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The Impact of Capecitabine and Oxaliplatin in the Neoadjuvant Treatment for Patients with Locally Advanced Rectal Cancer

KEYWORDS: CTH:Chemotherapy ,RTH :Radiotherapy ,pCR:pathological Complete Response ,CR:Complete Response ,CRC: Colorectal Cancer

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ABSTRACT *Background:Colorectal cancer (CRC) is one of cancer-related mortality in digestive system.Egypt has early onset colorectal cancers allover the world, and few studies designed to understand this cancer.*

Objectives: Primary: evaluate curative effects and safety of addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) improves 2-year Local Control in locally advanced rectal cancer. Secondary : determine 2-year progression-free survival (PFS),2-year overall survival and toxicity of this neoadjuvant regimen .

Patients and Methods: 33 patients were randomly assigned to preoperative CT-RT with CAPOX (50.4-Gy RT for 5 weeks with concurrent capecitabine and oxaliplatin). Patients underwent preoperative Pelvic high resolution MRI or abdominal and pelvic MDCT scans for restaging of middle and lower thirds cancer. Thereafter Sphincter –Preserving Surgery performed after 6 weeks . statistical methods: p-values less than 0.05 were considered significant. SPSS ver.21 for Windows (SPSS Inc., Chicago, IL, USA).

Results: 18 patients (54.5%) achieved complete response to neoadjuvant therapy , 8(24.2%) achieved partial response, and 7 (21.3%) had stable disease. The overall accuracy of MRI/MDCT restaging was 66.7% and 78.8% respectively.Sphincter –Preserving Surgery performed in 27 patients (81.8%),6 patients (18.2%) underwent abdominoperineal resection. Mean overall survival(Mean ± S.D) is (11.00 ±8.18) months and reported 60.6% local control rate and39.4%local failure rate after follow up period of 24 months. Disease free survival(Mean ± S.D) is 9.25±6.37.

Conclusions:At 2 years, there is significant difference in clinical outcome achieved with the CAPOX regimen.These results indicate that neoadjuvant concurrent administration of oxaliplatin and capecitabine with RT could change the course of management.

Introduction:

Colorectal cancer (CRC) is one of the most common causes of digestive system cancer-related mortality, and is the fourth main cause of cancer-related mortality worldwide . The American Cancer Society has identified colorectal cancer as a major priority because the application of existing knowledge has such great potential to prevent cancer, diminish suffering, and save lives.

Mortality data were provided by the National Center for Health Statistics,in 2014, 71,830 men and 65,000 women is diagnosed with colorectal cancer. During the period 2013–2050, population of Egypt is expected to increase to approximately 160% the 2013 population size.This increase reflected both population growth and demographic change mainly due to aging of population. Population growth alone would increase the number of incident cases by 55.2% in 2015. This fraction progressively decreased to become 32.8% in 2050. The fraction due to ageing gradually increased to reach 67.2% in 2050,this decrease may be due to both earlier diagnosis through screening and better treatment modalities. [1]

Mid to low rectal cancers lying below the anterior peritoneal reflection and extending through the rectal wall, or involving locoregional lymph nodes (T3/4 or N1/2), have historically been more difficult to cure. The confines of the bony pelvis and the necessity of preserving the autonomic nerves makes surgical extirpation challenging, which accounts for the high rates of local and distant relapse in this setting.[2]

Surgery is usually the main treatment for rectal cancer, with the exception of some patients with distant-stage disease. Additional treatments, such as chemotherapy and radiation, are often used before surgery (neoadjuvant therapy) and/or after surgery (adjuvant therapy) to reduce the risk of recurrence and metastasis. In T3-4 M0 rectal cancers, total mesorectal excisionremains the cornerstone of treatment. Local control rate is further improved with preoperative radiotherapy. European Organisation for the Research and Treatment of Cancer trial 22921 and Fe´de´ration Francophone de Cance´rologie Digestive (FFCD) trial 9203 further showed that the addition of fluorouracil to radiotherapy significantly increased the pathologic complete response rate (ypCR) and local control. The German Rectal Cancer Study Group established preoperative chemo radiotherapy as a standard for most T3-4 rectal adenocarcinoma. [2-4]

Several phase I/II trials have shown the feasibility and safety of the addition of oxaliplatin to the preoperative regimen . In addition, there have been trials in colorectal cancer showing that capecitabine, an oral prodrug of 5-FU, can be substituted for infusional 5-FU .With the feasibility of High-Resolution MRI and its extreme sensitivity in delineating tumor margins,nodal involvement,mesorectal invasion and distant metastases,MRI is

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currently one of the most accurate non-invasivemodalities for staging rectal cancer with predictive sensitivities of T3 80-86% and specificity 71-76%. [5-7]

The time needed to heal after surgery is different for each person. Patients often have some pain for the first few days; however, this can usually be controlled with medication. It can take a few days to be able to eat normally again. Patients are monitored for signs of bleeding, infection, or other problems requiring immediate treatment. Side effects from surgery for colorectal cancer may include:Fatigue, Constipation or diarrhea.A temporary or permanent colostomy,Sexual dysfunction (e.g., erectile dysfunction in men) after more extensive operations for rectal cancer[8]

Aim Of Work:
Evaluation of the pathologic response rate, resectability rate, rate of conservative surgery.Evaluation of toxicity profile.Detection of the2-year progression-free survival (PFS),2-year overall survival and toxicity of the neoadjuvant regimen of oxaliplatin with capecitabine in Locally advanced rectal cancer.

Patients and methods
This study is a non randomized uncontrolled single arm phase II trial to evaluate the efficacy and safety of neoadjuvant concurrent capecitabine and oxaliplatin with RT in locally advanced cancer rectum.

Inclusion criteria:
- Age >18 years age
- ECOG PS of 0 or 1
- Histologically confirmed rectal adenocarcinoma
- TNM Staging:T3-4, Nx, M0 or any T, N+, M0 diseases
- No previous Chemotherapy or pelvic irradiation
- Patients with colostomy can be included
- The minimum BM reserve include TLC>3,000/mm3, HB >11 gm/dL, PLT>100.000 /mm3, normal renal and hepatic functions.

All eligible patients will undergo the following:
- o History, physical examination, DRE
- o CBC, blood chemistry (RFT, LFT, electrolytes), CEA
- o Pelvic high resolution MRI, abdominal CT, chest X-ray
- o Colonoscopy to exclude other colonic primaries
- o Proctoscopy and biopsy

***Protocol of concurrent chemoradiation*:**
***Chemotherapy* :**
- oxaliplatin 45mg/m2 weekly as 2 h infusion .The first dose will be just before radiation setting.
- capecitabine 825mg/m2 twice daily (1650mg/m2 daily), the 1st daily dose will be given 2 h before radiation setting, and chemotherapy will continue throughout the radiotherapy course.

Radiotherapy protocol:
CTV for phase I includes the tumor, presacral LN, perirectal LN, external and internal iliac LNs, and inguinal LN for tumors extending below the dentate line, while CTV for phase II includes the tumor + 3 cm safety margin

Setup : The patients should be in prone position with full bladder, radioopaque markers in the anal verge, vagina, lower limit of the tumor, inguinal LNs (if present), and avoid flashing the posterior skin.

Field borders: include {1} for phase I, PA field, upper border at L5-S1, lateral border 1.5 cm outside bony pelvic wall, lower border 3 cm below the tumor or at obturator foramen, lateral field, upper and lower as PA field, while posterior field should cover the sacral hollow, and anteriorly at posterior border of SP in T3 and anterior border of SP in T4 lesion, {2} for phase II the tumor +3 cm safety margin through 2 lateral opposed fields similar to previous phase

Field arrangement: for phase I; 3fields (1 PA, and 2 laterals), or 4 fields (1 PA, 1 AP, and 2 laterals), for phase II; 2 lateral opposed fields, if inguinal LNs will be irradiated through separate anterior electron fields

Dose prescription: for phase I; 45 Gy/25 fractions/ 5 weeks, for phase II; 5,4 Gy/3 fractions/half a week

The energy used: for PA field 6MV, for PA/AP fields 15 MV (mainly according to the separation whether <18 cm or ≥18 cm), but for lateral fields it is 15 MV all fields will be given on LINAC.

Dose limitations: small bowel 45-50 Gy, femoral head and neck 42 Gy, bladder 65 Gy, rectum 60 Gy

During the treatment: repeated CBC and renal function will be done, the toxicity will be recorded according to National Cancer Institute Common Terminology Criteria For Adverse Events version 4 (**NCI CTCAEs**)

Follow-up imaging studies:
Assessment by high resolution pelvic MRI; 1.5T machine (Philips Achieva, Medical Systems, Best, The Netherlands);using phase array coil. it was performed in 23patients. There is no need for bowel preparation or intravenous contrast. Multiplanar T2-weighted(sagittal, transversal and coronal) fast spin echo using echo time (TE) 150, repetition time (TR) 3,427 ms, matrix 256 × 256. Thin slice (3 mm) axial images through rectal cancer perpendicular to long axis rectum was used.

Multidetector computed tomography(MDCT) using 64 row slice (Toshiba Aquilion,Medical system Corp.,Tokyo, Japan) scanner was performed in 10 patients. A total of 70 to 100 ml nonionic contrast medium was given intravenously with an automatic injector at a flow rate of 3-4 mL/s. Imaging was performed from the level of the diaphragm to the pelvic floor at the arterial phase (start –delay after 25 sec) and portal phase (about 65 sec after the initiation of IV contrast media administration). Routinely 120 kV was used for exposure but mAs value was changed according to body weight due to automatic tube modulation technique.

Image analysis:
Response criteria of primary tumour was based on assessment T category. The definition of residual tissue after CRT was based on the primary tumour location. The length from the anal verge , depth of the tumor invasion, the mesorectal infiltration, and number of enlarged lymph nodes were assessed. Each rectal tumor was restaged according to the imaging findings and was later correlated with the operative and pathological finding for accuracy, sensitivity and specificity.

Follow-up lab (CBC, CEA, RFT, LFT).

Surgical intervention :
Surgery: the patients were subjected to surgery 6 weeks after chemoradiation depending on the restaging data by-high resolution MRI and /or multidetector computed tomography(MDCT)and site of the tumour and the feasibility of performing the laproscopic technique and the surgical technique was determined.

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The patients went either anterior resection of Dexon (open or laparoscopic),abdominoperineal resection (open or laparoscopic), transanal localized resection and only colostomy in few cases.

In cases were low anastomosis was performed temporary ileostomy was performed.

Follow up at the out patients clinic was performed for all patients.

The outcome criteria were determined including the respectability,type of surgery,complications encountered,hospital stay and operative time.

Statistical Analysis

The clinical end points evaluated were defined as follows:

Local recurrence(LR): A clinically proven relapse, but preferably confirmed by a biopsy, anywhere within the pelvis.Disease Free Survival(DFS):Any death, any local relapse or DM, or any second cancer, whicheveroccurred first. Overall Survival(OS): from the date of diagnosis to death or the last follow-up date in survivors. Progression free survival (PFS): from the date of completion of CCRT to the date of progression. Survival curves were achieved using the Kaplan-Meier method and the differences were evaluated by log-rank test. Treatment response was assessed by comparing abdomen MRI/CTs taken before and after radiotherapy using Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 (9). To identify the relationship between toxicities and radiation dose, Pearson correlation analysis was used. The chi-square and Person's correlation were used to analyze categorical variables (including toxicities) between groups. When interpreting the results, p-values less than 0.05 were considered significant. All data were computed and analyzed with SPSS ver.21 for Windows (SPSS Inc., Chicago, IL, USA). [10]

Results

The present prospective study included 33 rectal cancer patients, presented toClinical Oncology , Surgical and diagnostic radiology departments in Assiut university Hospital from June 2012 to September2013.

1- Patient's characteristics:

The age of the patients ranged between 17 to 80 years. Nineteen (57.6%) of patients ≤ 40 y , 14 (42.4%) of patients ≥ 40 years. Male constituted 54.5% of the patients while female constituted 45.5%.

According to karnofasky performance status 6 (18.2%) patients have P.S 70% while 8 (24.2%) have P.S 80%, 10 (30.3%) patients have P.S 90% and 9 (27.3%) patients have P.S 100%. Also about residence of patients 14 (42.4%) of patients from rural and 19 (57.6%) of patients from urban. (table1)

Table (1): General characteristics among study group:

Item	No (%) "n=33"
1- Age: ≤ 40ys. ≥ 40ys. Mean ± S.D	 19 (57.6%) 14 (42.4%) 42.48 ± 16.30
2- Sex: Male Female	 18 (54.5%). 15 (45.5%)
3- P.S: 70% 80% 90% 100%	 6 (18.2%) 8 (24.2%) 10 (30.3%) 9 (27.3%)
4- Residence: Rural. Urban.	 14 (42.4%) 19 (57.6%)

Clinical Presentation

The main presenting symptoms were bleeding per rectum 22(66.67%) while 17 (51.51%) patients had tenesmus &17 (51.51%) patients had colic abdominal pain,15(45%) alteration of bowel habitsand 3 patients (0.09%) had intestinal obstruction.

DATA REGARDING PREOPARATIVE CHEMORADIOTHERAPY:

All patients had adenocarcinoma, conventional adenocarcinoma represented 23(70%), mucinous 5(15%) and signet ring adenocarcinoma 5(15%). Fifteen patients (45.4%) had well differentiated adenocarcinoma, 9 (27.3%) have moderately differentiated adenocarcinoma, 9 (27.3%) have poorly differentiated adenocarcinoma

Preoperative investigations

Evaluation of Laboratory investigations were (12.1%) of pts have abnormal urea and Creatinine, (12.1%) of pts abnormal in L. F. Ts1 on presentation and (9.1%) of pts are abnormal in both L. F. Ts2 (after chemo- radiotherapy) and L. F. Ts3 (preoperative).

About other laboratory investigations: there were no change in mean value of CBC in pre-treatment, post treatment and follow up with no significant difference so treatment with capecitabine/oxaliplatin does not result in toxicity as regards elements of blood,About tumor markers,as regard CEA decrease in post treatment from 164.56 ±156.68 to 118.54 ± 72.93 and decrease to 105.88 ± 59.14 in follow up with significant difference with pre-treatment values and CA19.9 there is a decrease in post treatment from118.54 ± 72.93 to 82.27 ± 51.44.

Response of treatment to preoperative chemoradiotherapy

Evaluation of response to preoperative chemo-radiotherapy showed that the number of patients achieved complete response were 18 (54.5%), while 8(24.2%) of patients have partial response and 7 (21.3%) of patients have stationary course.

DATA REGRADING RESTAGING BY MRI/MDCT:

The characteristic imaging findings of local advanced rectal tumour represented on Table (2).

Table (2): Tumor Characteristics revealed by MRI/MDCT

Item	No (%) "n=33"
1-T stage	
pT2	10 (30.30%)
pT3	14 (42.42%)
pT4	9 (27.27%)
2-N stage	
pN0	15 (45.45%)
pN+	18 (54.54%)
3-Tumour localization (cm from anal verge)	
0–5	12 (36.36%)
>5 – 10	16 (48.48%)
>10-15	5 (15.15%)

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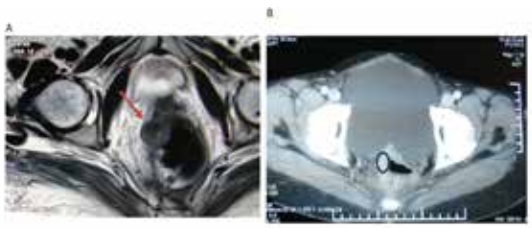
Regarding T staging, MRI/MDCT correctly staged 22 of 33 patients. Four patients were undestaged asT2 or T3 and 7 patients was overstaged as T4. The overall accuracy of MRI/MDCT for T restaging was 66.7%, with overstaging and understaging occurring in 21.2% and 12.1% of the patients respectively. Positive predictive value (PPV) and negative predictive value (NPV) were 85.7% and 57.9% respectively. (Fig.1)



Fig(1). A 50-years female patient had T3 local advanced rectal cancer. Axial T2WI pretreatment MRI (A) and follow-up MDCT. (A) show circumferential thickening (T)of the rectal wall anteriorly and right laterally 11 O'clock (arrowed) with loss of the muscularis propria and infiltration of the adjacent mesorectal fat.(B) after chemoradiotherapy follow –up MDCT show slight shrinkage of the T .

Regarding N staging, MRI/MDCT correctly staged 26 of 33 patients. Six patients were overstaged as N1-N2 and 1 patient were understaged as N0. The overall accuracy was 78.8%, whereas 18.2% of the patients were overstaged and 3% were understaged.Positive predictive value (PPV) and negative predictive value (NPV) were 76.2% and 83.3% respectively.

DATA REGARDING SURGERY:

A significant difference was found regarding the response to chemo-radiotherapy affects the type of surgery (P<0.05) (table3). T stage of 33 patients postoperatively was 7 (21.21%) of patients were pT2, 12 (36.36%) were pT3 and 14 (42.42%) were pT4, also 26 (78.78%) of patients pN+, and (24.24%) of patients had (0-5) cm from anal verge and (45.45%) had tumor (>5-10) cm from anal verge and 30.31% of(>10) cm patients. (Fig.2)

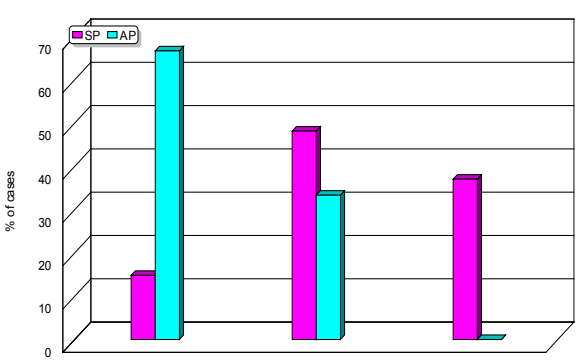
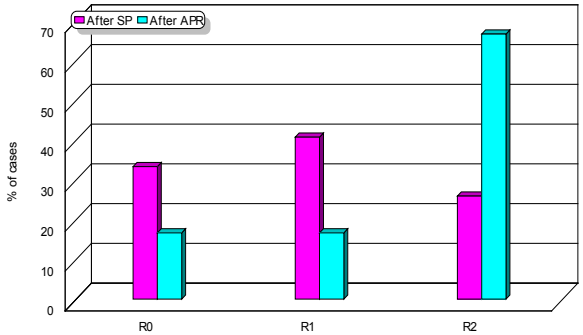


Fig (2)Relation between Surgical approach and Tumour Height

Relation between Surgical approach and Tumour Height

Four patients out of 6(18.2%) of patients with their tumor distance (0-5) cm from the anal verge, which thereby necessitates abdominoperineal Resection, while distance from>5 cm to 15cm which facilitates Sphincter Preserving Surgery in the rest of patients 27patients(81.8%)with moderate significant difference (P < 0.001)(Fig.3)

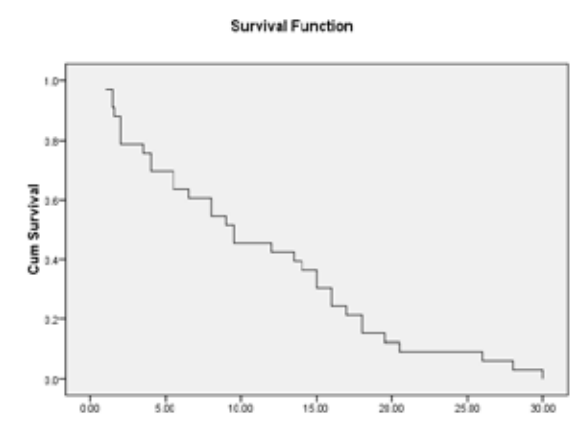


Fig(3): Relation between Pathological Response after Chemoradiotherapy and Type of Surgery:

The pathological response after surgical approach and type of surgery with moderate significant difference relationship (P < 0.001) with 7 patients (25.92%) who underwent Sphincter-preserving surgery had (R2). And 11(40.74%) underwent also SPS had (R1) while 9(33.33%) had (R1). (Fig.4) (table4).

Table (4): Relation between Pathological Response after Chemo-radiotherapy and Type of Surgery:

Pathological response after CRT	After SP (n=27)	After APR (n=6)	P-value
1- CR (R0)	9 (33.33%)	1 (16.67%)	P < 0.001**
2- Mic. Incomplete resec. (R1)	11 (40.74%)	1 (16.67%)	
3- Mac. Incomplete resec. (R2)	7 (25.92%)	4 (66.67%)	



Fig(4):Overall Survival in 33 pts.

The relation between response of patients to the whole protocol of treatment and overall survival show a moderate significant difference (P < 0.05) (table5).

Table (5): Relation between response and overall survival

Item	O.S
Response: C.R P.R Stationary	 15.72±7.22 11.88 ± 10.14 10.00 ± 0.00
P-value	P < 0.0.02*

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TOXICITY OF TREATMENT:

Post treatment sequalae

The toxicity in this study, for the chemotherapy used 5 patients (15.15%) develop deep venous thrombosis, 7 patients (21.2%) develop hand and foot syndrome. For the radiotherapy used, 19 patients (57.5%) develop wet desquamation. The median overall survival is 9.5 months, the morbidity consisted mainly of residual mass (69.69%)while regressive mass was achieved in10 patients(30.3%)

Surgical Complications:

The surgical complication wereabnormal bowel habits in 12 (36.36%) had , minor leakage in 14 patients (42.42%) and fistula in 7 patients (21.21%).

Mean Overall Survival & Disease free survival:-

The mean overall survival(Mean ± S.D) is eleven months(11.00 ±8.18).Disease free survival(Mean ± S.D) is 9.25±6.37 which is comparable to other trials.(Fig.5)

Discussion:

Locally advanced rectal cancers are typically given concurrent chemo-radiotherapy which increases complete resection and improves local control rates and continuous modification of the protocols improves outcomes and lowers toxicity.In our study, addition of oxaliplatin to capecitabine further increases the choice of surgical procedure, this is in contrast to the reported NSABP-R 04 trialwhich showed that the addition of oxaliplatin did not improve the clinical outcomes including PCR, sphincter-saving surgery, and surgical downstaging,this difference may be due to the small sample size of this study in comparison to a large clinical trial (NSABP=R 04).[11]

Preoperative CRT enthusiastic support in the management of rectal cancer is evident in German CAO/ARO/AIO – 94 study protocol which has shown improved locoregional control and reductions in toxicity with preoperative CRT vs postoperative combined modality treatment for stage II/III resectable rectal cancer. The rationale for preoperative CRT is powerful, as it combines early systemic chemotherapy treatment simultaneously with a locoregional treatment.[12]

Different reported phase I and II studies integrating oxaliplatin into fluoropyrimidine-based CRT schedules (Ge´rard et al, 2003; Gambacorta et al, 2004; Aschele et al, 2005). However, there are variations between these and the current study. Gambacorta et al (2004) evaluated the combination of raltitrexed and oxaliplatin with 50.4 Gy radiation. Aschele et al (2005) used a weekly schedule of oxaliplatin combined with continuous infusion 5FU and 50.4 Gy irradiation. Ge´rard et al (2003) used the same doses of 5FU/LV as this study, but delivered this as a continuous infusion over 24 h for days 1–5 and 29–33.[13]

According to ACCORD 12 trial, there was an increased rate of minimal residual disease at time of surgery that has impact on improving local control,this is similar to the results of this study there is an increased rate of minimal residual disease at sphincter preserving surgery.[14]

The following three different schedules for incorporating XELOX into preoperative CRT have been published :(1) synchronous oxaliplatin, capecitabine, RT, and elective surgery (SOCRATES) (2) RT, oxaliplatin, and capecitabine (RadiOxCape) and (3) capecitabine, oxaliplatin, RT, and excision (CORE) . The cumulative doses of capecitabine, oxaliplatin, and RT with these three different regimens were as follows: (1) 42,900 mg/m2, 260 mg/m2, and 45 Gy; (2) 41,250 mg/m2, 250 mg/m2, and 45 Gy, and (3) 46,200 mg/m2, 200 mg/m2, and 50.4 Gy, respectively, defined to test the feasibility and tolerability of incorporating combination therapies in the preoperative CRT for rectal cancer patients.All three XELOX-RT schedules seem to be equally active and tolerable and tested in larger phase III trials.

In RadiOxCape;Machiels et al applies RTH dose 45Gy in 1.8 fractionation in 40 patients with Capecitabine dose 825mg/m2 bid,5d/wk;oxaliplatin 50mg/m2 once weekly with 30% diarrhea and 14 % for pCR rate.This study was more or less similar to ours in sample size,regimen and clinical outcomes.[15]

Despite the limitations of cross-study comparisons, this preoperative XELOX-RT regimen seems to be more active in terms of local tumor regression (pCR) compared with standard FU CRT protocol.[16]

The CORE study reported with 87 patients received neoadjuvant XELOX,applies RTH dose 45Gy in 1.8 fractionation in 40 patients with Capecitabine dose 825mg/m2 bid,5d/wk;oxaliplatin 50mg/m2 once weekly with 15% diarrhea and 10 % for pCR rate.This study more or less similar to ours in clinical outcomes but differs in toxicity which shows more residual disease in sphincter preservation[17]

In ASCO2014 interim results indicate that addition of oxaliplatin to capecitabine plus radiotherapy does not improve DFS(Disease Free Survival) may be due to large sample size (1094pts.) which differs from our study results which shows improvement in DFS.[18]

In the current study, the overall accuracy of MRI/MDCT for T and N restaging was 66.7% and 78.8% respectively in spite of thesmall number of patients included in the current study. this is consistent with study by De Nardi and Carvello, ,2013[19] who reported the diagnostic accuracy of clinical examination, rectal ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography using 18F-fluoro-2′-deoxy-D-glucose ranges between 25% and 75% being less than 60% in most studies, both for rectal wall invasion and for lymph nodes involvement.This low accuracy is owing to understaging and overstaging because of radiotherapy induced changes. [20,21] In study of 94 patients, the authors reported the overall accuracy of MRI for T restaging was 49%, with overstaging and understaging occurring in 40.4% and 10.6% of the patients, respectively.[22] In line with our findings, 21.2% tumours were overstaged in this study with a lower NPV(57.9%) and 12% tumours were understaged. One explanation for these findings may be therapy-induced changes in the tissue surrounding the tumor. It has been suggested that external beam radiation produces a strong desmoplastic reaction and fibrosis which impede the detection of tumor regression by morphological imaging modalities.[23,24] moreover, 10 patients underwent local pelvic restaging by mdctin the current study.Restaging lymph nodes after neoadjuvant course could also be more complex since radiotherapy has the ability to reshape and modify the size and the texture of the nodes. [19] Thus,18.2% of the lymph nodes in the current study were overstaged as N1-N2 that it is consistent withZhan, et al [22]who reported the overall accuracy of N restaging was 63.8%, whereas 26.6% of the patients were overstaged. Also, Kuo et al [25], and Chen et al [26]whoreported lymph nodes restaging often results in overstaging because, usually, alteration of nodes structure after radio-

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therapy is associated with tumor invasion.

Of the 53 patients, 31 (58%) had a clinical response including 2 complete and 29 partial responses. This data may not be comparable with other experiences, which generally report a 70%–90% clinical response rate. However, evaluation of clinical response still remains a difficult problem in this tumor site. The primary end point of the study was to determine the pCR rate. Compared with clinical stage at baseline, tumor downstaging was observed in 29 of 51 evaluable patients (57%), including 12 patients (24%) with pCR. Nodal downstaging was reported in 78% of patients. The pCR rate of 24% was consistent with that observed in other recently reported phase II studies with capecitabine and RT. [27-29] In patients with T3 and T4 Schou et al studied the effect of capecitabine and oxaliplatin with concurrent chemoradiotherapy followed by total mesorectal excision and reported that TRG(Tumor Regression Grading) grade was not associated with overall survival or disease free survival.[29]Moreover in 46 patients treated with the same regimen a R0 of 12% which is less than our study reporting 33.33% in SP surgery and 16.67% in APR totally 30.3% R0 resection .This difference may be due to greater number of patients in the first study.[30] Several phaseIII studies analyzed the effect of preoperative chemotherapy in patients with advanced rectal carcinoma.After 10 years preoperative treated patients had a lower cumulative incidence of local relapse(7.1% vs 10.1%,P=0.048).The addition of oxaliplatin increases the PCR rate (17%vs13%)24-25 In a pilot study of 5 patients withdistant metastases who had XELOX after resection ,a tumor reduction rate of 44.3% and PFS of 10.3 months which is similar to our study.[31]

In ourstudy several limitations that should be taken in mind. This is not a randomized controlled study so we only compare our results with the results of similar studies.All our patients were from a single institution so the results are not generalized.Prospective randomized studies that compare our regimens with others are needed to demonstrate treatment efficacy.

In contrast to the impact ofpreoperative therapy, the German CAO/ARO/AIO – 94 studied the role of postoperative versus postoperative regimen and reported 8 out of 31 patients who underwent exenteration or resection of adjacent organs. Unfortunately this study did not seek the impact or control the use of postoperative chemotherapy. Only 7% of the study group received such treatment and this consisted of 5FU LV.[32]

The present study has a number of important differences from the above studies. Firstly, the total dose of radiation was fixed at 54 Gy, a total dose that is 10% higher than the other studies. This dose might be expected to be associated with a higher incidence of late complications. Secondly, this study formally determined the MTD and recommended dose of oxaliplatin when added to a validated CRT fluoropyrimidine schedule as used in two recent phase III trials (Bosset et al, 2005; Gerard et al, 2005). Finally, this study reports outcome data that is relatively mature (36 month median follow-up) and is also based on the circumferential margin status. We are not aware that any other combination CRT study has reported such data.

Some patients in our study had unidimensionally computed tomography or MRI evaluation and, therefore, tumor response could have been underestimated.Thus , Larger studies with different tumor invasion depths and recent functional MRI are needed

In conclusion, the addition of oxaliplatin to capecitabine has made a significant change in the management of locally advanced rectal cancers in terms of clinical outcome and toxicity. Also results achieved with the CAPOX regimen in the preoperative setting is in parallel with those achieved in the postoperative setting. When compared with other recent randomized trials, our results indicate that concurrent administration of oxaliplatin and radiotherapyis recommended.

Table (3): Relation between response & surgery procedure:

Surgery	Response			
	C.R "n=18"	P.R "n="8"	Stationary "n=7"	p-value
AP.	4(22.22%)	2 (25.0%)	----	
SP.	14(77.77%)	6(75.0%)	7 (100.0%)	P<0.03*

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