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Original Research Paper

Radiotherapy

CLINICAL OUTCOME OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CHEMORADIATION IN LOCALLY ADVANCED CARCINOMA OF RECTUM

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ABSTRACT

Introduction: Rectal cancer is the growth of abnormal cancerous cells in the lower part of the colon that connects the anus to the large bowel. Colorectal cancer is the third most common cancer in men and the second in women worldwide.

Materials & Methods: Locally advanced rectum cancer attending the Out Patient Department of Radiotherapy from August 2018 to January 2020, meeting specified Inclusion and Exclusion Criteria, willing to participate in the study were included. The clinical outcome, acute and late side effects, loco-regional control and recurrence of each patient were assessed. **Results:** The characteristic toxicities, and response were assessed using the common terminology criteria for adverse events (CTCAE) version 4.0. After 3 cycles of NACT radiological response was 3.58%, Partial response 78.58%, Stable disease 7.14% and Progressive disease 10.70% and feasibility of surgical resection were 92.90%.

Conclusions: NACT followed by chemoradiation, represent the standard of care. Pre-operative CTRT have greatly lowered the rates of local recurrence.

KEYWORDS : Rectal cancer, Chemoradiation , Chemotherapy

INTRODUCTION:

Colorectal cancer is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women(614,000 cases, 9.2% of the total) worldwide[1].The major symptom of rectal cancer is bleeding from the rectum with altered bowel habits. Family history of colorectal cancer in a first degree relatives, personal history of colorectal adenoma or polyp and relatives of patients with colonic cancers[2]. The impact of genetic risk factors is evident, especially in hereditary conditions, including Familial Adenomatous Polyposis (FAP), and Lynch Syndrome (LS), [Hereditary Nonpolyposis Colorectal Cancer(HNPCC). Personal history of long standing chronic Ulcerotiv colitis or Crohn colitis[3],and Obesity. Other risk factors were prior diagnosis of gynecologic malignancy.[4] increased red-meat intake and exposure to carcinogens[5], excessive Alcohol drinking[6] and Cigarette smoking [7].

For diagnosis, exams and tests may include faecal occult blood testing, endoscopy, digital rectal examination, sigmoidoscopy, CT/MRI imaging studies, along with routine blood tests and detection of serum CEA. More than 90% of colorectal carcinomas are adenocarcinomas [8,9]. In practice, most colorectal adenocarcinomas (~70%) are diagnosed as moderately differentiated. Neo-adjuvant chemotherapy followed by chemoradiation, is currently the standard approach for locally advanced rectal cancer and local extent of the disease that often influences the surgical decision making and need for neoadjuvant therapy.[10]

MATERIALS AND METHODS :

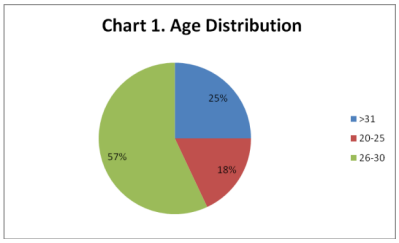
Patients with locally advanced rectal cancer attending the Radiotherapy Out Patient Department (OPD), Kolkata, From August 2018 to January 2020, meeting specified Inclusion and Exclusion Criteria, willing to participate in the study. Out of 36 patients, 28 patients were included in the study. Pre-treatment diagnostic evaluation consisted of a panel of laboratory and radiological tests: haematology and biochemistry blood test, chest radiography, computed tomographic/magnetic resonance imaging scan of the abdomen and pelvis. On completion of 3 cycles of NACT with CAPOX regimen,patients began chemo-radiation (50Gy 25 fx plus Capecitabin). Response was assessed using the Response Assessment Criteria in solid tumours. (RECIST version1.1). Surgery was performed 6 to 8 weeks after completion of chemo-radiation (CTRT). The prognostic outcome were assessed by

1. Acute and late Side effects (grading by RTOG criteria).
2. Disease free survival(DFS) for minimum of 6 months.
3. Loco-regional control for complete or partial response.
4. Recurrence.

RESULTS:

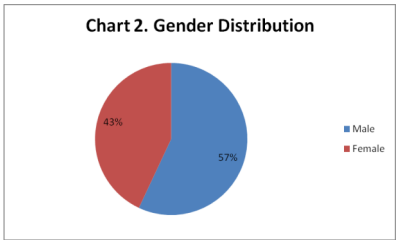
During the treatment patients were assessed for toxicity profile every week. But after completion of treatment patients were assessed after 6 weeks, then monthly follow up for six months, after that, they will be reviewed every 3 months for 10 months. The baseline characteristic toxicities and response were assessed.

Fig 1:Distribution of age of patients:



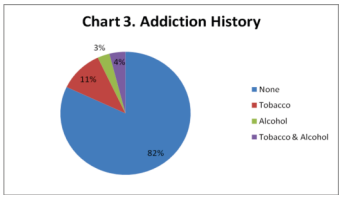
Majority of the patients were aged between 25-30 years.

Fig 2: Gender distribution of patients



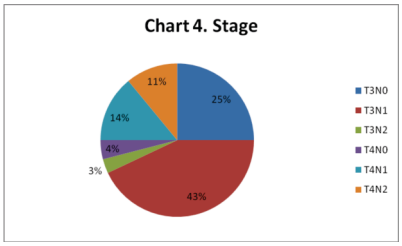
Male patients were more in number 57% and female patient 43%.

Fig3: Distribution of addiction history of patients



Majority of patients with no history of addiction.

Fig 4: Distribution of Staging



Patient with pre-treatment clinical stage T3N1 were maximum number fallowed by T3N0. T4 diseases with adjacent organ invasion are bladder,cervix,vagina and sacral plexus.

TABLE 1: HISTOPATHOLOGICAL PRESENTATION

SL NO	HISTOPATHOLOGICAL PRESENTATION	NO OF PATIENTS
1	WELL DIFFERENTIATED	11
2	MODERATELY DIFFERENTIATED	15
3	POORLY DIFFERENTIATED	2

All tumours were found to be adenocarcinoma. In well differentiated adenocarcinoma 39.3%(11 patients) ,Moderately differentiated adenocarcinoma shows53.6%(15 patients) ,Poorly differentiated adenocarcinoma is 7.1%(2 patients) respectively.

TABLE 2: TOXICITY

SL NO	TOXICITY GRADE	NO OF PATIENTS
1	GRADE 1	14
2	GRADE 2	11
3	GRADE 3	3

The most common toxicities were grade 2 toxicities (50%) with capox were fatigue nausea and neutropenia . The grade 3 toxicities were diarrhea , fatigue , nausea , and vomitting .Hand foot syndrome were 17.9%(all grade). These were managed with dose reductions and growth factor support. No grade 4 toxicities or serious adverse events requiring a break in treatment occurred .

TABLE- 3 :RESPONSE TO NACT

SL NO	RESPONSE TO NACT	NO OF PATIENTS
1	CR	1
2	PR	22
3	SD	2
4	PD	3

Only one among the twenty eight patients had a radiological complete response(CR) (3.58%) .partial response, stable disease, and progressive disease was respectively 78.58%, 7.14% and 10.70% after neo-adjuvant chemotherapy.

TABLE- 4: FEASIBILITY OF SURGERY

SL NO	FEASIBILITY OF SURGERY (RESPONSE RATE)	PERCENTAGE
1	SURGERY	92.90%
2	Ro RESECTION	92.90%
3	PATHOLOGICAL RESPONSE RATE(pCR)	14.30%

DISCUSSION:

Locally advanced rectal cancer (LARC), with the combination of preoperative chemoradiotherapy and improved surgical techniques, has led to significant improvements in local disease control and Local recurrence rates are less than Distant recurrence rates.[11,12] The current standard management for stage II (T3/T4N0) and stage III (TanyN1/N2) rectal cancer is neoadjuvant chemoradiotherapy, followed by surgery, with 4 months of adjuvant systemic chemotherapy given at the end.[11,12] Although neoadjuvant chemoradiotherapy has been shown to decrease the incidence of local recurrence, overall survival and the risk of distant metastases have not been shown to be impacted by radiation therapy.[13,14]

The concept of neoadjuvant initial chemotherapy before radiotherapy in LARC was first explored in a clinical trial by Chau et al, [15,16] which showed an 88% objective tumor control rate with neoadjuvant capecitabine/oxaliplatin. In a single-institution trial that began in March 2007 at MSKCC, 32 patients with clinical stage II or III rectal cancer were treated with neoadjuvant FOLFOX plus bevacizumab, without planned radiation therapy unless clinical progression was noted. All patients experienced tumor regression and were able to undergo an R0 resection[17] The EXPERT and GCR-3 studies both examined 12 weeks of induction CAPOX (capecitabine + oxaliplatin) followed by chemoradiation [15,18].The EXPERT trial enrolled 104 patients who were treated with this approach as well as 12 weeks of adjuvant capecitabine. Ninety seven patients underwent resection and 20% of all patients were noted to have a pCR. In this high risk group, 3-year progression free survival (PFS) was 68%, with a 74% 3-year relapse free rate in those patients who underwent resection [15].

In our study, on completion of 3 cycles of NACT with CAPOX regimen, patients began chemoradiation .MRI and/or endorectal ultrasound to assess for response to chemotherapy. Surgery was performed 6 to 8 weeks after completion of CTRT. R0 resection were observed 92.90% patients and pathological complete response (pCR) was achieved 14.30% patients. Patient who had received 3 cycle of NACT, received the remaining 5 cycles in adjuvant chemotherapy. With improvements in surgical techniques and the use of preoperative chemoradiotherapy, the local recurrence rates in rectal cancer have decreased. Response rate was only one among the twenty eight patients had a radiological complete response(CR). Other outcome in the form of Partial response 78.58% , Stable disease 7.14% and Progressive disease 10.70% after neoadjuvent chemotherapy. None of the patients had locoregional failure till last follow up. Progression free survival was 16.6 months. Thus, most patients with LARC who ultimately succumb to their disease die as a result of distant metastases. Many patients reported rapid relief of symptoms, such as rectal pain or bleeding, often in the first week of receiving systemic chemotherapy.

Two cycles of CAPOX prior to chemoradiation was evaluated by a Danish Group, producing encouraging results in a phase II study of 85 patients with poor risk rectal cancer. A pCR rate of 25% was obtained, with 5-year for DFS and overall survival (OS) of 63% and 67%, respectively [19].Initial chemotherapy therefore seems to be faster at achieving control of tumor-related symptoms than what has been historically seen with initial chemoradiotherapy

CONCLUSIONS:

In rectal cancer, neoadjuvant treatment offers a unique opportunity to improve the current paradigm. Early treatment with systemic chemotherapy could theoretically allow for a higher likelihood of successful eradication of micro metastatic disease. Upfront chemotherapy could make it more difficult for patients to tolerate subsequent pelvic radiation but manageable. There is opportunity to both improve disease free and overall survival outcomes through the differential layering of therapy, as well as to reduce toxicity through the selective use of therapeutic modalities. Improved surgical technique, incorporation of pre-operative radiotherapy and the use of adjuvant chemotherapy all appear to confer additional benefit for a large portion of patients.

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