statistics 2001. *CA Cancer J Clin.* 2001;51:15-36.
- Rise LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER Cancer statistics review, 1973-1998. Bethesda (MD): National cancer Institute 2001. p. 1-22.
- Rao DN, Ganesh B. Estimates of cancer incidence in India in 1991. *Indian Journal of Cancer* 1998;10-8.
- Mohandas KM, Jagannath P. Epidemiology of digestive tract cancers in India VI. Projected burden in new millennium and the need for primary prevention. *Indian J Gastroenterol* 2000;19:74-8.
- National Cancer Registry Programme. Biennial report 1988-1989: An epidemiological study. Indian Council of Medical Research, Delhi: 1992. p. 136-7.
- Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, et al. Influence of interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter sparing surgery for rectal cancer; the Lyon R90-01 trial. *J Clin Oncol* 1999;17:2396-402.
- Jacobs L, Kuvshinoff BW, Lin KM. Preoperative 5-FU and radiation therapy increases sphincter preservation rates and improves R0 resection rates for rectal cancer. 55th Proc Soc Surg Oncol 2002.
- Heald RJ. A new approach to rectal cancer. *Br J Hosp Med* 1979; 22:277-81.
- MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993;341:457-60.
- Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 1995;181:335-46.
- Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Eng J Med* 2001;345:638-46.
- Havenga K, Enker WE, McDermott K, Cohen AM, Minsky BD, Guillem J. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. *J Am Coll Surg* 1996;182:495-502.
- Masui H, Ike H, Yamaguchi S, Oki S, Shimada H. Male sexual function after autonomic nerve-preserving operation for rectal cancer. *Dis Colon Rectum* 1996;39:1140-5.
- Maurer CA, Z'graggen K, Renzulli P, Schilling MK, Netzer P, Buchler MW. Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery. *Br J Surg* 2001;88:1501-5.
- Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Eng J Med* 1997;336:980-7.
- Kapiteijn E, Putter H, Van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002;89:1142-9.
- Martling AC, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of surgical training programme on outcome of rectal cancer in the county of Stockholm. Stockholm Colorectal Study Group. Basingstoke Bowel Cancer Research Project. *Lancet* 2000;356:93-6.
- Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, et al. Postoperative adjuvant chemotherapy and radiation therapy for rectal cancer: Results from NSABP protocol R-01. *J Natl Cancer Inst* 1988;80:21-9.
- National Institute of Health consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444-50.
- Wolmark N, Weiland HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project protocol R-02. *J Natl Cancer Inst* 2000;92:388-96.