Clinical outcomes among patients with non-metastatic Rectal Cancer after chemo-radiotherapy

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***Abstract*- Background:** Globally, colorectal cancer(CRC) is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cases and 608,700 deaths estimated to have occurred in 2008. (1)Rates are substantially higher in males than in females. Globally, the incidence of CRC varies over 10-fold. The highest incidence rates are in Australia and New Zealand, Europe and North America, and the lowest rates are found in Africa and South-Central Asia. These geographic differences appear to be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility. At our center, where head and neck, breast and cervical cancers predominate, rectal cancers make for a small percentage of malignancies. In between 2009 and 2013, out of a total of 4307 patients treated with radiotherapy, carcinoma rectum accounted for only 97 cases (2.2%).

Surgery remains the mainstay of curative treatment for carcinoma of the rectum. Surgical management depends on the stage and location of a tumor within the rectum. Very early cancers can be managed with limited surgery (i.e., local excision) in selected situations; however, the majority of tumors tend to present as more advanced disease and require either a low anterior resection (LAR) or abdominoperineal resection (APR). For patients with resected stage II or III rectal cancer, early randomized trials from Gastrointestinal Tumor Study Group (GITSG) and Mayo Clinic/North Central Cancer Treatment Group (NCCTG) demonstrated a significant local control and survival benefit for postoperative combined modality therapy over surgery alone. Thus, most of these patients stand to benefit from further adjuvant treatment in the form of concurrent chemo-radiotherapy and adjuvant chemotherapy.

Neoadjuvant or induction chemoradiotherapy is an increasingly used strategy for patients with rectal cancer. Advantages of the neoadjuvant approach include better local control, an increased likelihood of sphincter saving surgery, and a lower risk of chronic anastomotic stricture. Essential to the planning of Neoadjuvant therapy is an initial multidisciplinary assessment including the departments of surgery, radiotherapy and medical oncology.

This study was conducted to evaluate our experience with Neoadjuvant and adjuvant chemoradiotherapy for rectal cancers. The study aims to estimate the local control rates and disease free survival of rectal cancer patients who undergo Neoadjuvant/adjuvant chemoradiotherapy with a curative intent at Shiridi Sai Baba Cancer Hospital, Manipal.

METHODS:

- Study was a observational (Retrospective and Prospective) study conducted at Kasturba Hospital, Manipal.
- Total 67 patients meeting the inclusion criteria were enrolled in this study.
- STUDY PERIOD**:** Study was conducted from January 2009 to December 2013
- Institutional ethical committee clearance was obtained.

FINDINGS:

- From our study we observed that
    1. Our patients who defaulted from surgery following Neoadjuvant chemo-radiotherapy(CT-RT) had a significantly poorer local control rates and disease free survival.
    2. Neoadjuvant therapy didn't seem to increase the sphincter preservation rates in our study.
    3. The acute toxicity of CT-RT was within reasonable limits in our patients and there were no life threatening consequences during treatment.
    4. In the short follow up period, the local control rate was very good. Achieving a negative margin status at the time of surgery was found to be of significant importance in local control.
    5. The patients who completed the treatment as prescribed had a Disease Free Survival comparable with those reported in the literature.
    6. Even though the number of patients receiving Neoadjuvant Chemoradiotherapy and surgery was small, their outcomes was comparable to those who underwent adjuvant Chemoradiotherapy.
    7. Disease Free survival was found to be significantly poorer in patients with higher stage disease and positive resection margin status.
    8. Interestingly, though not of statistical significance, patients receiving adjuvant 5-Fluorouracil(5FU) appeared to perform better when compared to those receiving capecitabine.

INTERPRETATION:

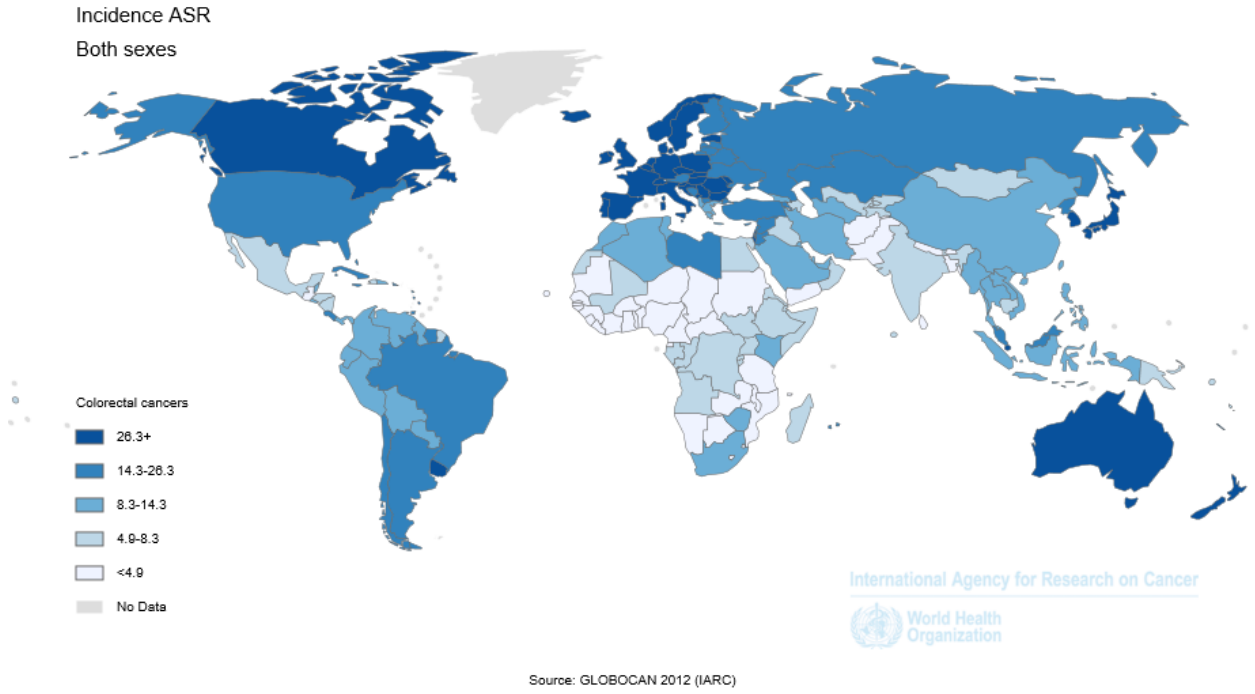
A multi-disciplinary evaluation prior to treatment could help in optimal management of carcinoma rectum

FUNDING: None

I. Introduction

Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cases and 608,700 deaths estimated to have occurred in 2008. (1) Rates are substantially higher in males than in females. Global, country-specific incidence and mortality rates are available in the World Health Organization.

Figure 1: Incidence of colorectal cancers in the world



Source: GLOBOCAN 2012 (IARC)

II. TREATMENT OF RECTAL CANCERS

Rectal cancers, like several other malignancies, are treated with a multidisciplinary approach. While surgery continues to be the primary treatment modality in nearly all patients with non-metastatic rectal cancers, systemic chemotherapy and radiotherapy have an important role to play in treatment with curative intent. Chemotherapy and radiotherapy can be delivered in an adjuvant, or more frequently of late, in a neoadjuvant setting. The roles of these individual modalities and combination of the modalities for optimal treatment are discussed in brief below.

Surgery:

Surgery is the primary therapy for resectable non-metastatic rectal cancers. The surgical options for resection of early stage, potentially resectable disease are local excision, sphincter-sparing procedures, and abdominal perineal resection.

Principles of resection — The principle components for a curative resection include performing a wide resection of the cancer by achieving histologically negative margins, and performing a total mesorectal excision (TME) and resection of local lymph nodes with sphincter-sparing procedures or an APR. Anorectal sphincter function should be preserved if it is possible to obtain a negative distal margin when using a sphincter-sparing approach.

Radiotherapy:

Traditionally, rectal cancers were known to have high local recurrence rates. Though radiotherapy was not successful as a primary modality in achieving local control, several trials proved its benefit in improving local control following surgery, though the overall survival benefit was unclear. In the present era of treatment for rectal cancers, radiotherapy combined with chemotherapy has become the standard of care in either neoadjuvant or adjuvant setting, based on several trials that have showed the benefit of concurrent chemo-radiotherapy in both local control and survival. The usual dose given to initial pelvic fields is 45 Gy in 25 fractions of 1.8 Gy each. An additional tumor boost may be administered, usually through opposed lateral fields, to an additional 5.4 to 9 Gy. Small bowel should be excluded from the boost volume after about 50 Gy in an effort to minimize acute and late toxicity.

Chemotherapy:

Addition of chemotherapy to the treatment is based on the fact that several patients have a metastatic recurrence despite a successful local control following surgery and radiotherapy. The aim of chemotherapy, administered either in Neoadjuvant or in adjuvant setting, is to sterilize the micro-metastatic disease, in

addition to potentiating the local control rates achieved by surgery and radiotherapy. Anti-metabolites, principally fluropyrimidines, formed the mainstay of chemotherapy in rectal cancers. Presently, the chemotherapeutic agents effective in rectal cancers include platinums and camptothecins, in addition to biological agents such as monoclonal antibodies against Epidermal Growth Factor Receptors (eg. Cetuximab) and Vascular Endothelial Growth Factor receptors (eg. Bevacizumab).

Chemotherapy Regimens with Radiotherapy

There is considerable variability in the administration of chemotherapy in many of the trials undertaken and those that are ongoing. 5-Fluorouracil(5FU) has been used concurrent with radiation because of its well-established potentiating effect with radiation. However, several studies have used bolus 5-FU, whereas others have administered LV-modulated 5-FU during the first and last weeks of radiation. New drugs, including oral fluoropyrimidines (capecitabine), oxaliplatin, and irinotecan, have been shown to be effective in the treatment of metastatic colorectal cancer. Oral fluoropyrimidines, as part of a CT-RT regimen, are replacing infusional 5-FU. Capecitabine is an oral fluoropyrimidine prodrug that is readily absorbed in the gastrointestinal tract and mimics the efficacy of continuously infused 5-FU while avoiding the risk of side effects and complications due to a central line for continuously infused 5-FU . (2)Capecitabine requires the presence of thymidine phosphorylase (TP) for conversion to the active form of 5-FU within the cells. TP is present in higher concentration in tumor cells, particularly colorectal cancer than in normal tissues, and this potentially creates a therapeutic advantage for capecitabine as compared to intravenous 5-FU. (3)

Capecitabine is generally given in two divided doses twice a day during the course of radiation treatment.

Multidisciplinary approach to treatment of rectal cancers:

As stated before, a combination of surgery, radiotherapy and systemic therapy is required for the optimal treatment of non-metastatic rectal cancers, except for very early stage rectal cancers (pT1N0M0 and pT2N0M0 tumors) where surgery is sufficient. Chemotherapy and radiotherapy can be administered either prior to surgery in a neo-adjuvant setting, or following surgery, as an adjuvant therapy.

INDICATIONS FOR NEOADJUVANT TREATMENT — Neoadjuvant or induction chemoradiotherapy is an increasingly used strategy for patients with rectal cancer. Advantages of the neoadjuvant approach include better local control, an increased likelihood of sphincter saving surgery, and a lower risk of chronic anastomotic stricture.

The only definitive indication for neoadjuvant chemoradiotherapy, supported by the results of randomized trials, is the presence of a T3 or T4 rectal cancer.

Relative indications for neoadjuvant chemoradiotherapy include the presence of clinically node-positive disease in a patient with an MRI or transrectal ultrasound (TRUS)-stagedT1/2 rectal cancer, a distal rectal tumor for which an abdominoperineal resection (APR) is thought to be necessary, and a tumor that appears to invade the mesorectal fascia on preoperative imaging, because of the decreased likelihood of achieving a tumor-free circumferential resection margin with upfront surgery.

Timing of surgery — The optimal interval between completion of neoadjuvant conventional fractionation radiotherapy and surgery in rectal cancer is unknown. Traditionally, this interval has been six weeks (approximately 11 to 12 weeks after the start of Radiotherapy), as this was the duration used by the seminal German Rectal Cancer study. (4)

III. MATERIALS AND METHODS

his study was conducted at the Department of Radiotherapy, Shirdi Sai Baba Cancer Hospital and Research Center, Manipal, from January 2009 to December 2013. Of the total of 97 rectal cancers treated in this time, 67 patients meeting the inclusion criteria were enrolled in this study.

STUDY DESIGN: Observational (Retrospective and Prospective) study

TARGET POPULATION: Patients with rectal adenocarcinomas who received neoadjuvant or adjuvant chemo radiotherapy, meeting the inclusion/exclusion criteria.

STUDY PERIOD: January 2009 to December 2013
The following inclusion and exclusion criteria were used:

INCLUSION CRITERIA

1. Histopathologically proven case of adenocarcinoma rectum
2. No evidence of metastatic disease at presentation
3. Patients being treated with neoadjuvant and/or adjuvant chemo radiotherapy
4. Baseline performance status of 2 or lower according to Eastern Cooperative Oncology Group (ECOG) criteria

EXCLUSION CRITERIA

1. Synchronous colon cancer
2. Recurrent rectal disease
3. Patients with comorbidities that prevent the use of concurrent/adjuvant systemic chemotherapy.

IV. METHODOLOGY

Patients with rectal adenocarcinomas who received neoadjuvant or adjuvant chemo radiotherapy, meeting the inclusion/exclusion criteria were identified from the radiotherapy and/or medical records. The details of the patients were collected as per the proforma from the records. The last follow up of the patient was noted, and an attempt was made to contact the patient if last follow up was more than 3 months ago.

RADIOTHERAPY:

Radiotherapy was administered to all patients as per the protocol followed by the Department. 3-D Conformal radiotherapy(3D-CRT) was planned for all patients after appropriate immobilization in supine position using a thermoplastic mould. All patients were treated with megavoltage beams on a multiple energy ELEKTA Linear Accelerator, with conventional fractionation (1.8 Gy or 2 Gy per fraction, one fraction per day, five days per week). As per the recommendations, external-beam treatment fields for rectal

carcinoma should encompass potential sites at greatest risk for harboring disease, including the presacral space, primary tumor site, (for post-APR cases) the perineum and other areas at risk including the internal iliac and distal common iliac nodes. For preoperative radiotherapy, Gross tumor volume (GTV) included the primary tumor and any gross peri-rectal lymph nodes. In postoperative cases, the surgical tumor bed was marked as CTV-boost. Clinical Target Volume (CTV) included from the level of bifurcation of common iliac vessels into internal and external iliac vessels, with a circumferential margin of 7 mm around the vessels, excluding the muscles and bones in proximity. For postoperative cases the distal field edge was placed about 5 cm below the best estimate of the preoperative tumor bed and, if an APR was performed, below the perineum. One cm margin generated in all directions was given to the CTV to create the Planning Target Volume (PTV). The treatment planning was done on Elekta PrecisePLAN planning system (version2.16). All patients were treated with 4-field technique, incorporating AP-PA and RL-LL parallel opposed beams. All plans used Source To Axis(SAD) technique, with the dose usually prescribed to the isocentre. Field-in-field technique was used to ensure that no region received more than 107% of the prescribed dose. It was ensured that 95% of the planning target volume receive at least 95% of the prescribed dose. After completion of 45 Gy to the pelvis, Field Size Reduction (FSR) was done to cover the PTV tumor/surgical bed (PTV primary in case of Neoadjuvant treatment). Additional 5.4 Gy to 9 Gy over 3-5 # was delivered to the boost volumes, usually with a 4-field cross-fire technique with avoidance of bilateral femoral heads.

Prior to all the chemotherapy cycles, blood counts, renal parameters and electrolytes were done and chemotherapy was administered only if they were within acceptable limits (Hb>10gm%, TLC>3500/mm^3, ANC> 1500/mm^3, Platelets>1.5lakhs/mm^3 and Urea< 40mg/dL, Creatinine<1.2 mg/dL, Na^+>130mg/dL, K^+ 3.6 to 5mg/dL, Calcium 9 to 10.3 mg/dL). Chemotherapy was given with adequate anti emetic measures including dexamethasone, pheniramine, ranitidine, ondansetron, metoclopramide. The toxicities associated with this chemotherapy and radiotherapy such as diarrhoea, anaemia, neutropenia, thrombocytopenia were monitored. Categories were made to monitor the toxicity profiles (every week during all the weeks of CT-RT). All the toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
Follow up of the patients were done every 3 monthly for 2 years, 6 monthly for the next 3 years and yearly subsequently. Follow up visit consisted of a physical exam and further investigations like colonoscopy, CEA or CT scan as clinically indicated. No routine imaging studies or colonoscopy was performed.
In the event of a recurrence, the sites of relapse were recorded, and the recurrence was classified as either local, distant or both.
Disease free survival estimates were calculated from the date of presentation till the date of last follow up or relapse.
All the statistical analysis were done using SPSS v16 and Microsoft Excel 2007. Disease free survival was estimated using Kaplan-Meier curves, and Log-rank test was used for identifying the statistical significance in differences in the curves between the parameters. Chi-Square test was used to evaluate the statistical significance of the factors that affected local control.

V. OBSERVATIONS AND ANALYSIS

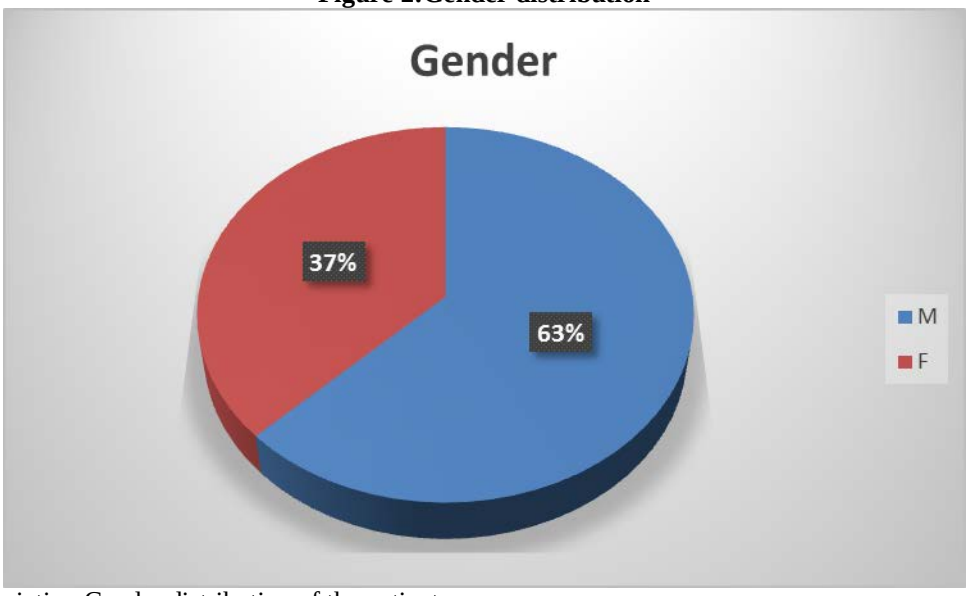
A total of 67 patients who were diagnosed to have non metastatic rectal adenocarcinoma and meeting other eligibility criteria were enrolled in this study.

The median follow up time was 333 days (range: 58-1674 days).

Gender distribution

Of all the 67 patients, 25 patients were females and 42 were males. F:M ratio was 1:1.68.

Figure 2:Gender distribution

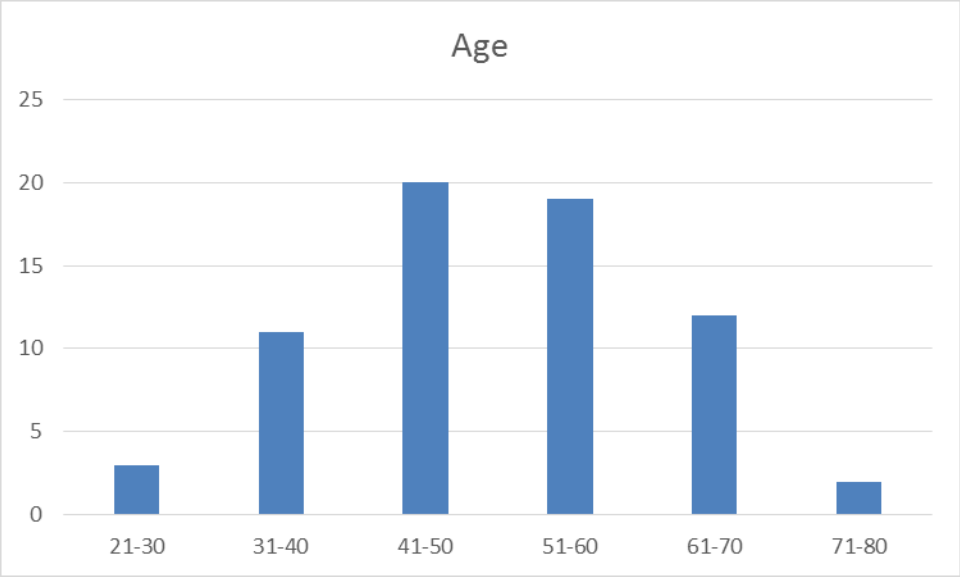


A Pie chart depicting Gender distribution of the patients

Age of the patients

The median age of all the analyzable 67 patients was 50 years (Range: 26-72 years). Median age of the female cohort was 51 years (Range: 32-72 years). Median age of the male cohort was 50 years (Range: 26-72 years).

Figure 3: Age distribution



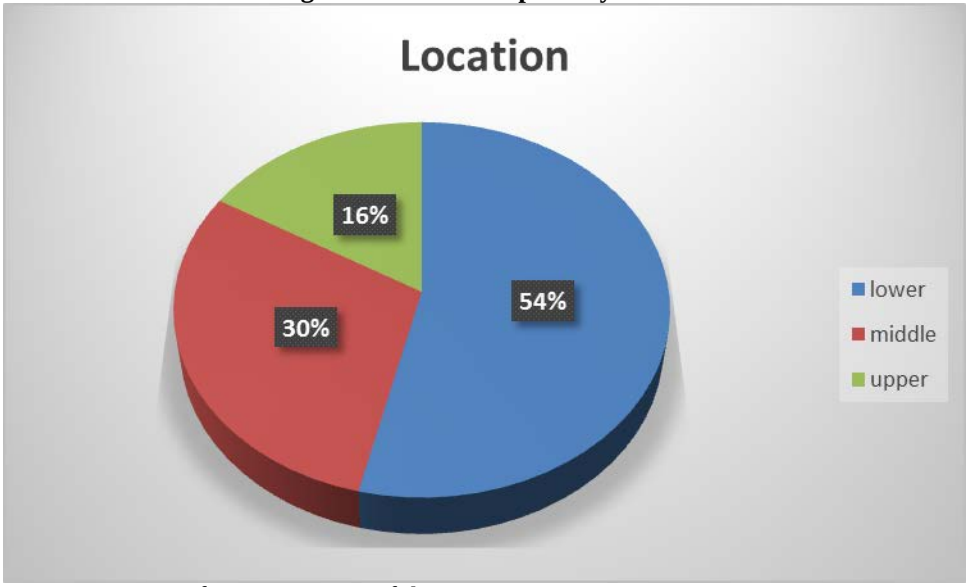
Bar chart depicting the age distribution of the patients

Twenty patients (30%) belonged to the 41-50 years age group, 19 (28%) belonged to the 51-60 years age group, 12 (18%) belonged to the 61-70 years, 11(16%) belonged to the 31-40 years, 3 (5%) belonged to 21-30 years and 2 (3%) patients belonged to the 71-80 years.

Location of primary

36 patients (54%) had a growth in the Lower third of the rectum, 20 patients (30%) had a growth in middle third and 11 patients (16%) had growth in the upper third of the rectum.

Figure 4:Location of primary tumor

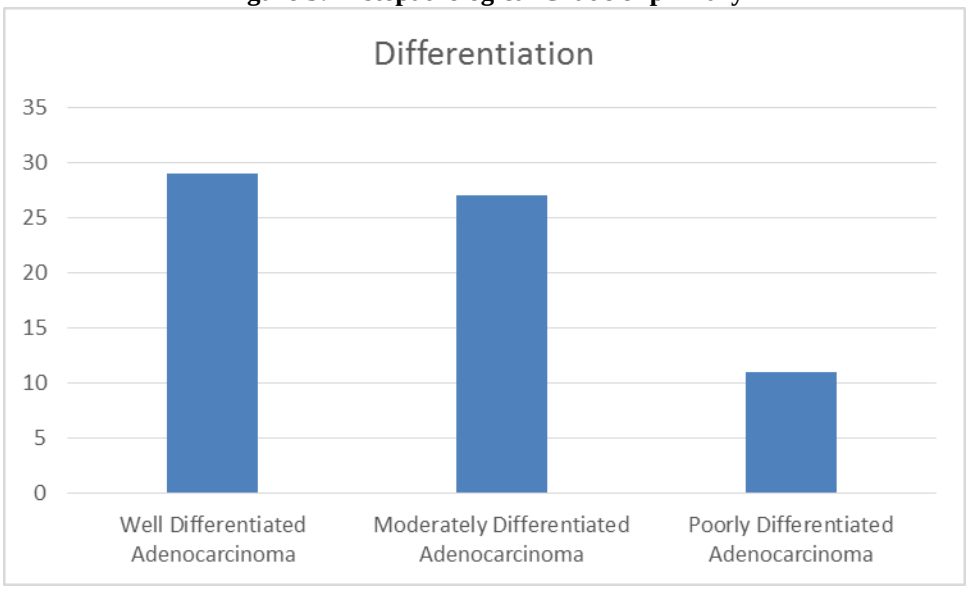


A Pie chart depicting Location of primary tumor of the patients

Histopathological grade of primary

All patients included into the study had adenocarcinomas. Twenty nine patients (43%) had well differentiated tumors, 27 patients (40%) had moderately differentiated tumors, 11 patients (17%) had poorly differentiated tumors.

Figure 5: Histopathological Grade of primary

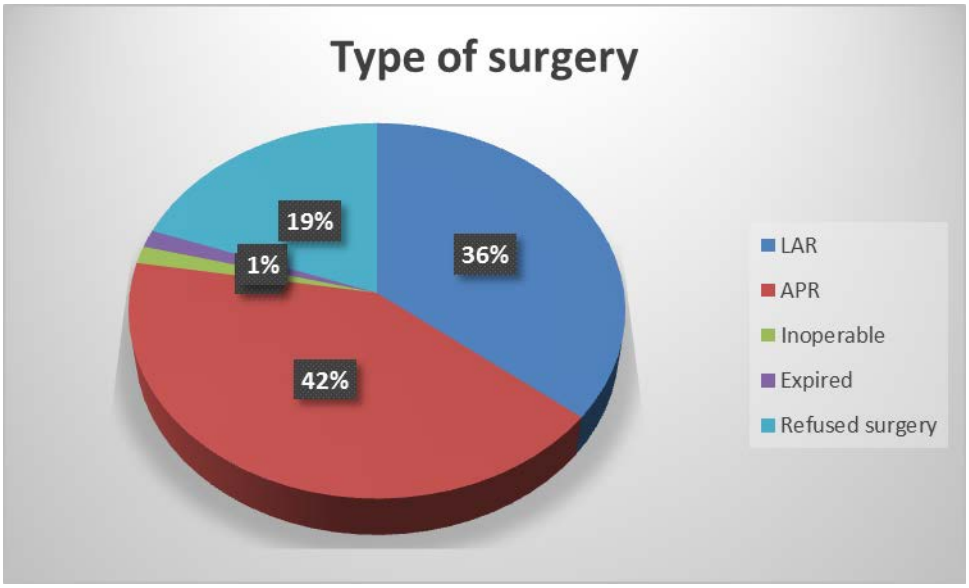


Bar chart depicting the Differentiation of tumor of the patients

Surgical resection

Forty four patients underwent upfront surgery, while the remaining 23 received neo-adjuvant therapy. Following Neoadjuvant therapy, 15 didn't undergo definitive surgery; as a result, only 52 patients in the group had a curative resection. Of these, 24 (36%) underwent Sphincter preserving surgery (Low Anterior Resection), and the other 28 (42%) underwent Abdomino-Perineal resection. Following Neoadjuvant therapy, 13 patients (constituting 57% of the patients receiving Neoadjuvant therapy) refused further treatment, one was found to be inoperable and one expired. The Surgical treatment received by the cohort is given in the figure below.

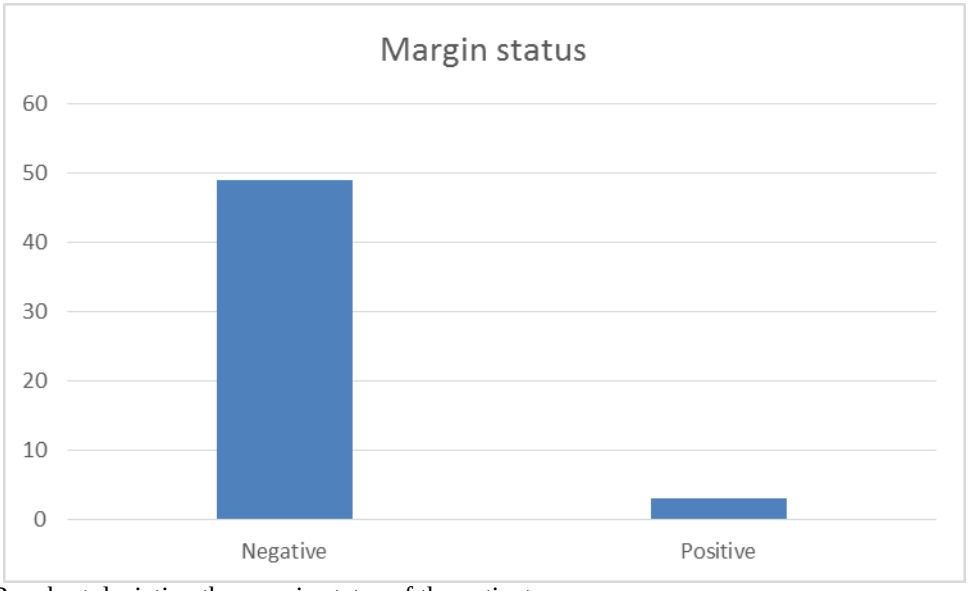
Figure 6:Type of surgery performed



A Pie chart depicting type of surgery of the patients

No patient had grossly positive surgical margins (R2 resection). However, microscopic positive surgical margin (R1 resection) was noted in 3 patients, all of whom had undergone upfront surgery.

Figure 7:Margin status

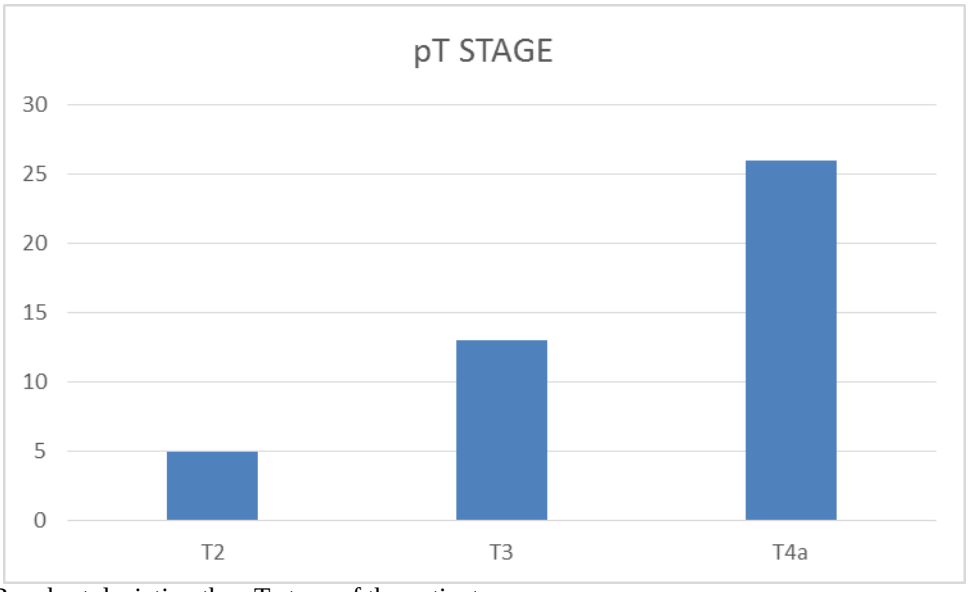


Bar chart depicting the margin status of the patients

Stage of Primary

All patients, by inclusion criteria, had non-metastatic disease at presentation. Forty four patients underwent upfront surgery, and had staging information available. Twenty six patients (59%) had pT4a disease, 13 patients (30%) had pT3 disease and 5 patients (11%) had p T2 disease. None of the patients had pT1 or pT4b disease.

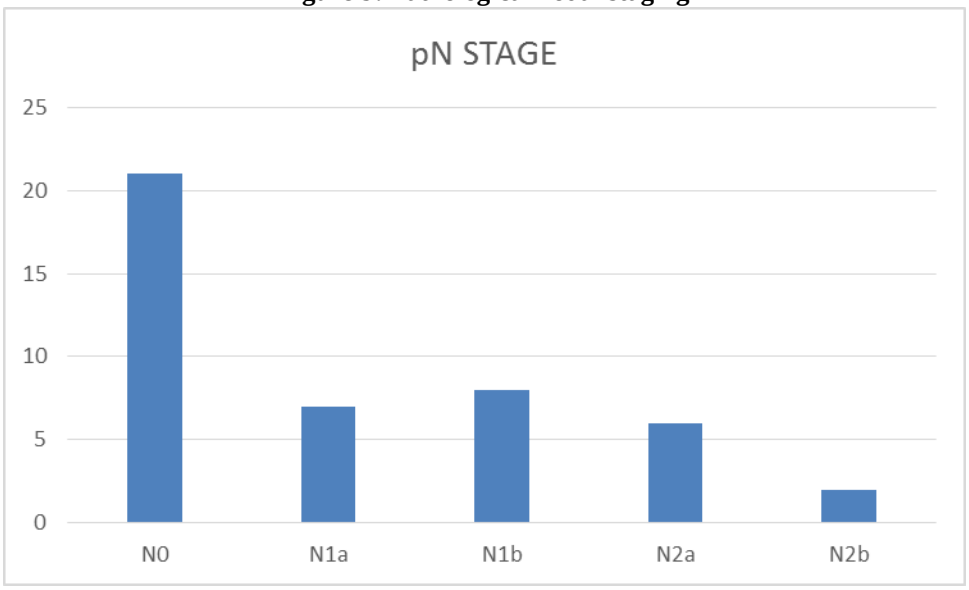
Figure 8: Pathological primary tumor staging



Bar chart depicting the pT stage of the patients

On the other hand, Twenty one patients (48%) had pN0 disease status. Fifteen (34%) had pN1 disease and 8 patients (18%) had N2 disease status.

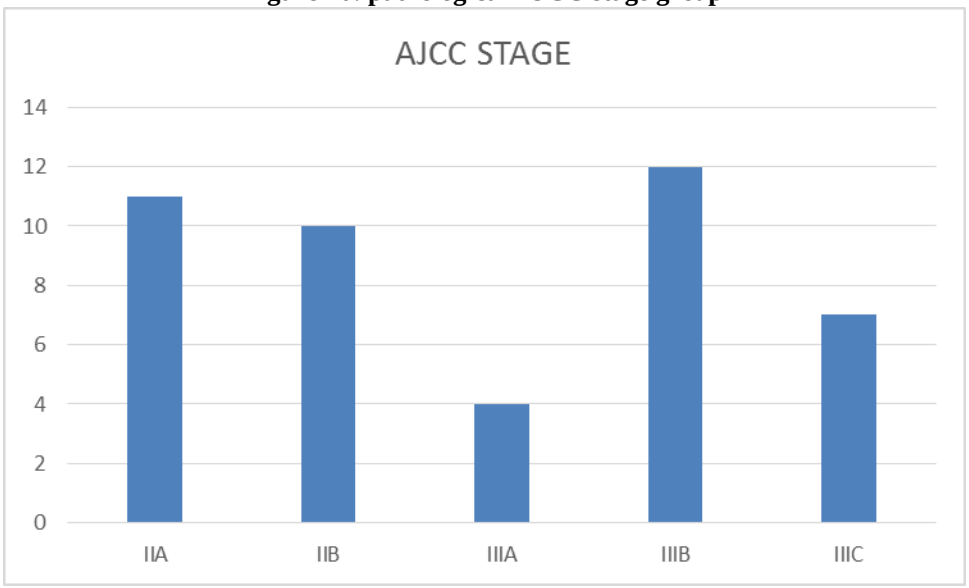
Figure 9: Pathological nodal staging



Bar chart depicting the pN stage of the patients

Twelve patients (27%) were in stage IIIB, 10 (23%) in stage IIB, 7 (16%) in stage IIIC, 6(14%) in stage IIA,5(11%) in stage I,4 (9%) in stage IIIA after primary surgery.

Figure 10: pathological AJCC stage group



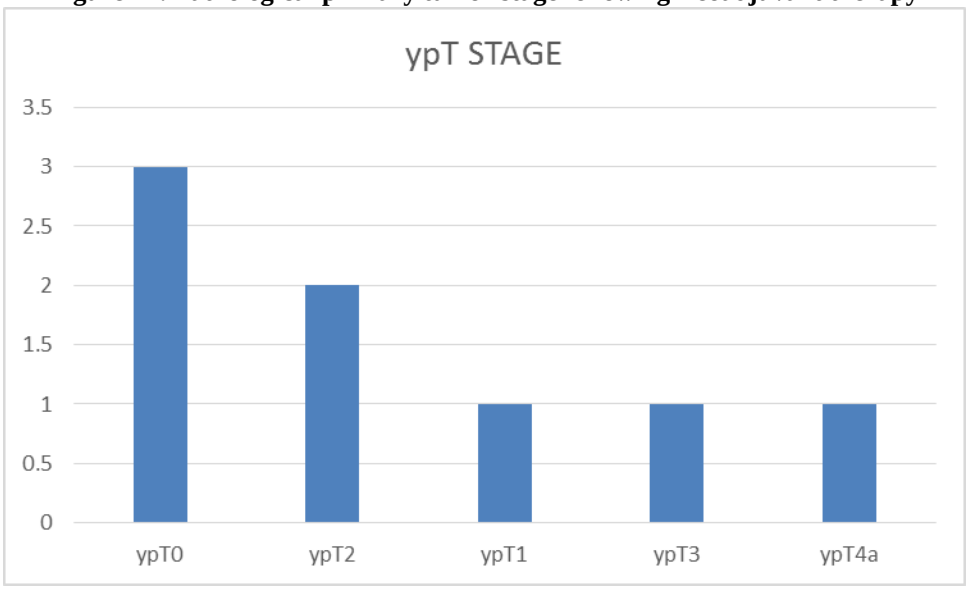
Bar chart depicting the pAJCC stage of the patients

Stage of disease following neoadjuvant therapy

Of the 23 patients of the 67 enrolled who underwent Neoadjuvant chemo-radiotherapy, three patients (13%) underwent sphincter saving procedure (Low Anterior Resection), 5 patients (22%) underwent Abdomino-Perineal Resection, 13 patients(57%) refused surgery, 1 (4%) was found to have inoperable disease, and one expired after completing neo-adjuvant therapy, due to sepsis.

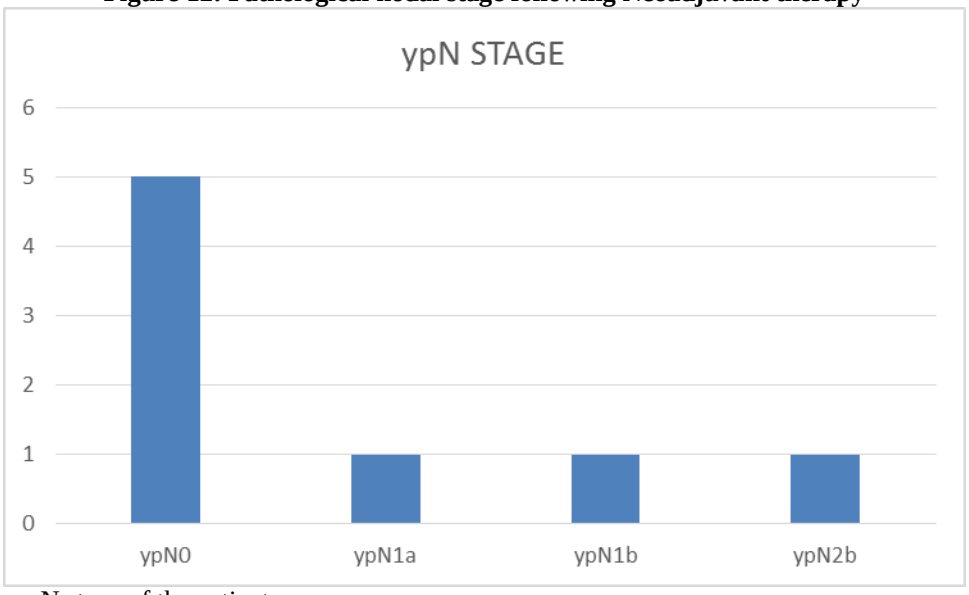
Of the patients who underwent surgery following Neoadjuvant therapy, 3 patients (37%) had pathological complete response (ypT0N0M0), 2 patients (25%) had ypT2 disease and 1 patient each had ypT1, ypT3 and ypT4a disease, respectively (Figure 11). Five patients (62%) had ypN0, 1 patient each had ypN1a, ypN1b and ypN2b disease, respectively (Figure 12).

Figure 11: Pathological primary tumor stage following Neoadjuvant therapy



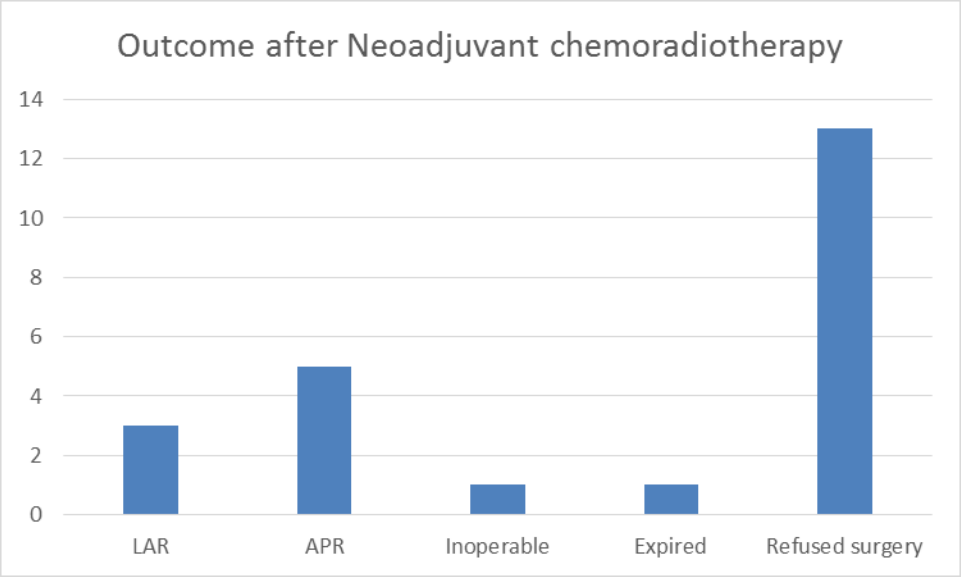
Bar chart depicting the ypT stage of the patients

Figure 12: Pathological nodal stage following Neoadjuvant therapy



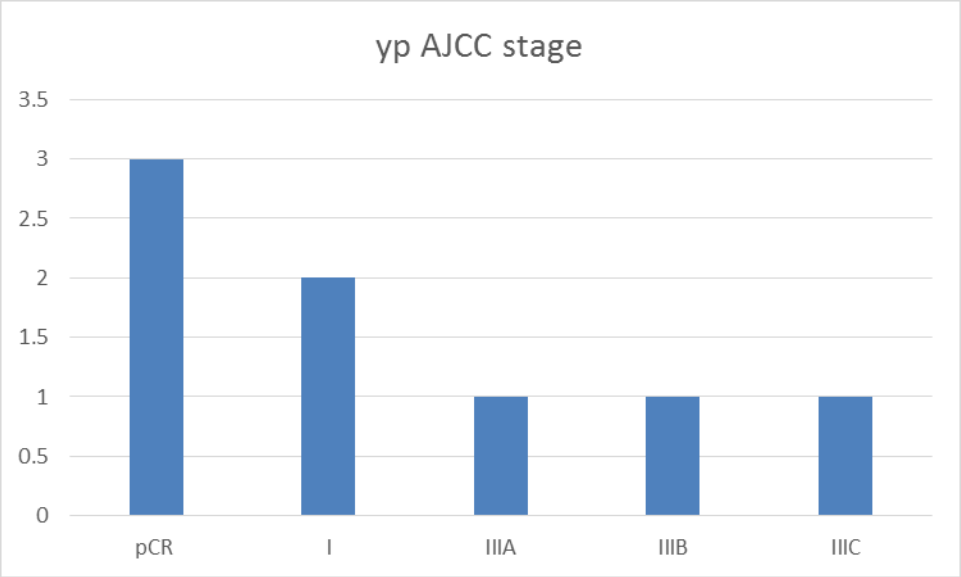
Bar chart depicting the ypN stage of the patients

Figure13: Outcome after Neoadjuvant chemo-radiotherapy



Bar chart depicting the outcome after Neoadjuvant CT-RT

Figure 14: yp AJCC stage



Bar chart depicting the yp AJCC stage of the patients

Three patients (37%) had pathological complete response, 2 (25%) had stage I, whereas 3 patients (38%) had stage III disease after Neoadjuvant chemoradiotherapy.

Toxicity experienced with chemo-radiotherapy

All the patients underwent chemo-radiotherapy, either in neo-adjuvant or in adjuvant setting. Only one patient failed to complete the prescribed course of chemo-radiotherapy, defaulting the treatment after completing 10 sessions, citing poor tolerance. She was experiencing Grade 2 diarrhoea at the time of withdrawal. The hematological and gastro-intestinal toxicities are discussed below.

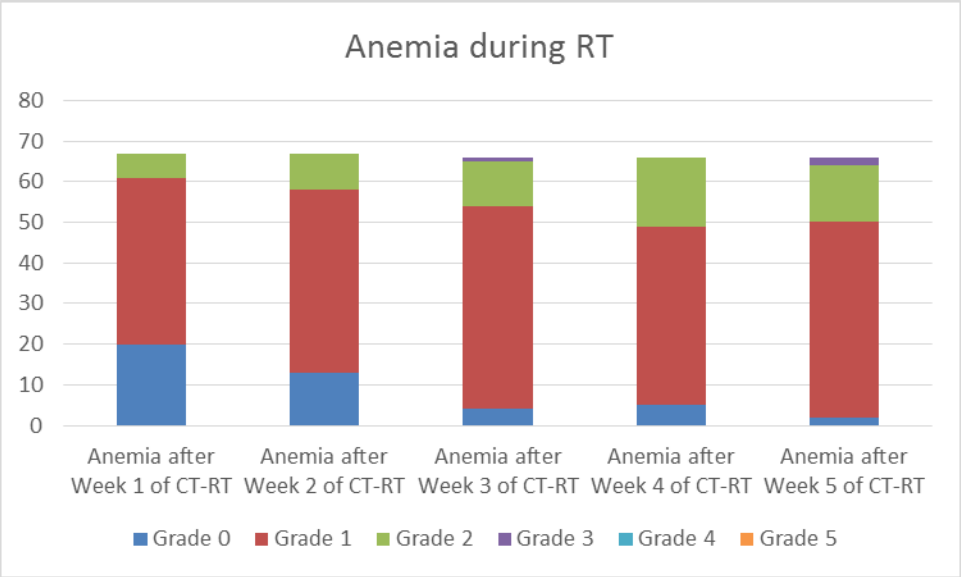
Hematological Toxicity:

Except for 6 patients (9%), all had grade 1 or lower Anemia at the start of chemo-radiotherapy. Anemia progressively worsened over the course of treatment, peaking by the 5th week, where 2 patients experienced Grade 3, and 14 patients experienced Grade 2 toxicities.

Table 1: Anemia during chemo-radiotherapy

Anemia during CT-RT	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Week 1	20	41	6	0	0	0
Week 2	13	45	9	0	0	0
Week 3	4	50	11	1	0	0
Week 4	5	44	17	0	0	0
Week 5	2	48	14	2	0	0

Figure 15:Anemia during chemo-radiotherapy

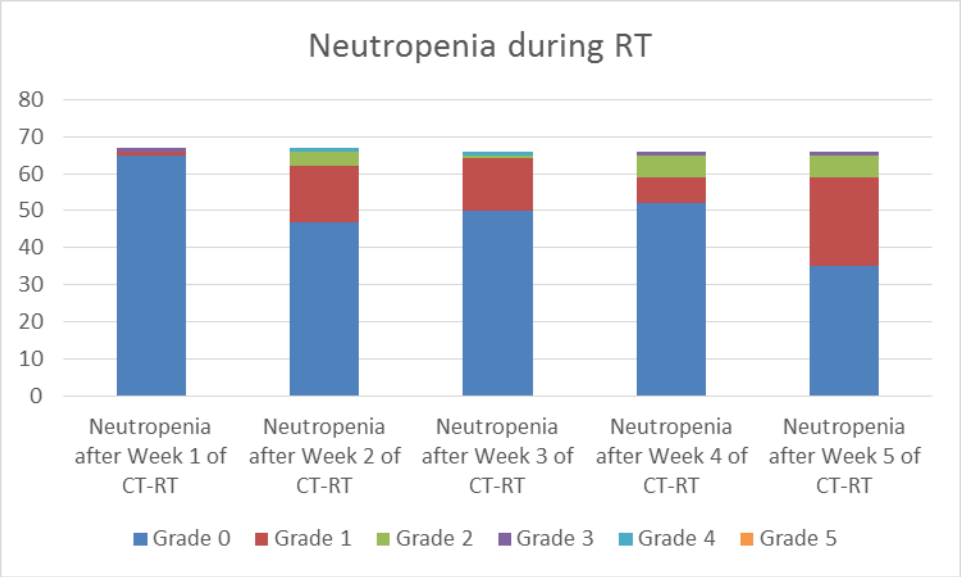


The incidence of grade 2 or lower neutropenia peaked by the 5th week of treatment, when 30 patients (45%) had grade 1 or grade 2 neutropenia. Five patients experienced grade 3 or higher toxicity, with one patient each having grade 4 toxicity in weeks 2 and 3, respectively. None of these patients had febrile neutropenia, and all patients had spontaneous recovery in their neutrophil counts to ≤ grade 2 within 1 week. Radiotherapy was not interrupted for any of these patients, however, chemotherapy was avoided until the neutrophil counts recovered to Grade 2 or lower.

Table 2:Neutropenia during chemo-radiotherapy

Neutropenia during CT-RT	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Week 1	65	1	0	1	0	0
Week 2	47	15	4	0	1	0
Week 3	50	14	1	0	1	0
Week 4	52	7	6	1	0	0
Week 5	35	24	6	1	0	0

Figure 16: Neutropenia during chemo-radiotherapy

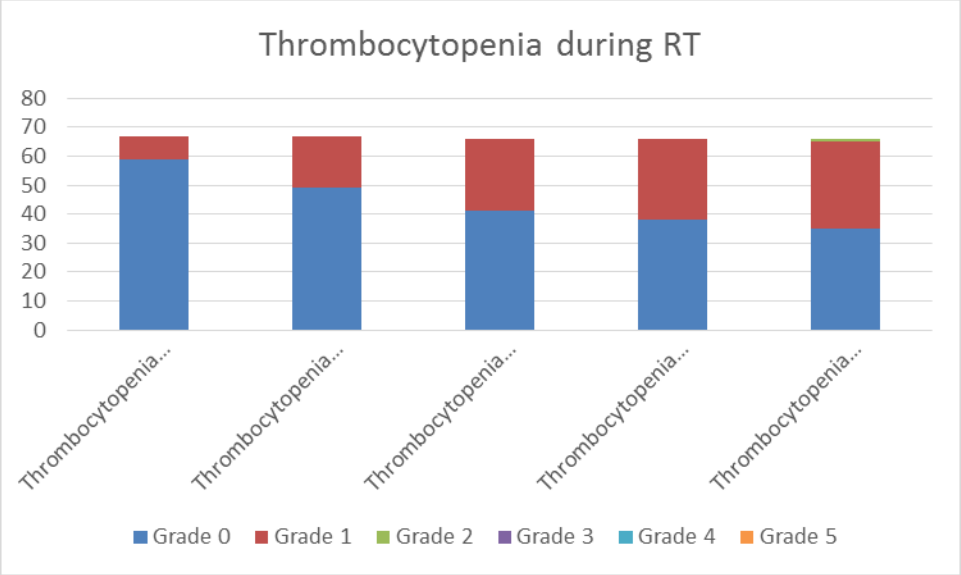


Grade 2 or lower thrombocytopenia was experienced by 31 (47%) of patients by the end of treatment. No patient had > Grade 2 thrombocytopenia.

Table 3: Thrombocytopenia during chemoradiotherapy

Thrombocytopenia during CT-RT	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Week 1	59	8	0	0	0	0
Week 2	49	18	0	0	0	0
Week 3	41	25	0	0	0	0
Week 4	38	28	0	0	0	0
Week 5	35	30	1	0	0	0

Figure 17: Thrombocytopenia during chemoradiotherapy



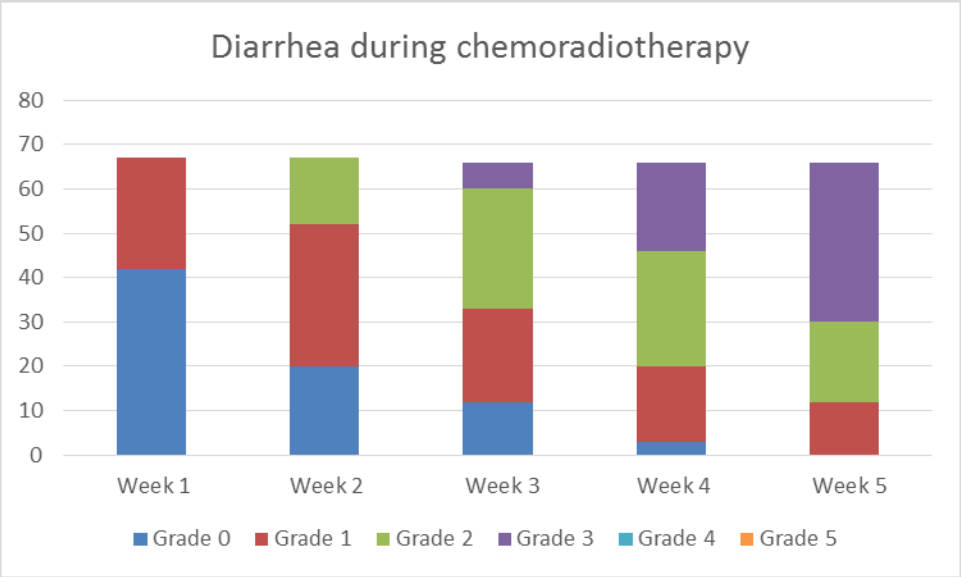
Gastrointestinal Toxicity:

The incidence and severity of diarrhea progressively worsened during the course of treatment. The incidence of Grade 3 Diarrhea was 9 % (6 patients), 30 % (20 patients) and 54 % (36 patients) in weeks 3, 4 and 5, respectively. By the completion of treatment, all patients had at least Grade 1 small bowel toxicity. One patient discontinued treatment after the 2nd week, citing poor tolerance. She had Grade 2 diarrhea at the time of discontinuation. The incidence and severity of gastrointestinal toxicity was similar between Neoadjuvant and adjuvant therapies. Even though a higher percentage of patients in the Neoadjuvant arm had Grade III diarrhea (15 of 23 patients; 65%) compared to the patients in adjuvant arm (21 of 44 patients; 48%), the difference was not statistically significant. The incidence of diarrhea was comparable between the patients receiving concurrent capecitabine and Leucovorin modulated 5-FU regimens.

Table 4: Diarrhea during chemoradiotherapy

Diarrhoea during CT-RT	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Week 1	42	25	0	0	0	0
Week 2	20	32	15	0	0	0
Week 3	12	21	27	6	0	0
Week 4	3	17	26	20	0	0
Week 5	0	12	18	36	0	0

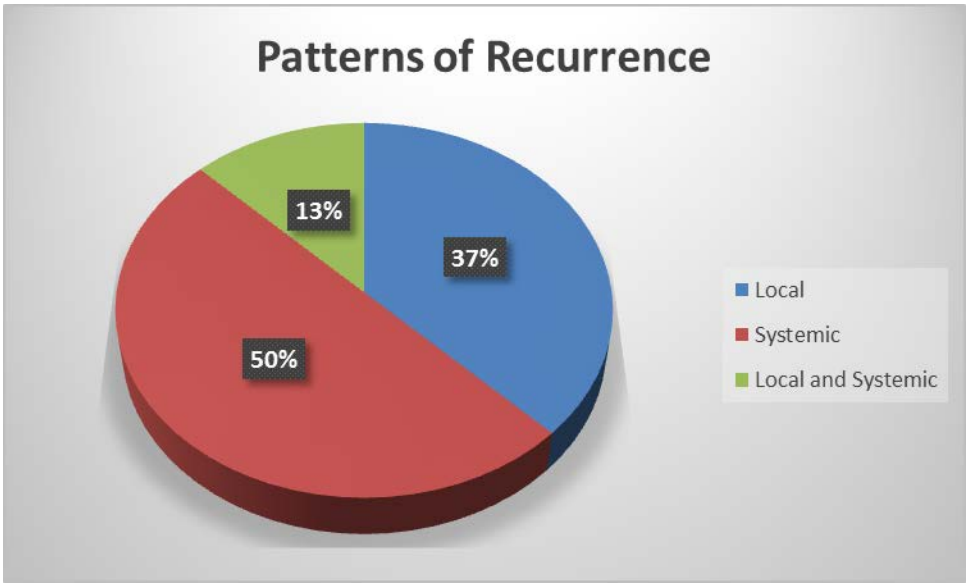
Figure 18: Diarrhea during chemoradiotherapy



Patterns of Recurrence

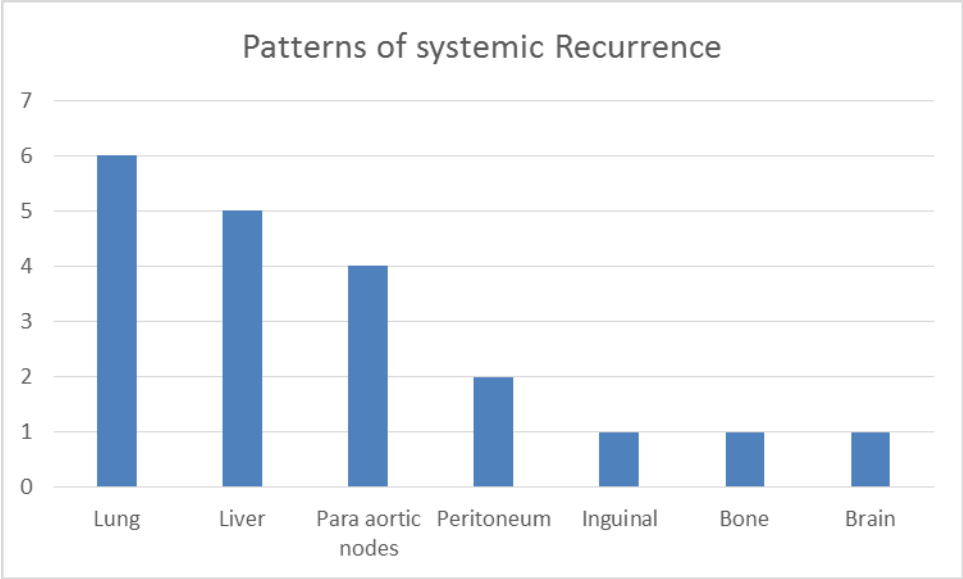
With a median follow up duration of 11.1 months (Range: 1.9 to 55.8 months), a total of 24 patients (36%) had recurrences. Nine patients (13%) had local recurrence, 12(18%) patients had systemic recurrence and 3 (4%) had a simultaneous local and systemic recurrence.

Figure 19:Patterns of recurrence



A Pie chart depicting patterns of recurrence

Figure 20: Patterns of systemic recurrence



A Bar chart depicting patterns of systemic recurrence

Most common site of systemic recurrence was Lung followed by Liver, Para aortic nodes, Peritoneum, Inguinal nodes, Bone and Brain.

On excluding the 15 patients who did not undergo surgery following neo-adjuvant radiotherapy, local recurrences was noted in only 3 patients (6%). None of the eight patients who completed the prescribed treatment following neo-adjuvant chemo-radiotherapy suffered a local recurrence.

Deferring from surgery significantly decreased disease control rates; 9 patients (60%) of the 15 not undergoing surgery had a local residual or recurrent disease.

Table No: 5 Effect of surgery on local control (p < 0.001)

Loco regional control	No Recurrence	Recurrence	Total
Surgery +RT-CT	49 (73%)	3 (4%)	52 (77%)
RT-CT - No surgery	6 (9%)	9 (14%)	15 (23%)
Total	55 (82%)	12 (18%)	67 (100%)

Factors affecting local control

The effect of various disease parameters on local control are studied below, after excluding the patients who deferred surgery.

Margin status after surgery: None the patients undergoing Neoadjuvant chemoradiotherapy had positive margins or local recurrence. Out of 49 patients with negative margins, two patients had local recurrence whereas one patient had recurrence out of 3 patients with positive margins.

Table No. 6 Effect of Margin status on local control (p= 0.035)

Margin status	Local recurrence		Total
	Yes	No	
Negative margin	2 (4%)	47 (90%)	49 (94%)
Positive margin	1 (2%)	2 (4%)	3 (6%)
Total	3 (6%)	49 (94%)	52 (100%)

Pathological T stage: Out of 44 patients who underwent surgery prior to adjuvant RT-CT, all 3 local recurrences were in patients with pT4a disease.

Table No. 7 Effect of pT Stage on local control (p = 0.328)

Pathological T stage	Local recurrence No (%)	Yes (%)	Total
pT2	5 (11%)	0 (0%)	5 (11%)
pT3	13 (30%)	0 (0%)	13 (30%)
pT4a	23 (52%)	3 (7%)	26 (59%)
Total	41 (93%)	3 (7%)	44 (100%)

Pathological N stage: Out of 21 patients with pN0 status, one patient had local recurrence, whereas two of 15 with pN1 disease suffered a local failure. None of the eight pN2 patients had a loco-regional failure.

Table No. 8 Effect of pN Stage on local control (p = 0.782)

Pathological N stage	Local recurrence		Total
	No (%)	Yes (%)	
pN0	20 (45%)	1 (2%)	21 (47%)
PN1a	6 (14%)	1 (2%)	7 (16%)
pN1b	7 (16%)	1 (2%)	8 (18%)
pN2a	6 (14%)	0 (0%)	6 (14%)
pN2b	2 (5%)	0 (0%)	2 (5%)
Total	41 (94%)	3 (6%)	44 (100%)

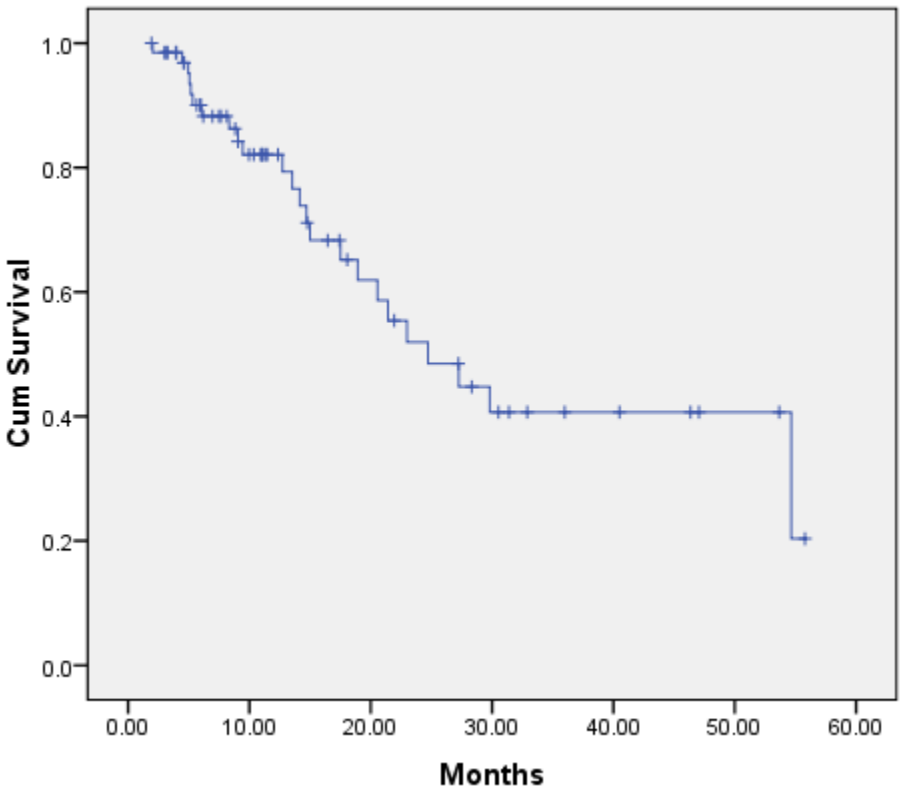
Stage of disease after upfront surgery: One patient had local recurrence out of 21 patients with stage II disease, whereas 2 out of 23 patients with stage III disease had loco-regional recurrence on follow up.

Table No. 9 Effect of Stage of disease on local control (p = 0.605)

Pathological AJCC stage group	Local recurrence No (%)	Yes (%)	Total
II	20 (45%)	1 (2%)	21 (47%)
III	21 (48%)	2 (5%)	23 (53%)
Total	41 (94%)	3 (6%)	44 (100%)

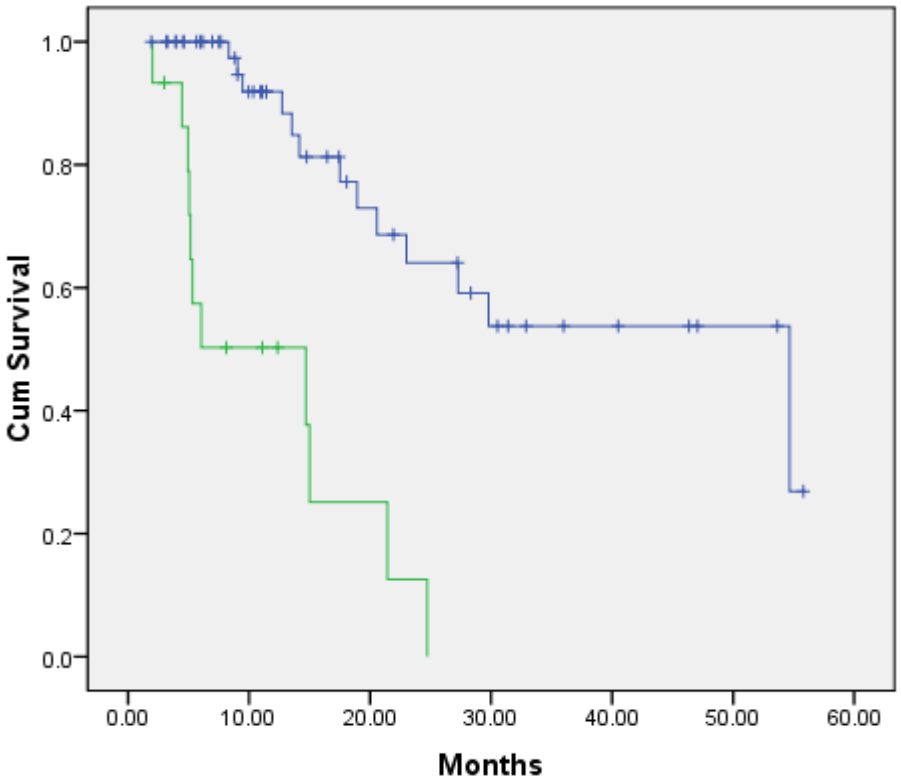
Disease free survival

The estimated median disease free survival of the study group was 24.7 months (95% CI: 15.6-33.8 months) (Figure No.21). Figure No. 21: Disease free survival of all patients



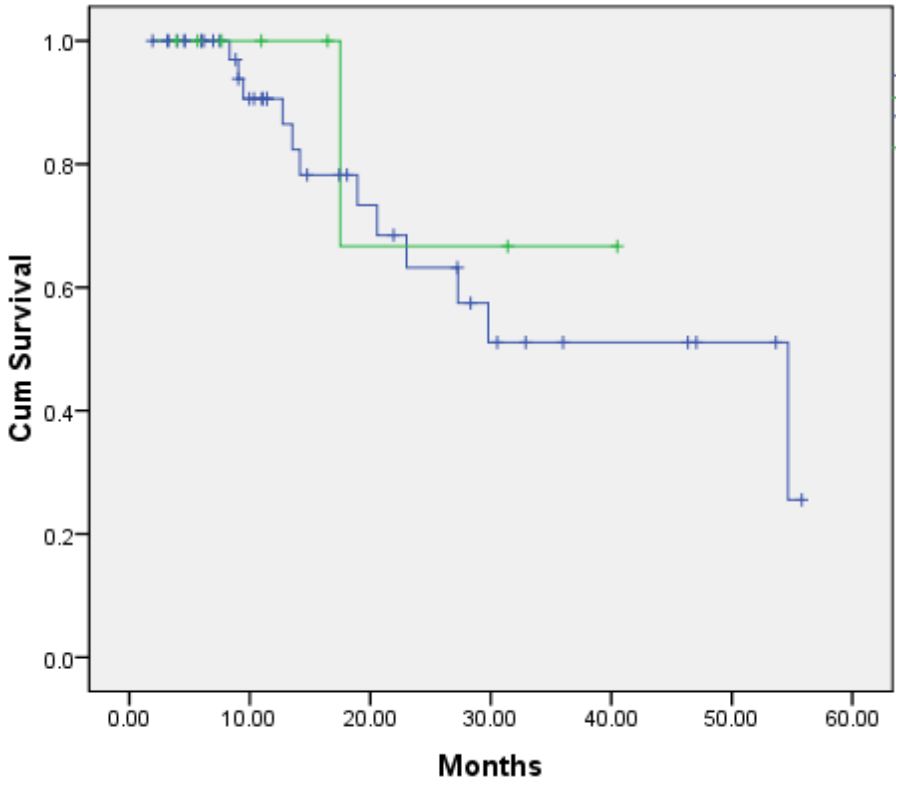
The estimated median disease free survival of the 52 patients who underwent surgery and radiotherapy was 54.7 months (95% CI: 22.8-86.4 months) compared to the significantly poorer disease free survival of 14.7 months (95% CI: 0.9-28.4 months) among the patients who didn't undergo any surgery ($p<0.0001$) (Figure No.22).

Figure No. 22: Disease free survival of patients who completed the planned treatment (blue) compared to patients who refused surgery following neoadjuvant CT-RT (green) ($p<0.0001$)



The median survival of 54.7 months (95% CI: 22.8-86.4 months) was noted for those who underwent adjuvant treatment following surgery. The median survival in the Neoadjuvant+ surgery arm was not reached, due to only one patient having recurrence, and limited follow up within the group. (Figure No.23) The difference in DFS between the Neoadjuvant and adjuvant arms was not statistically significant (p=0.54).

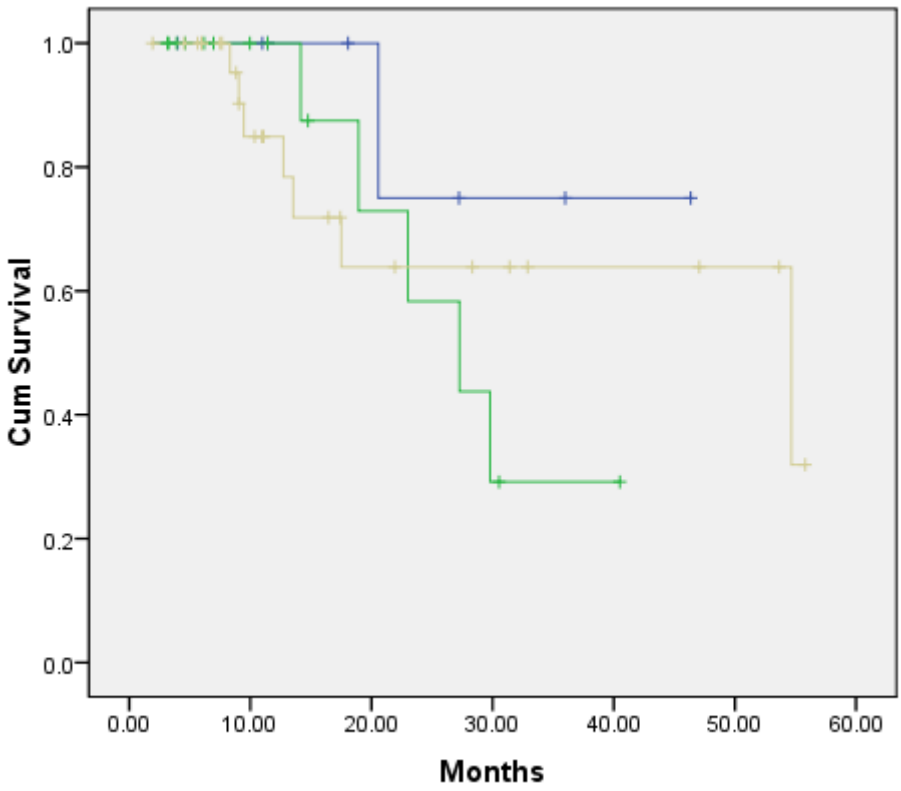
Figure No. 23: Comparison of Disease free survival between neoadjuvant therapy (green), adjuvant therapy (blue). (p=0.54)



In view of incomplete treatment, and significantly poorer outcomes among patients not undergoing surgery, further analyses of the disease free survival data was limited to patients who underwent surgery.

Location of primary: The estimated mean survival for primaries of the upper, middle and lower third rectum were 39.9 months (CI: 29-50.8), 28.0 months (CI: 21.2-34.7) and 39.7 months (CI: 29.6-49.9), respectively. The difference was not statistically significant (p=0.54).

Figure No. 24: Disease free survival by upper (blue), middle (green) and lower (brown) site of origin of primary.



Histopathological grade: The estimated mean disease free survival was 48.7 months (CI: 39.3-58.1) for well differentiated tumors, compared to 30.7 months (CI:23.1-38.2) and 31.2 months (CI: 9.3-53) for grade II and grade III tumors, respectively. The difference was not statistically significant (p=0.49)

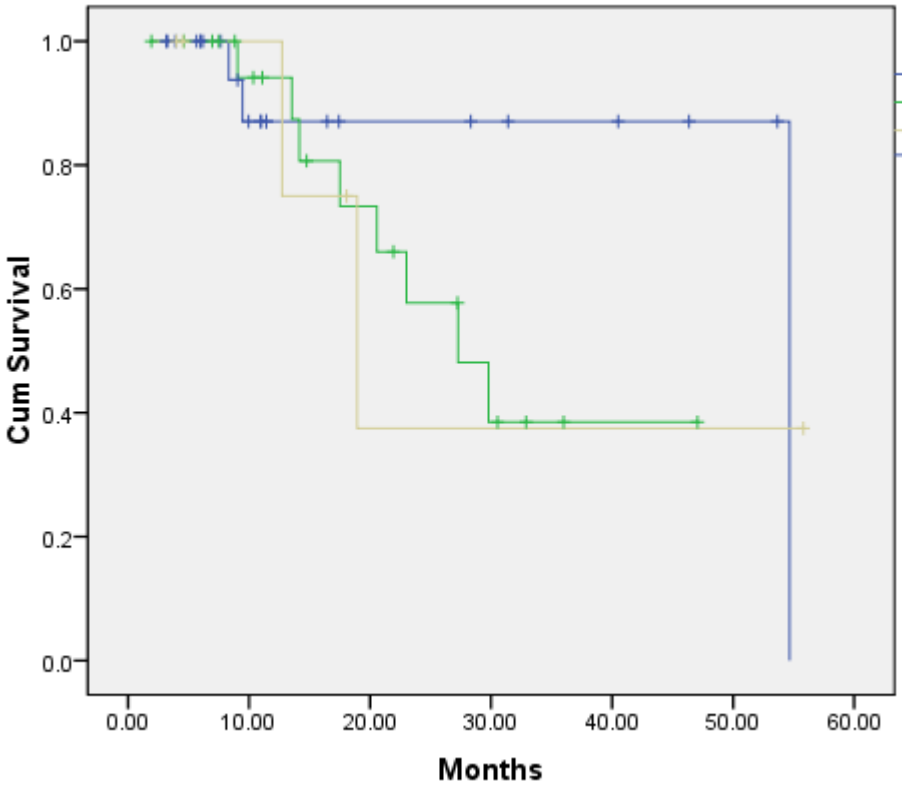
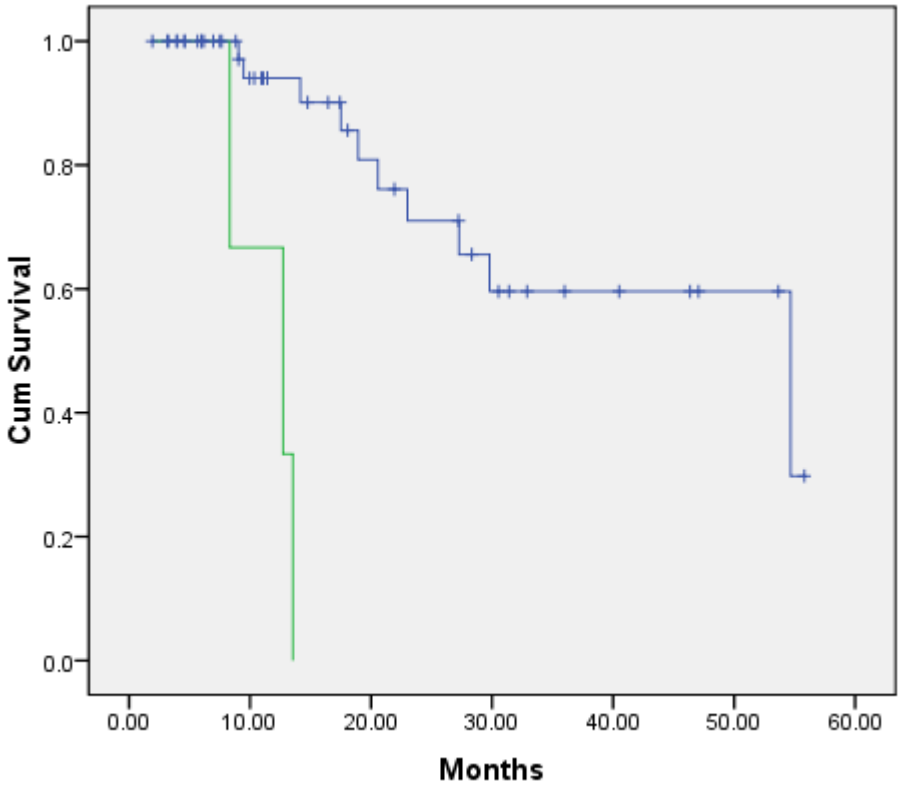


Figure No. 25: Disease free survival based on grade of primary (Grade I: blue, Grade II: green, Grade III: brown)

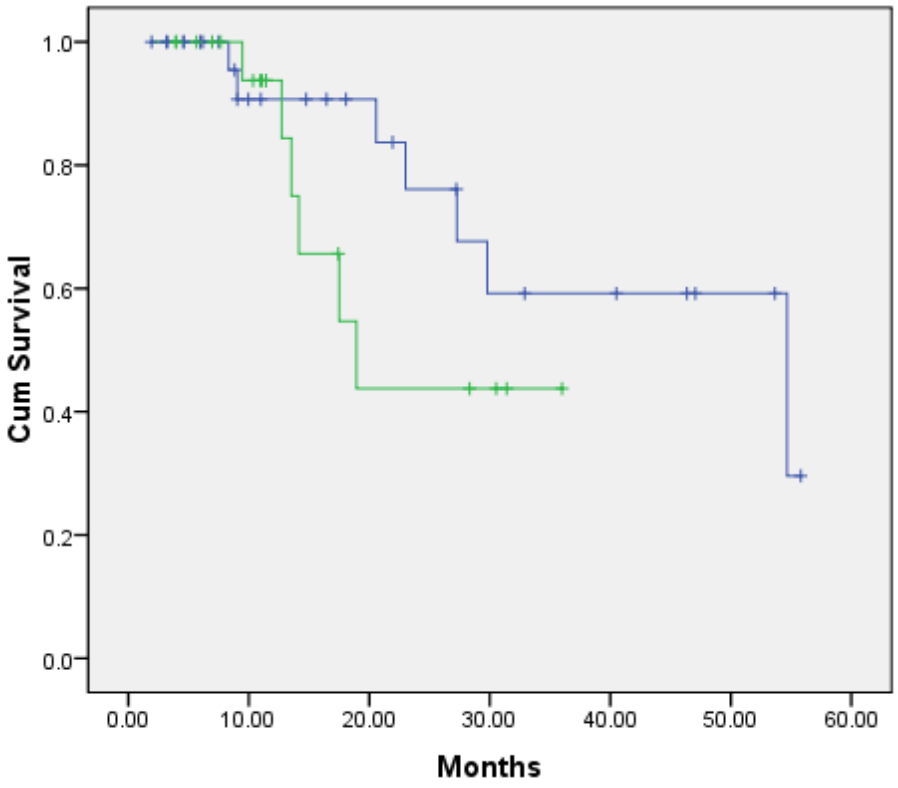
Resection margin status: Negative resection margins significantly impacted on disease free survival; the patients with R0 resection had a mean survival of 41.1 months (CI: 33.8-48.5) compared to 11.5 months (CI: 8.4-14.7) for patients who had a R1 resection ($p<0.0001$).

Figure No. 26: Disease free survival based on margin status (Negative margins: blue, positive: green)



Type of chemotherapy: The estimated mean disease free survival was 41.5 months (CI: 32.7-50.2) for 5FU-LV regimen, compared to 24.1 months (CI:17.6-30.6) for capecitabine. The difference was not statistically significant (p=0.235). Nevertheless, of the 8 patients treated with Neoadjuvant CT-RT prior to surgery, all the patients achieving pCR or yp Stage I received capecitabine. Both the patients who received Neoadjuvant 5-FU chemotherapy had yp Stage III disease.

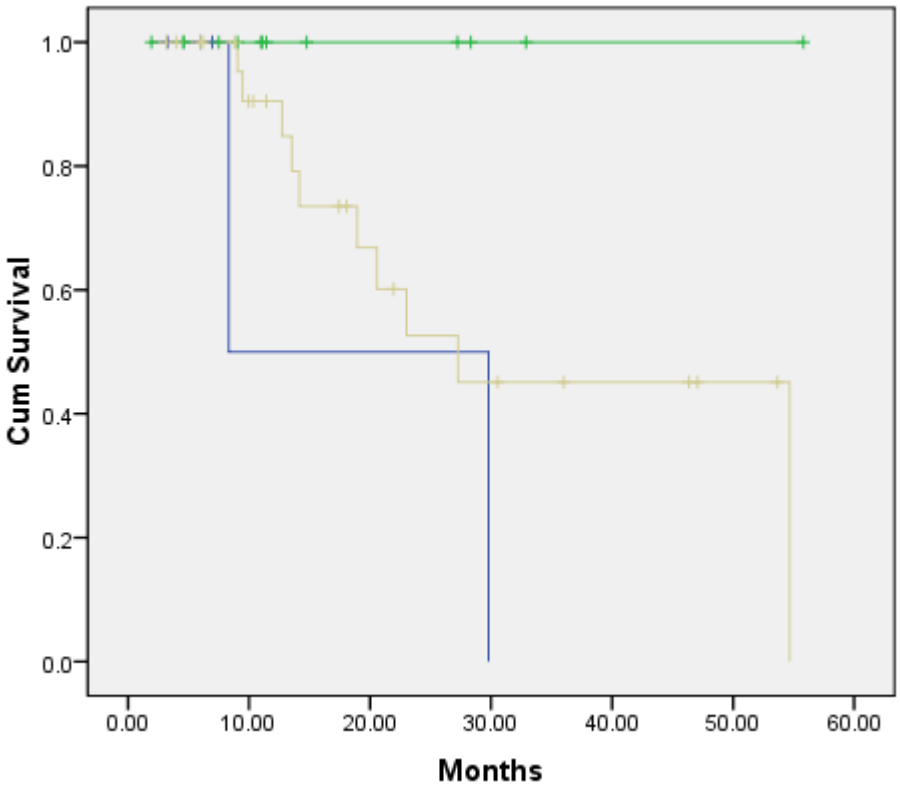
Figure No. 27: Disease free survival based on chemotherapy regimen (5FU-LV: blue, capecitabine: green)



Stage of disease: As patients with Neoadjuvant therapy were few in numbers, analyses of the impact of stage of disease on disease free survival data was limited to patients who underwent adjuvant therapy.

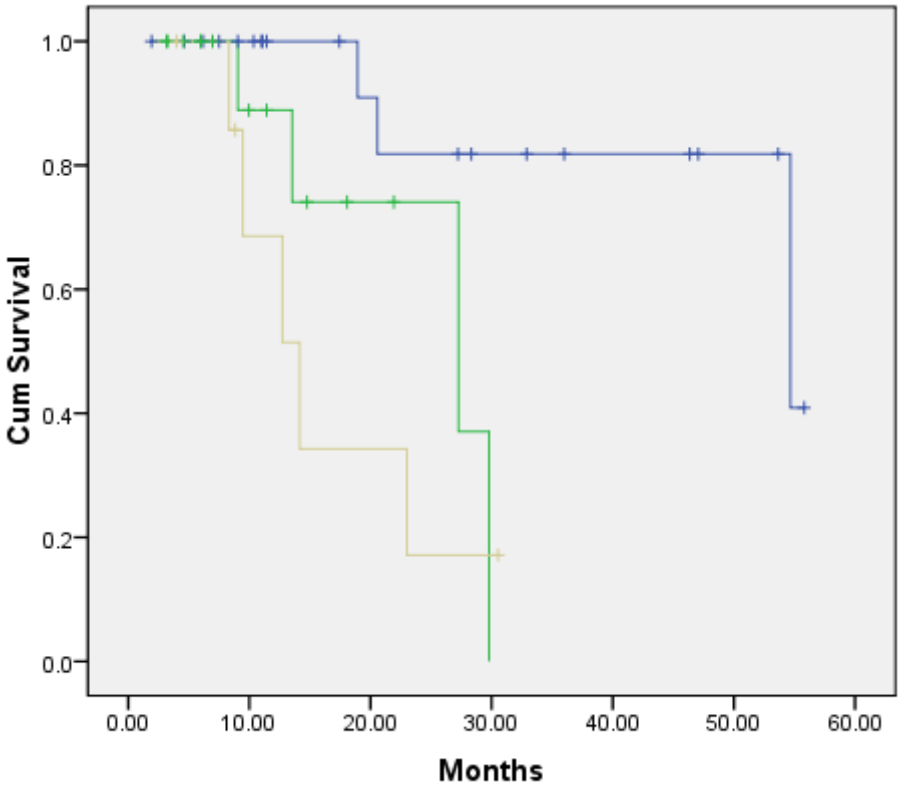
pT stage: The estimated Disease free survival at 2 years was 50% for pT2, 100% for pT3 and 52% for pT4a. The median survival couldn't be calculated because of the censored data; however, the difference in survival was statistically significant (p=0.036).

Figure No. 28: Disease free survival based on pT stage (pT2: blue, pT3: green, pT4a:brown)



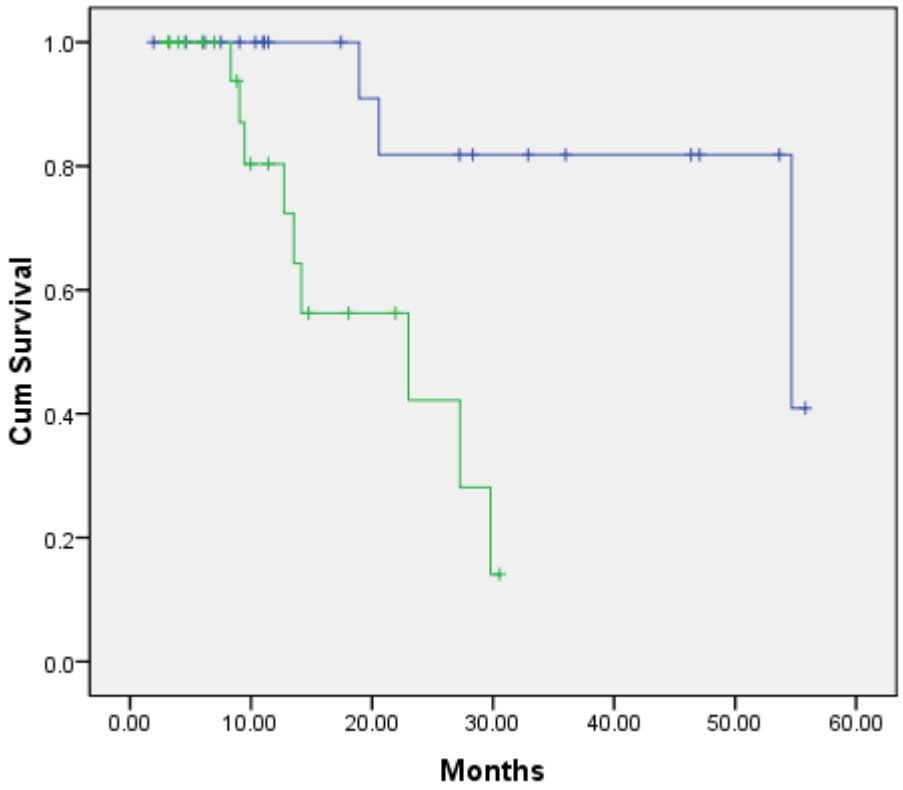
pN stage: The estimated mean disease free survival was 48.8 months (CI: 40.6-56.9) for pN0 tumors, compared to 24.1 months (CI:17.8-30.4) and 16.6 months (CI: 10.3-22.9) for pN1 and pN2 tumors, respectively. The difference was statistically significant (p=0.003).

Figure No. 29: Disease free survival based on pN stage (pN0: blue, pN1: green,pN2:brown)



pAJCC stage: The estimated median disease free survival was 54.6 months (CI: 6.4-102.8) for p stage II tumors, compared to 23.0 months (CI:3.4-42.6) for p stage III. The difference was statistically significant (p=0.002)

Figure No. 30: Disease free survival based on pAJCC stage (stage II: blue, stage III: green)



VI. DISCUSSION

This observational study was conducted to identify the outcomes of patients with rectal cancers undergoing chemo-radiotherapy as a part of definitive treatment at our centre. A total of 67 patients were found to be eligible during the study period, between 2009 and 2013. Though a major cancer worldwide, at our centre where head and neck, cervical and breast cancers predominate, it constitutes a relatively small proportion.

Of the 67 patients, 25 patients were females and 42 were males. F:M ratio was 1:1.68. this difference is likely the result of higher incidence of the disease in males. Age standardized Female:Male incidence ratio of 1:1.35 has been reported for colo-rectal cancers in the United States .(1)

In our study the median age of all the analyzable 67 patients was 50 years (Range: 26-72 years). Median age of the female cohort was 51 years (Range: 32-72 years). Median age of the male cohort was 50 years (Range: 26-72 years). Age groups of 40-60 years constituted more than 50% of the patients in the study. Age is a major risk factor for sporadic CRC. The incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter. (5) However, nearly 15% of our patients were younger than 40 years.

By predominant location of primary, nearly 85% of our patients had primary in the middle third or lower third rectum. Location of primary impacts on the choice of treatment, and potentially also on outcomes. Middle and lower third rectal cancers are more likely to be considered for upfront chemo-radiotherapy with an intent on organ preservation.

Despite a predominance of lower rectal cancers, only a third of our patients received neoadjuvant chemoradiotherapy; the rest were referred to us after primary surgery. A significant percentage of patients (42%) with Abdomino-Perineal resection in our study is probably a result of this.

However, compliance to the prescribed treatment following Neoadjuvant chemoradiotherapy was shockingly poor; nearly 56% of the patients receiving Neoadjuvant CT-RT, constituting 20% of all the patients, refused surgery, despite being informed that not undergoing surgery would lead to a significantly poorer outcome. As expected, the median disease free survival was 14.7 months in these patients, compared to 54.7 months among the patients who underwent surgery. The reason for such poor compliance is not clear, but could be due to the fear that the general public has in undergoing surgery. It also seems to suggest that a similar percentage of patients probably completely refuse recommended treatment options. Epidemiological studies are required to identify the percentage of patients refusing all treatment, and the potential factors that lead to their refusal to treatment.

In view of incomplete treatment, and clearly poorer outcomes, the patients who refused surgery were excluded from further analyses.

Surgical outcomes following neaoadjuvant therapy:

Neoadjuvant or induction chemoradiotherapy is an increasingly used strategy for patients with rectal cancer. Advantages of the neoadjuvant approach include better local

control, an increased likelihood of sphincter saving surgery, and a lower risk of chronic anastomotic stricture.

In our study, out of eight patients who underwent surgery after Neoadjuvant chemoradiotherapy, three patients (37%) underwent sphincter saving procedure (Low Anterior Resection). However, two of these patients had middle third rectal cancers. When considering the six of these patients who had lower rectal cancers, sphincter preserving surgery was done in only one, leading to a sphincter preservation rate of only 16%. Considering the 28 patients with lower third rectum tumors, only four had sphincter preserving surgeries. It is not sure whether high rates of Abdomino-perineal resection despite Neoadjuvant therapy are due to poor response, or due to the cautious approach of the surgeons in avoiding a positive resection margin. Neoadjuvant chemoradiotherapy has been evaluated and proven to be of benefit in several trials for sphincter preservation. The incidence of sphincter preservation varied from 72%to 81%, observed in single-institution studies ,(6) and to 23% to 62% in randomized trials.(7,8) In a study by Rich et.al from MD Anderson Cancer Institute, preoperative chemoradiotherapy was shown to preserve the organ in 68% of the patients.(9) In another phase II study by Valentini et.al evaluating the role of Neoadjuvant chemo-radiotherapy, sphincter preserving surgery could be performed in 12 of 27 patients (44%) who would have surely undergone APR otherwise .(10)

Pathological Complete Response following Neoadjuvant treatment is known to predict a good outcome. Three (37%) out of 8 patients had pCR following Neoadjuvant therapy in our study. pCR rates of upto 20% have been reported in literature. In a randomized study by Kim et.al assessing the benefit of Neoadjuvant capecitabine with radiotherapy reported a pCR rate of 16.9%, and a spinchter preservation rate of 88.7%. Similarly, other study by De Paoli et.al reported a 24% pCR rate. (11, 12)

Acute toxicity of adjuvant therapy:

Hematological toxicity experienced by the patients were recorded while on treatment. Hematological toxicity was generally mild, with only five patients experiencing grade III or higher neutropenia, three patients developing grade III anemia and no patient developing higher than grade II thrombocytopenia.

On the other hand, gastrointestinal toxicity was more prominent. By the end of treatment, all patients had developed at least grade I diarrhea, and more than half had grade III diarrhea. However, no one experienced Grade IV toxicity. The incidence of diarrhea was comparable between the patients receiving concurrent capecitabine and Leucovorin modulated 5-FU regimens. Acute gastrointestinal toxicity is recognized as the most frequent acute toxicity of chemoradiotherapy. Around 5 to 25% of grade III toxicity has been reported in literature. (13, 14, 15) In comparison with other studies, the incidence of grade III toxicity is higher in our study. But the toxicity was self limited, and no patient developed life threatening consequences following the treatment regimen.

Local control:

The importance of surgery in the treatment of rectal cancers is clearly highlighted in the study. Of the patients who underwent only Neoadjuvant chemoradiotherapy, the local control rates were significantly poorer at 40% in comparison to more than 90% among patients who underwent surgery. This is despite the fact that the follow up duration was substantially shorter among these patients. Radiotherapy has been shown to significantly improve local control rates, compared to surgery alone. A metanalysis by Colorectal Cancer Collaborative group, published in 2001, reported that the yearly risk of local recurrence was 46% lower in those who had radiotherapy compared to surgery alone.(16) Addition of chemotherapy to radiotherapy was shown to reduce the local recurrence rates further by the NSABP-R01 and the NCCTG studies. (17, 18, 19)

Among our patients who completed the planned treatment, the local control rates was nearly 95%. In view of few local recurrences and short follow up, no other variable was found to impact on local control other than resection margin status. Even microscopically positive margin seemed to increase the local recurrence rates; of the three patients who developed local recurrence, one had positive microscopic resection margin. Residual tumor after definitive therapy is a well-recognized adverse prognostic factor. (20-23) All the patients identified to have local recurrence had pT4a disease.

Disease Free Survival

With a median follow up duration of 11.1 months (Range: 1.9 to 55.8 months), a total of 24 patients (36%) had recurrences. The estimated DFS of the patients who completed the treatment was 52 months. The DFS seemed to be similar between patients receiving Neoadjuvant or adjuvant therapy. Location of primary also had no effect on DFS. As expected, the DFS was significantly shorter among patients who had a microscopic positive resection margin. Though patients with well differentiated tumors appeared to have a longer relapse free survival (48.7 months) compared to moderately or poorly differentiated tumors (30.7 and 31.2 months, respectively), the difference was not statistically significant. Similarly, though patients receiving 5-FU had a longer relapse free interval (41.5 months) compared to patients receiving capecitabine (24.1 months), no statistical significance was obtained. Concurrent capecitabine chemotherapy has been proven to be superior to leucovorin modulated bolus 5-FU. (24-27) Though the difference was not statistically significant, the reason for this discrepancy from published literature is not clear. A larger randomized study conducted in Indian patient population could identify if there is any racial difference in the outcomes of therapy.

The most important indicator of outcome after resection of CRC is the pathologic stage at presentation. (28) Our study showed a significantly improved DFS in patients with AJCC stage II (54.6 months) compared to stage III (23 months).

Limitations of the study

This study has several limitations. It was conducted during a relatively short period of time, and had a small number of patients. Most of the patients were referred to the department after initial surgery, and hadn't undergone an initial multidisciplinary assessment to see if they could be considered for organ preservation therapy. Moreover, 15 of the 23 patients who received neo-adjuvant chemo-RT failed to undergo surgery. The follow up duration is also short, with several patients being lost to follow up a few months after completion of treatment.

VII. CONCLUSION

- Our patients who defaulted from surgery following Neoadjuvant chemo-radiotherapy(CT-RT) had a significantly poorer local control rates and disease free survival.
- Neoadjuvant therapy didn't seem to increase the sphincter preservation rates in our study.
- The acute toxicity of CT-RT was within reasonable limits in our patients and there were no life threatening consequences during treatment.
- In the short follow up period, the local control rate was very good. Achieving a negative margin status at the time of surgery was found to be of significant importance in local control.
- The patients who completed the treatment as prescribed had a Disease Free Survival comparable with those reported in the literature.
- Even though the number of patients receiving Neoadjuvant Chemoradiotherapy and surgery was small, their outcomes was comparable to those who underwent adjuvant Chemoradiotherapy.
- Disease Free survival was found to be significantly poorer in patients with higher stage disease and positive resection margin status.
- Interestingly, though not of statistical significance, patients receiving adjuvant 5-FU appeared to perform better when compared to those receiving capecitabine.

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