A comparative study of neoadjuvant chronomodulated folfox and radiotherapy vs. Conventional folfox and radiotherapy in locally advanced carcinoma rectum

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ABSTRACT

Aim: This study was undertaken to determine and compare the efficacy and toxicity of chronomodulated FOLFOX + radiotherapy to conventional FOLFOX + radiotherapy in the neoadjuvant setting of locally advanced rectal cancer. **Materials and methods:** A total of 44 patients were randomly assigned to the two arms with 24 in chronomodulated arm (Arm A) and 20 in conventional arm (Arm B).Four cycles of FOLFOX chemotherapy followed by radiotherapy were given to18 patients in Arm A and all the 20 patients in Arm B completed the treatment. All the patients were evaluated for surgery. Tumor down staging and toxicity profile were compared. **Results**: tumor down staging and sphincter preservation rates were similar in both the arms. Incidence of grade-III and grade-IV stomatitis, diarrhea and paresthesia was more in Arm B than in Arm A. Nausea was the most common symptom in both the treatment arms.83% patients in Arm A and 86% patients in Arm B experienced nausea at some point during the treatment. Diarrhea was more common in Arm B with 15 % patients experiencing grade 3-4 diarrhea when compared to 5.55% in Arm A. Stomatitis was more common in Arm B with 10% patients experiencing grade 3-4 toxicity as compared to 5.5% in Arm A. It was observed with increased frequency in Arm B with 7(20%) patients experiencing grade 3 sensory neuropathy compared to 2(11.1%) in Arm A. The incidence of hematological toxicities was similar in both arms with only grade 1 and 2 neutropenia occurring in both the arms. The incidence of leucopenia was greater in the conventional arm (Arm B).**Conclusions**: we conclude that the administration of Chronomodulated FOLFOX followed by radiotherapy has a better toxicity profile and hence better tolerance and similar tumor down staging when compared to conventional FOLFOX and radiotherapy in the neoadjuvant treatment of locally advanced carcinoma rectum.

Key words: Colorectal, male, cancer**.**

Introduction

Globally, colorectal cancer is the third commonest cancer in men since 1975. In the developed countries it is now the second most common cancer after lung cancer in men. Incidence rates in Africa, except South Africa and South and Central Asia including India are quite low (2 to 8 per 100,000). Colorectal cancer burden has been steadily rising in women. It was the fourth commonest cancer in 1975 and has reached the second position by 1990[1].Rectal cancer ranks 7th among the most common cancers in males and is the 6th most common cancer in women in India.[i]An estimated 35,635 new cases of colorectal cancer occurred in 2006, accounting for 3.9 percent of all new cases of cancer[2].Age standardized incidence rate per 100,000 populations in men ranges from 1.5 to 6.9 and in women it ranges from 2.5 to 7.4 in the various urban population based cancer registries.**Error! Bookmark not defined.** The incidence rates are low in the rural areas ranging from 1.6 to 2.4 in males and 1.1 to 1.3 in females. Out of the seven PBCRs (population based cancer registries) an increasing trend in the age adjusted annual incidence rates (AAR) in the colorectal cancer was observed[3]. Statistics from MNJ Institute of Oncology and Regional Cancer Centre from the year 2001-2009 shows the incidence of rectal cancer to range from 1.12%-2.48 % of all cancers registered

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during the ten years. Average male to female ratio is **1.56:1.**A working definition of "***locally advanced rectal cancer***" is one that cannot be resected without leaving microscopic or gross residual disease at the local site because of tumor adherence or fixation to that site. It includes those tumors reaching to and beyond the endopelvic fascia (extensive T3 and T4 tumors).The 5 year survival rate in these patients with surgery alone which includes wide en bloc resection of adjacent organs is only 19-33 %.**Error! Bookmark not defined.**About 75% patients fail locally, therefore good local control is essential to achieve good survival rate.Surgery remains the mainstay of treatment for rectal cancer. Transmural involvement and node positive disease pose a challenge to surgery as it is difficult to achieve free circumferential margins even with total mesorectal excision (TME). Neoadjuvant radiotherapy, by down staging the tumor, improves the surgical outcome and reduces the local failure rates but does not alter the overall survival.

Materials and methods

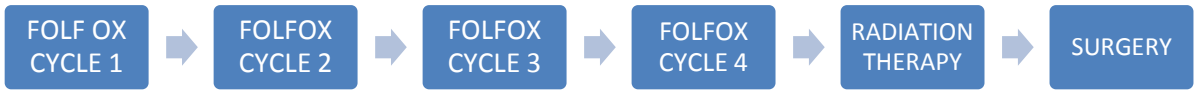
The patients treated between October 2008 and April 2010 at MNJ Institute of Oncology and Regional Cancer Center with the following inclusion and exclusion criteria were taken into the study.

Inclusion Criteria: Age less than 75 years Adeno carcinoma of rectum proven by biopsy, Stage III or beyond rectal cancer either clinically or image logy (CECT abdomen, trans rectal ultrasound),ECOG performance status of 0-2, Hematological parameters with total leukocyte count of>4000cells/mm^3, platelet counts of >1.5 lakhs /$mm^{3.}$

Exclusion Criteria: Age greater than 75 years , Patients with demonstrable distant metastasis at the start of treatment , Histopathology other than adenocarcinoma, Previous treatment for any pelvic malignancy, Poor performance status ECOG PS >2, Deranged hematological and renal parameters and Patients not likely to be available for follow up.

Complete history and physical examination, Digital rectal examination- The distance between the anal verge and the lower pole of the tumor was assessed by digital rectal examination.

Haematological, Radiological investigations, Endoscopic study and Histopathology of the tumor and grade. After thorough pre-treatment evaluation, the intent regarding the type of surgery was recorded before proceeding for pre-operative chronomodulated FOLFOX and radiotherapy or conventional FOLFOX and radiotherapy, by randomly assigning the patients to each arm.



Study Design

CHEMOTHERAPY

Arm A: Selected patients were explained regarding the course of treatment and were started on chronomodulated FOLFOX with Oxaliplatin 85 mg/m^2on day 1 administered from 0945hrs to 1600hrs followed by simultaneous infusion of calcium leucovorin in one arm and 5 fluorouracil in the other arm from 2200hr to 0915hr the next day for five days. The cycle was repeated every three weeks for four cycles. After chemotherapy the patients were evaluated for response by DRE, serum CEA, X ray chest and CT scan abdomen and pelvis.

Arm B:In this group the patients were administered FOLFOX conventionally with Oxaliplatin 85mg/m^2 on day 1 and calcium leucovorin and 5 fluorouracil from day 1 to day 5 repeated every 3 weeks for 4 cycles. The response was evaluated with DRE, CT scan of abdomen and pelvis, serum CEA and x- ray chest.

Radiotherapy to the pelvis by external beam with either Cobalt 60 or Linear accelerator was planned by either 4 field, 3field or 2 field techniques to a total dose of 45-50.4 Gy. Patients were simulated on a Ximatron x-ray simulator and planned with the following field borders:

- ***Superior margin***: Lower border of L5 or L5 – SI junction or 1.5 cm above the sacral promontory.
- ***Lateral margin***: 1.5 – 2 cm lateral to the true bony pelvis.
- ***Inferior margin***: Lower border of the obturator foramen in case of upper rectal cancers or 2 – 5 cm below the most inferior extent of the gross tumor.

- ***Lateral Fields***: The upper and lower margins remain the same. The anterior margin was at least 4 cm anterior to the rectum, as determined by the rectal contrast. The posterior field margin is 1to1.5cm behind the sacrum to include whole of the sacral canal.All the patients from both the arms were taken up for surgery after 4-6 weeks of radiotherapy. Total mesorectal excision coupled with low anterior resection or abdominoperineal resection or pelvic exenteration was planned based on preoperative evaluation.During the course of the radiotherapy or concurrent chemo radiation and in the post-RT follow up period the patients were examined regularly for acute toxicity using Common Toxicity Criteria (Ver-2)[108]. Toxicities were managed symptomatically with analgesics, intravenous fluids, and antibiotics. In patients with grade-III or IV toxicity, treatment was interrupted. Packed cell transfusions and colony stimulating factors were used whenever necessary.All the patients were taken up for adjuvant chemotherapy and were followed up regularly once in a month for 1 year and 3 monthly in the next 2 years and 6 monthly follow up afterwards with clinical examination, S.CEA, periodical CECT-abdomen, colonoscopy.

Results

Patients treated from October 2008 to April 2010 were analyzed. A total of 294 rectal cancer patients were treated during the period. Of the 294 patients 132(44.8%) patients were treated with post-operative radiotherapy.47 (15.9%) patients presented with metastatic disease at diagnosis. Three patients had other than adenocarcinoma histology.112 (38%) patients received neoadjuvant treatment.Of the 112 patients who received neoadjuvant treatment 63 received only concurrent chemo radiation. Of the remaining 49 patients 5 patients did not fulfil the inclusion criteria (2 had renal failure ,PS of 2 patients was 3-4 and one patient was irradiated previously).A total of 44 patients fulfilled the inclusion criteria and were included in the study. 24 patients were included in the Chronomodulated arm (Arm A) and 20 patients in the conventional arm (Arm B).Of the 24 patients in Arm A, 6(25%) patients received incomplete treatment (3 patients developed distant metastases while on treatment and 3 patients refused further treatment after 2 cycles of chemotherapy).So a total of 18(75%) patients completed treatment in Arm A.

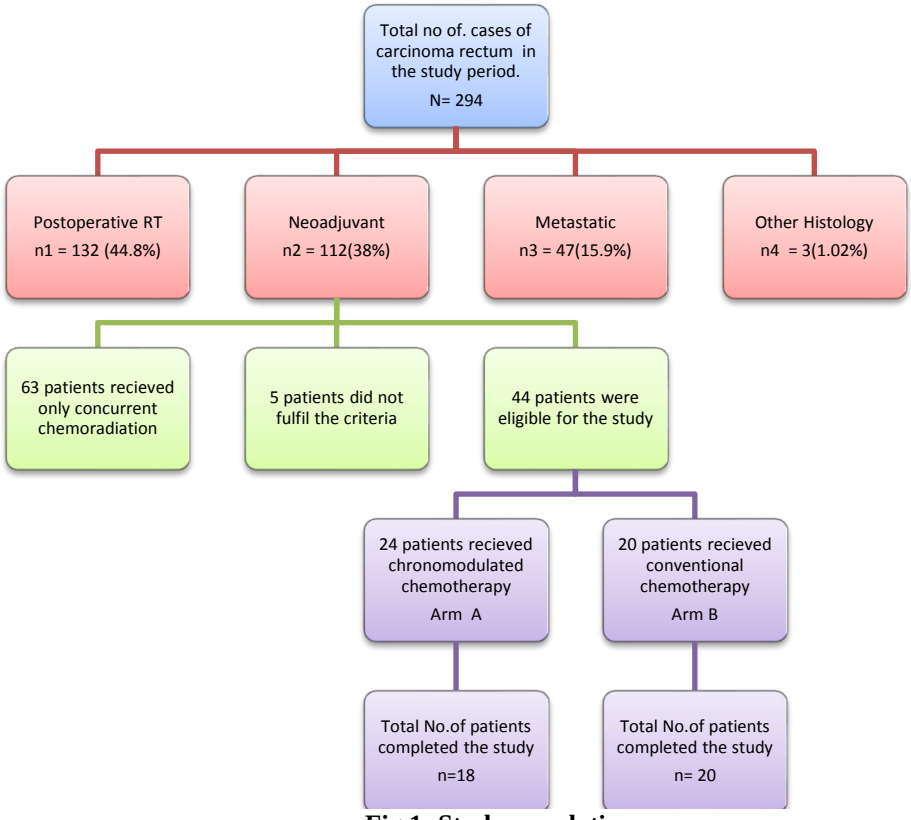


Fig 1: Study population.

Table 1: Patient Profile

Patient Characteristics	Arm-A Chronomodulated	Arm-B Conventional
Total No of patients included in the study	24	20
Total No of patients completed the study	18(75%)	20(100%)
Mean Age at diagnosis	42.2 yr	38.4 yr
Sex Ratio(Male: Female)	1.4	2
Mean distance from the anal verge	2.7 cm	3.2 cm
Type of surgery		
Abdominoperineal resection or Low anterior resection	12 3	15 2
Exenteration	1	1

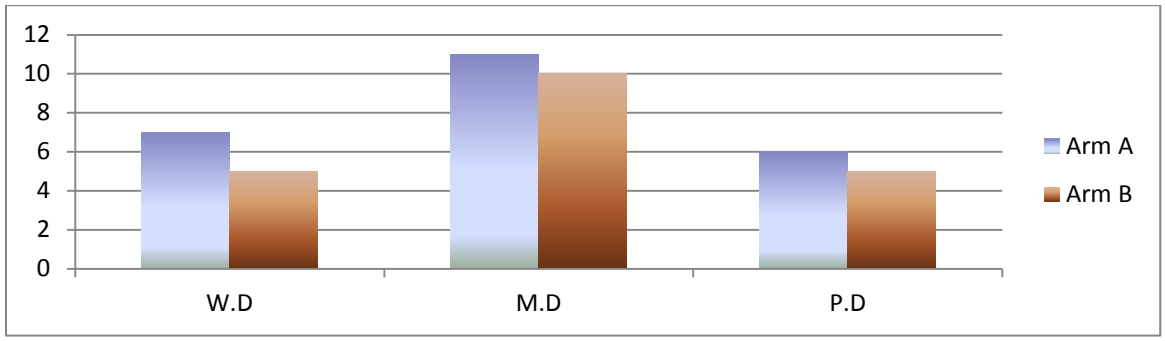


Fig 2: Grade of the Disease in Both Arms

Tumor downstaging

The tumor down staging in post-operative histopathology is as follows:

- *Arm-A*:- 16(88.9%) patients underwent significant down staging, 7 patients from T4 lesion to T3 and T2 stages and 9 patients from T3 to T2. 5 patients who had node positive disease as per imaging studies had node negative disease at surgery.
- *Arm-B:*- 18(90%) patients had tumor down staging. 11 patients from T3 to T2 ,7 from T4 to T2 and 4 patient who was node positive became node negative at the time of surgery.

SPHINCTER PRESERVATION:

Arm A: Of the 16 patients who underwent surgery,3(18.7%) had low anterior resection with sphincter preservation.

Arm B: Of the 18 patients who were operable after neoadjuvant treatment,2(11.1%) underwent sphincter preserving surgery.

Acute toxicities:-All the toxicities were graded according to WHO Common Toxicity Criteria version 2.0.

Table 2: Incidence of Side effects

	Grade 1	Grade 2	Grade3	Grade4
Nausea				
Arm A	12(66.6%)	1(5.5%)	2(11.1%)	-
Arm B	14(70%)	1(3.44%)	2(10%)	-
Vomiting				
Arm A	4	2 (11.1%)	-	-
Arm B	3	2 (10%)	-	-
Diarrhea				
Arm A	4	1	1	0
Arm B	5	4	3	0

Stomatitis				
Arm A	-	2	1(5.5%)	0
Arm B	-	6	2(10%)	0
Peripheral sensory neuropathy				
Arm A	3	1	2	0
Arm B	2	4	4	0
Hematuria				
Arm A	3	1	0	0
Arm B	3	2	0	0
Dysuria				
Arm A	4	3	1	0
Arm B	5	4	2	0
Anemia				
Arm A(Chrono)	4	2	-	-
Arm B(Conv.)	5	3	-	-
Leucopenia				
Arm A(Chrono.)	2	0	-	-
Arm B(Conv.)	5	4	-	-

- Incidence of grade-III and grade-IV stomatitis, diarrhea and paresthesia was more in Arm B than in Arm A. Nausea was the most common symptom in both the treatment arms.83% patients in Arm A and 86% patients in Arm B experienced nausea at some point during the treatment. There was no significant difference in the incidence of nausea in both the arms. Diarrhea was more common in Arm B with 15 % patients experiencing grade 3-4 diarrhea when compared to 5.55% in Arm A.All the patients with severe symptoms were managed accordingly with intravenous fluids. Stomatitis was more common in Arm B with 10% patients experiencing grade 3-4 toxicity as compared to 5.5% in Arm A. It was observed with increased frequency in Arm B with 7(20%) patients experiencing grade 3 sensory neuropathy compared to 2(11.1%) in Arm A. The incidence of hematological toxicities was similar in both arms with only grade 1 and 2 neutropenia occurring in both the arms. The incidence of leucopenia was greater in the conventional arm (Arm B).

Discussion

Surgery forms the main stay of cure in carcinoma rectum. However in locally advanced rectal cancer, results of surgery as the lone modality of treatment showed increased incidence of local recurrence. Hence adjuvant therapy in the form of pre-operative or post-operative radiation therapy with or without chemotherapy has become the accepted modality of treatment.The most important information regarding the use of pre-operative radiation therapy and its advantages compared with surgery alone comes from the Swedish rectal cancer trial and the Dutch TME study. The Swedish rectal cancer study group randomized 1168 patients to preoperative short course radiotherapy(25 Gy in 5 fractions)followed by surgery after 1 week in Arm A or only surgery in Arm B with a median follow up of 7 years.

Table 3: Results of Study Group

Study related to our study	Arm A	Arm B	P value
Swedish Rectal Cancer Study			
Treatment given	Pre op RT (25Gy in 5#) followed by surgery	Surgery alone	
Local recurrence rate	11%	27%	<0.001
5 yr Overall survival	58%	48%	0.004
The Dutch TME Study			
Treatment given	Preop RT+TME	TME alone	
2 yr OS	82%	81.8%	0.84
2 yr local recurrence	2.4%	8.2%	<0.001

This was the only study that showed a significant survival benefit after the use of pre-operative radiation therapy[4,5].A meta-analysis of 14 randomized control trials done over 2 decades comparing pre-operative RT+ surgery and surgery alone showed reduction in cancer related mortality(CI 0.38-0.62) and local recurrence rates in RT + surgery group but there was no change in the rate of distant metastasis[6].After the advent of the technique and the concept of Total Mesorectal Excision (TME), the incidence rates of local recurrence drastically fell down. Studies have shown that the surgical technique and the experience of the operating surgeon are the most important factors in determining the local recurrence after surgery. The Dutch TME study Number of patients were 1861 patients with resectable rectal cancer. This showed that pre-operative radiation therapy helps in reducing the local recurrence rates[7].There are some biological, functional and physical advantages with preoperative radiotherapy, which include decreased tumor seeding at the time of surgery, increased radio sensitivity of the tissues as compared to the postoperative hypoxic tissues, no postoperative small bowel fixation in the pelvis and hence less chances of complications and increased chances for a sphincter sparing surgery. But the major disadvantage is potential over treatment of the early stage and more disseminated presentations of the disease.

Pre-operativeVs.post-operative radiotherapy;There has been a debate regarding the timing of radiotherapy. Several studies were done comparing the pre-operative and post-operative approaches. German rectal cancer study group randomly assigned 421 patients to receive preoperative chemo radiotherapy and 402 patients to receive postoperative chemo radiotherapy. The conclusion was that Preoperative chemo radiotherapy, as compared with postoperative chemo radiotherapy, improved local control and was associated with reduced toxicity but did not improve overall survival[8].

Studies such as FFCD9203[9], EORTC 22921[10-12]comparing radiotherapy alone and chemo radiation have been conducted and these found no difference in sphincter preservation rates though the tumor down staging was more significant in the chemo radiation arms. The timing of chemotherapy was suggested to have better compliance rates when given in the preoperative setting owing to lesser toxicity.The issue regarding the time gap between the end of pre-operative therapies and sphincter saving surgery was dealt with in 4 randomized studies namely the Polish rectal cancer group trial, German randomized trial[13], NSABBP R-03 trial[14], Lyon trial[15]because of the fact that rectal cancer shrinks slowly. All the studies showed no significant benefit in rates of sphincter preservation with delayed surgery.The role of induction chemotherapy prior to preoperative chemo radiation therapy has been explored both in poor-risk patients and conventional risk patients with locally advanced rectal cancer. The theoretical advantages of induction chemotherapy include the potential for improved tumor regression as well as improved treatment compliance allowing for the delivery of full systemic doses of chemotherapy.In a study conducted by The Royal Marsden Hospital 4 cycles of induction CapeOx followed by capecitabine CXRT (54 Gy)was administered in high risk rectal cancer patients. It was associated with a high rate of R0 resection (96%) and a pCR rate of 20%[16]The Spanish Gruppo Cancer de Recto 3 Study was a randomized phase II study that was built upon the lessons learned from the Royal Marsden experience.108 patients with locally advanced rectal cancer randomized study (Table-3)[17]Calvo et al[18]studied the incidence of pT0 down staging in locally advanced rectal cancer when treated with induction Oxaliplatin/5FU/LV when compared to concurrent chemo radiation alone.Studies on chronomodulated FOLFOX Levi et al performed a randomized phase II study comparing conventional and chronomodulated infusion of FOLFOX[19].

- Arm A: Conventional FOLFOX : 5 d continuous infusion Q21days
- Arm B: Chronomodulated FOLFOX :Oxaliplatin administered between 1015h and 2145h 5FU+LV administered from 2215 to 0945 h

This trial provided clinical data to corroborate the potential of chronomodulation with these agents and led to additional trials.

Levi et al. pooled and updated data from this trial and a second study. In the combined analysis, 140 patients were treated with the flat infusion and 138 with the chronomodulated infusion schedule. The objective response rates were 30% vs 51% and the resection rate was 13% vs 23%. Median survival was 16.5 vs 18.6 mo and 13% vs 15%of patient were alive at 5 yr after study entry[20]Another French group has published work using chronomodulated drug delivery schedules[21] In this trial, 50 patients with metastatic colorectal cancer, 37 of whom were pretreated, were given a regimen consisting of 300 mg/m2/d LV, 700 mg/m2/d 5-FU, and 25 mg/m2/d Oxaliplatin for 4 d every 2 wk. The drugs were delivered via a pump programmed to maximize peak flow rates of Oxaliplatin at 4:00 PM and 5-FU at 4:00 AM. The median 5-FU drug dose was 3200 mg/m2 per course, indicating that dose escalation was possible in many patients. The response rate was 48%, including a 40%

response rate in 5-FU-pretreated patients. Toxicity was moderate with grade 3 hand–foot syndrome in 14%, peripheral neuropathy in28%; grade 3–4 nausea and vomiting in 36%, and diarrhea in 7%.

Giachetti et al[22] conducted a trial to compare the response rates and toxicity profiles of chronomodulated 5FU+LV Vs chronomodulated Oxaliplatin+5FU+LV in locally advanced and metastatic colorectal cancer[22]

Arm A: 5-FU (700 mg/m2/d) and LV (300 mg/m2/d) infused from 2215 to 0945 h, peak delivery by programmable pump at 0400 h, d 1–5, q 21 d

Arm B: Oxaliplatin (125 mg/m2/d) infused from 1000 to 1600 h, d 1, q 21 d and 5-FU (700 mg/m2/d) and CF (300 mg/m2/d) delivered as in arm A, d 1–5, q 21 d.

Table 4: Results (Intent to treat) Error! Bookmark not defined.

	Arm 1:5FU/LV	Arm 2:5FU/LV/OXAL
No. of patients	100	100
No. of patients evaluated	92	88
Overall response rate	16%	53%(p=<0.001)
CR	0/100	3/100
PR	16/100	50/100
Stable	45/100	24/100

Toxicities were mild in Arm 1 with <5% patients experiencing grade 3-4 toxicities while 43%patients in Arm 2 experienced grade3-4 diarrhoea and 25% had grade 3-4 nausea/vomiting. In summary, this randomized multicenter phase III trial Showed threefold increase in response rates when Oxaliplatin was added to 5FU/LV. Overall, the Oxaliplatin-containing arm did have more toxicity. The most common side effect was diarrhoea, and the cumulative dose-limiting toxicity was sensory peripheral neuropathy.EXPERT study (Oxaliplatin Capecitabine and preoperative radiotherapy followed by TME) included 105 patients of poor risk rectal cancer. Patients were treated with four cycles of Oxaliplatin 130mg/m^2 and Capecitabine 2000mg/m^2/d D1-D14 repeated every 3 weeks followed by concurrent chemo radiation to a total dose of 54 Gy with capecitabine 1620mg/m^2/d. Resolution of symptoms was observed in majority of patients at a median of 32 days from the start of chemotherapy. Radiological response rate was 88% following neoadjuvant chemotherapy and increased to 97%after neoadjuvant chemo radiation. Complete radiological response was observed in 20% at the end of chemo radiation. There was no progressive disease during treatment,.R0 resection was achieved in 99% of patients. 16(24%) patients had PCR. Tumor down staging was observed in 76% of patients.

Conclusion

Tumor down staging and toxicity profile were compared. In our study the tumor down staging and sphincter preservation rates were similar in both the arms. Grade 3-4 toxicities of stomatitis, diarrhea and paresthesias were more common in the conventional arm Thus we conclude that the administration of Chronomodulated FOLFOX followed by radiotherapy has a better toxicity profile and hence better tolerance and similar tumor down staging when compared to conventional FOLFOX and radiotherapy in the neoadjuvant treatment of locally advanced carcinoma rectum. But given the small sample size in each group further studies with larger number of patients are required to come to a statistically significant conclusion

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