Induction Chemotherapy With Capecitabine And Oxaliplatin (CAPOX) Followed By Concomitant Chemoradiotherapy Before Surgical Resection In Patients With Locally Advanced Rectal Cancer

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Abstract: Background: Concomitant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is standard treatment for locally advanced rectal cancer. Induction chemotherapy has the advantage of earlier administration of systemic therapy and may improve distant control. **Purpose:** The purpose of the current study was to assess the efficacy and toxicity of induction chemotherapy (CAPOX) followed by concomitant CRT before surgery in patients with locally advanced rectal cancer. **Patients and Methods:** A total of 31 patients with locally advanced rectal cancer were randomly assigned to induction CAPOX followed by concomitant capecitabine-RT and surgery, then the patients were received an additional 4 cycles adjuvant capecitabine. The primary end point was assessment of pathological complete response (pCR) and the feasibility of surgical resection with sphincter preservation. **Results:** All patients underwent surgery with sphincter preservation procedure represented in 64.5% of patients. Complete resection (R0) was recorded in 93.5%, T downstaging in 61.3% and N downstaging in 51.6%. Pathological complete response was recorded in 19.4%. Two-year OS and DFS rates were 83% and 67.4%, respectively. Diarrhea was the most common grade 3/4 toxicity seen during the induction and concomitant CRT phases. **Conclusions:** Our results demonstrated that, induction CAPOX followed by capecitabine-RT is feasible with tolerable toxicity and results in encouragingly high rates of pCR, R0 resection, sphincter preservation and tumor downstaging in patients with locally advanced rectal cancer. Additional studies of this approach to examine more optimal regimens are warranted.

1. Introduction

Generally, treating locally advanced rectal cancer includes radiotherapy (RT), chemotherapy (CT), chemoradiotherapy (CRT), surgery, and subsequent incorporation of molecularly targeted agents. With multimodality treatment, local recurrence rates became less than 10% with the predominant mode of failure is the development of distant metastases (30–35%). Therefore, the addition of induction CT is not aimed to improve local efficacy, but to better control distant disease [1, 2].

The adjuvant treatment of rectal cancer has been shown to be inferior to the neoadjuvant RT/CRT for a variety of endpoints [3, 4]. Approximately 50% of patients did not receive the planned adjuvant CT dose commonly due to toxicity and patient refusal [5-7].

It has been shown that induction of primary CT for rectal cancer offers many advantages including; more better treatment compliance, ability to deliver full systemic doses of CT with possibility of tumor shrinking that facilitate more effective local treatment. The tumor shrinkage potentially improves tumor vascularity with eventually improving oxygenation and increase the intratumoral concentration of cytotoxic drugs [8, 9].

Additionally, induction CT has the potential to eradicate distant micrometastases early. On the other hand, it may be associated with a delay of definitive surgery, possibly reduced compliance to CRT, and induction of accelerated repopulation, [10].

Chau et al. reported that in patients with poor-risk rectal cancer treated at the Royal Marsden Hospital, induction capecitabine/oxaliplatin (CAPOX) before concomitant CRT (capecitabine/radiotherapy) and total mesorectal excision (TME) results in no tumor progression during induction CT, rapid symptomatic response, significant tumor regression, 99% complete resection (R0), and 24% pathological complete response (pCR) rates [11].

Chau et al. examined the use of 4 cycles of induction CAPOX in 3 weeks cycles, followed by CRT (54 Gy/6 weeks concomitant with capecitabine), followed by TME, and 12 weeks of adjuvant capecitabine. Radiological response rates after induction CT and CRT were 74% and 89%, respectively. A 20% pCR was reported with 3-year progression free survival (PFS) and overall survival (OS) were 68% and 83%, respectively [12].

On the basis of these encouraging results, this phase II trial was designed to evaluate the efficacy

and safety of this approach using CAPOX as induction CT with preoperative concomitant CRT with capecitabine followed by surgery and adjuvant CT in treating stages II & III rectal cancer patients.

2. Patients and Methods

This is a prospective phase II single arm study performed at Clinical Oncology Department, Tanta University hospital, throughout the period between June 2013 and December 2015. Thirty-one patients with locally advanced rectal adenocarcinoma were enrolled with a minimum follow-up period of 6 months.

All patients were informed of the nature of the study and had consented for admission into the study.

Eligibility criteria

Eligibility criteria included (a) age 18 to 70 years; (b) histopathologically confirmed rectal adenocarcinoma; (c) T3‑4 N0 or any T N+ve; (d) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; (e) adequate bone marrow reserve (hemoglobin ≥ 10 mg/dl, platelet count $\geq 100,000/mm^3$, leuocytic count $\geq 4,000/mm^3$); (f) adequate renal function tests (serum creatinine ≤ 1.5 mg/dl, calculated creatinine clearance ≥ 50 mg/min); (g) adequate liver function tests (transaminase levels ≤ 3 times the upper normal limit, serum bilirubin ≤ 1.5 mg/dl).

Exclusion criteria

The exclusion criteria included: (a) tumor type other than adenocarcinoma; (b) pregnant or lactating women; (c) metastatic disease; (d) previous CT or pelvic irradiation; (e) active GIT ulcers or history of gastric bleeding; (f) ischemic heart disease, cerebrovascular disease or other comorbid conditions.

Pretreatment evaluation

Personal history, clinical examination, including local and general examination was done for all patients. The tumor distance from anal verge was defined as the distance from the anal verge to the caudal tumor edge and was assessed by sigmoidoproctoscopy. Pretreatment tumor size was defined as the longest tumor diameter in any dimension. Pretreatment clinical staging was performed using physical examination and abdominopelvic CT and/or MRI scan. All patients were subjected to chest X-ray or thoracic CT scan and additional studies were done in the case of suspected metastatic disease.

The clinical and pathologic TNM stages were determined according to the American Joint Committee on Cancer (AJCC) TNM staging system (7th edition) **[13]** and the histologic grade of adenocarcinoma was described according to the World Health Organization (WHO) classification **[14].**

Complete blood count (CBC), serum blood chemistry including liver and renal function tests, as well as fasting, post-prandial blood sugar level and tumor marker levels (CEA and CA19-9) were done for all patients at initial presentation. Also, before the start of every cycle of preoperative CT all patients were investigated for CBC, liver and renal function tests.

Treatment protocol

Induction CT

Two cycles of induction CT with CAPOX were planned. Capecitabine was administered orally at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by 1-week rest. Oxaliplatin was given every 3 weeks at a dose of 130 mg/m^2 by intravenous infusion.

Concomitant CRT

Patients began concomitant CRT three weeks after the last induction CT cycle. Oral capecitabine was administered at a dose of 825 mg/m^2 twice daily throughout the RT course. The first dose was administered approximately 2 hours before RT with the second dose taken 12 hours after.

Linear accelerator (6 MV) was used to deliver RT through four fields to the tumor and pelvic lymph nodes extending up to the lower end of the 5th lumbar spine, and perirectal soft tissue structures at risk of microscopic disease.

A CT slices at a distance of 0.5 cm between them in treatment position was obtained allowing a three-dimensional conformal RT (3-DCRT) using a treatment planning system. The reference dose per fraction was 1.8 Gy at the isocenter and all patients were treated with conventional fractionation to a total dose of 45 Gy/25 fractions/5 weeks.

Response assessment

After the preoperative therapy, all patients were investigated by abdominopelvic CT and/or MRI scan to assure response to the studied protocol.

Surgery

Total mesorectal surgical excision technique was planned to undergo 6 weeks after completing CRT for all patients. The decision of surgical resection whether low anterior resection (LAR) or abdominoperineal resection (APR) was taken according to tumor response and the surgeon's discretion.

Adjuvant CT

Following surgery, all patients received an additional 4 cycles of adjuvant capecitabine (1250 mg/m^2 twice daily for 14 days every 3 weeks).

Toxicity Evaluation

Patients were evaluated weekly during the course of concomitant CRT to assess acute toxicity with CBC was taken each time. The intensity of side effects was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 **[15]**.

Dose Modification

Chemotherapy and RT were discontinued if grade 3 or 4 toxicity was developed. Treatment was restarted when toxicity had resolved to grade ≤1. The chemotherapeutic dose reduction was required after grade 3–4 toxicity. The treatment was resumed at 75% of the original dose for the first or 50% for the second occurrence of toxicity. The patient was withdrawn from the study if treatment was delayed for more than 3 weeks.

Follow-up

Subsequent follow-up visits to detect or confirm local tumor recurrence or distant metastasis by pelviabdominal CT and/or MRI scan, chest X-ray and others as indicated were scheduled at three monthly intervals for the first year, every 6 months for the second year and annually thereafter.

Statistical analysis

The primary endpoints of this research included assessment of response to treatment and the feasibility of surgical resection with sphincter preservation. The secondary endpoints included; evaluation of the safety profile of the treatment protocol, statistical analysis of clinical and pathological variables affecting response to treatment.

Response evaluation was defined both clinically and pathologically. Clinical response was assessed using imaging studies (abdominopelvic CT and/or MRI scan, chest X-ray or thoracic CT scan) according to the revised response evaluation criteria in solid tumors (RECIST) guideline (version 1.1) **[16]**. Complete response (CR) was defined as the disappearance of all lesions for at least four weeks. Partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions or the appearance of one or more new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

Absence of viable tumor cells in the surgical specimen in the primary tumor and in the lymph nodes (pT0N0) was defined as a pCR. Potential predictive factors for pCR were evaluated using a chi-square test. Lowering the T or N stage between the pretreatment clinical stage and the postoperative pathologic stage was encountered as tumor downstaging.

Overall survival was defined as the time from the date of diagnosis to the documented date of death or last follow-up. The disease free survival (DFS) was calculated from the date of treatment to the documentation of disease recurrence or the date of last follow-up. Loco-regional recurrence was defined as the evidence of tumor in the pelvis or perineum or at the anastomotic site as diagnosed by clinical, radiologic, or pathologic examinations. Distant metastases were defined as evidence of tumor in any other area.

Survival rates were estimated by the Kaplan-Meier method and a p-value <0.05 was considered statistically significant. All analyses were performed using SPSS (Statistical Package for the Social Sciences) version 21.0 (SPSS Inc., Chicago, IL).

3. Results

Patients and tumor characteristics

Patients and tumor characteristics are shown in Table 1. The median age of our patients was 51 years (range, 28-64) with mean ±SD 49.2±10, 58.1% of studied patients were males with male to female ratio were 1.4:1.

The median distance of the tumor from anal verge for all patients was 5 cm (range, 2-11 cm), with 61.3% of the patients had their malignancy in the lower rectum with a distance from anal verge ≤5 centimeters. The median tumor size in all patients was 5 cm (range, 3-10 cm) and the median circumferential tumor extent was 50% (range, 30-80%). Circumferential tumor extent involved more than 50% of the rectal lumen was represented in 45.2% of patients.

The median time interval between preoperative concomitant CRT and surgery in all patients was 6 weeks (range, 4-10 weeks) and in 74.2% of patients, surgical procedures had performed within ≤ 6 weeks from the end of the neoadjuvant concomitant CRT.

Tumor response

Through radiological assessment by CT and/or MRI scan of the clinical response following the neoadjuvant therapy, only 2 (6.5%) patients achieved CR, 15 (48.4%) patients achieved PR with overall response rate (CR+PR) was 54.8%. None of the patients had progressed during the course of treatment. Pathologically downstaging of T stage was achieved in 61.3%; downstaging of N stage was achieved in 51.6% of all patients with 19.4% achieved pCR without residual pathologic disease in the primary tumor site or the LNs (pT0N0), (Table 2). None of the predictive variables had significantly affected the pCR rate (Table 3).

Out of 31 rectal cancer patients, sphincter-saving surgical procedure (LAR) had been performed for 20 (64.5%) patients while the more invasive surgical procedure (APR) had been performed for 11 (35.5%) patients. Out of 19 patients with tumors situated in a distance ≤5 cm from the anal verge, LAR underwent in 9 (47.4%) patients of them and APR underwent for 10 (52.6%) patients (*p*=0.014). Twenty-nine patients had a radical R0 resection and the two patients with R1 resection were operated with APR.

Table 1: Patients and tumor characteristics.

characteristics	No.	%
Patients age (years): Median 51 (range, 28-64) Mean±SD 49.2 ±10		
≤50	16	51.6
>50	15	48.4
Gender		
Male	18	58.1
Female	13	41.9
ECOG PS		
0	14	45.2
1	17	54.8
Pathological grade		
Well differentiated	6	19.4
Moderately differentiated	20	64.5
Poorly differentiated	5	16.1
Tumor distance from anal verge (cm): Median 5 (range, 2-11)		
≤5	19	61.3
>5	12	38.7
Tumor size (cm): Median 5 (range, 3-10)		
≤5	19	61.3
>5	12	38.7
Circumferential tumor extent (%): Median 50 (range, 30-80)		
≤50	17	54.8
>50	14	45.2
Pretreatment clinical T stage		
cT1	2	6.5
cT2	9	29
cT3	14	45.2
cT4	6	19.4
Pretreatment clinical N stage		
cN0	8	25.8
cN1	16	51.6
cN2	7	22.6
AJCC grouping		
II A	6	19.4
IIB	2	6.5
IIIA	8	25.8
IIIB	11	35.5
IIIC	4	12.9
Pretreatment CEA level (µg/L)		
≤5	20	64.5
>5	11	35.5
Pretreatment CA 19-9 level (U/mL)		
≤37	19	61.3
>37	12	38.7
Interval between preoperative CCRT and surgery (week): Median 6 (range, 4-10)		
≤6	23	74.2
>6	8	25.8
ECOG PS: Eastern Cooperative Oncology Group; PS: Performance status; CEA: Carcinoembryonic antigen; CA 19-9 level: Carbohydrate antigen 19-9; CCRT: Concomitant chemoradiation.		

Table 2: Clinical response, pathologic response and disease downstaging.

Characteristics	No.	%
Clinical response		
Complete response (CR)	2	6.5
Partial response (PR)	15	48.4
Overall response (CR+PR)	17	54.8
Stable disease (SD)	14	45.2
Progressive disease (PD)	0	0
Pathologic response		
pT0	7	22.6
pT1	8	25.8
pT2	6	19.4
pT3	10	32.3
pT4	0	0
pN0	19	61.3
pN1	9	29
pN2	3	9.7
Pathologic down-staging		
T down-staging	19	61.3
N down-staging	16	51.6
pCR (pT0N0)	6	19.4

Table 3: Predictive factors affecting pCR.

Variable	pCR rate No,(%)	P
Age (year) ≤50 vs. >50	3/16 (18.8) vs. 3/15 (20)	1.00
Gender Male vs. Female	2/18 (11.1) vs. 4/13 (30.8)	0.208
Pathological grade Low /Intermediate vs. High	6/26 (23.1) vs. 0/5 (0)	0.553
Tumor distance from anal verge (cm.) ≤5 vs >5	2/19 (10.5) vs. 4/12 (33.3)	0.174
Pretreatment tumor size (cm.) ≤5 vs >5	5/19 (26.3) vs. 1/12 (8.3)	0.363
Circumferential tumor extent (%) ≤50 vs >50	4/17 (23.5) vs. 2/14 (14.3)	0.664
Pretreatment clinical stage II vs. III	2/8 (25) vs. 4/23 (17.4)	0.634
Pretreatment CEA level (µg/L) ≤5 vs >5	6/20 (30) vs. 0/11 (0)	0.066
Pretreatment CA 19-9 level (U/mL) ≤37 vs >37	6/19 (31.6) vs. 0/12 (0)	0.059
Interval between CCRT and surgery (week) ≤ 6 vs >6	6/23 (26.1) vs. 0/8 (0)	0.298
CCRT: Concomitant chemoradiotherapy; pCR: Pathologic complete response; PS: Performance status; CEA: Carcinoembryonic antigen; CA 19-9 level: Carbohydrate antigen 19-9.		

Treatment toxicity

During the induction phase, grade 3/4 diarrhea, nausea & vomiting, and fatigue were represented in 9.7%, 3.2% % 3.2% respectively in all patients. Two patients had required dose reduction of induction regimen by 25% of the planned dose due to non-hematological toxicity. The median time from the end

of CAPOX induction CT to the start of concomitant CRT was 4 (range 3-7) weeks.

During the concomitant CRT phase the most frequently occurring grade 3/4 adverse event was diarrhea (16.1%) followed by dysuria (6.5%); all other grade 3/4 events were uncommon (<5%). Four patients (12.9%) required dose reduction of capecitabine by 25% of the planned dose and only 1

patient discontinued capecitabine as he developed grade 3 neutropenic fever. No treatment-related death had been recorded (Table 4).

Only one patient required discontinuation of RT after 3600 cGy due to grade 3 non-hematological toxicity with median time for concomitant CRT was 35 (range 28-49) days.

Early postoperative complication, in the form of wound infection (6 events), intra-abdominal infections (3 events), anastomotic leak (3 events), stoma complications (1 patient), and delayed wound healing (5 events).

Delayed postoperative surgical complications were encountered in two patients who underwent LAR, one patient had anastomostic stenosis and the other one had fistula formation.

The total number of adjuvant CT cycles delivered was 83 cycles with median 3 cycles (range, 1-4). Twenty-one (67.7%) patients had received ≥3 CT cycles and about 80% of all cycles were given with full planned dose.

Table 4: Treatment-induced grade 3 and 4 toxic effects.

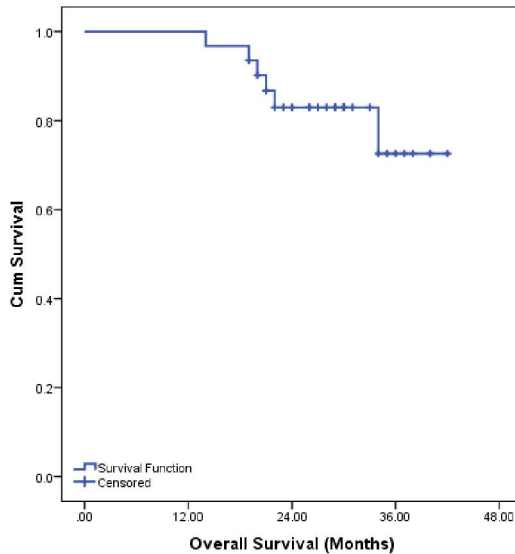| Toxicity	During induction CT		During concomitant CRT	
	Grade 3 No, (%)	Grade 4 No, (%)	Grade 3 No, (%)	Grade 4 No, (%)
Hematological				
Anemia	0	0	1 (3.2)	0
Leucopenia	0	0	1 (3.2)	0
Thrombocytopenia	0	0	2 (6.5)	0
Non-hematological				
Nausea & vomiting	1 (3.2)	0	0	0
Diarrhea	3 (9.7)	0	5 (16.1)	0
Fatigue	1 (3.2)	0	1 (3.2)	0
Anorexia	0	0	0	0
Neutropenic fever	0	0	1 (3.2)	0
Mucositis	0	0	1 (3.2)	0
Dysurea	0	0	2 (6.5)	0
Hand-foot skin syndrome	0	0	1 (3.2)	0

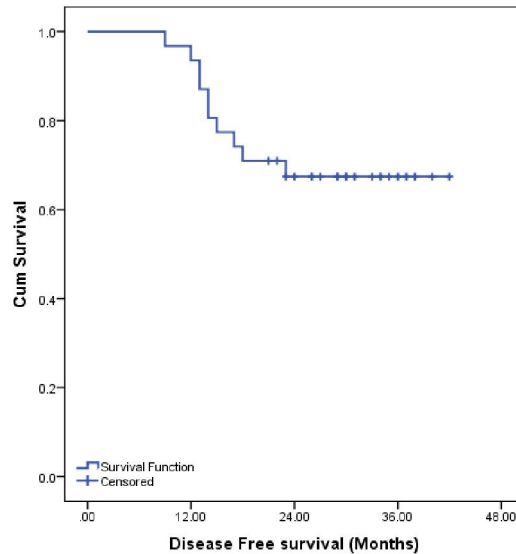**Figure (1):** Overall survival of all patients.

Figure (2): Disease free survival of all patients.

Survival

As regard the survival outcome for all patients, the median OS time was 28 months (range, 14-42), mean ± SD was 27.8±7.1 months and the 2-year OS rate was 83% (figure 1).

The median DFS time was 26 (range, 9-42) months, mean ± SD was 25.6±9.3 months and the 2-year DFS rate was 67.4% (figure 2).

Local failure had occurred in 4 (12.9%) patients, 2 (6.5%) of them had local failure alone and 2 (6.5%)

patients had both local and distant failures. Anastomosis site was the commonest site of local failure constituted 9.7% of all patients followed with perineum (3.2%). The median local recurrence free survival (LRFS) time was 27 (range 9-42) months, mean ± SD was 27±8 months and the 2-year LRFS rate was 86% (figure 3).

Distant failure had occurred in 9 (29%) patients, 7 (22.6%) of them had distant failure alone and 2
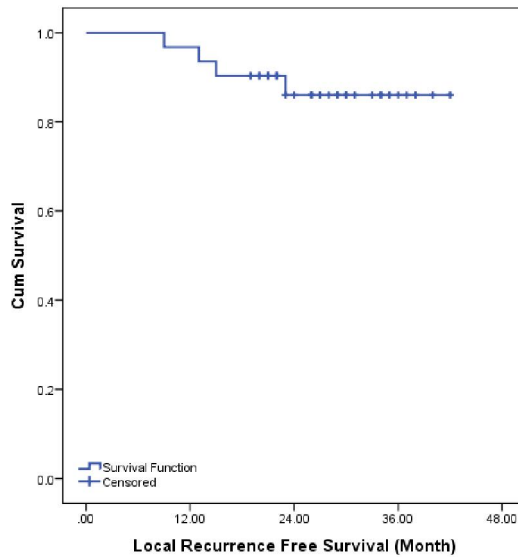
(6.5%) patents had both local and distant failures. The lung was the commonest site of distant failure that constituted 12.9% of all patients followed by the liver (9.7%), both lung and liver (4%) and lymph nodes (3.2%). The median distant metastases free survival (DMFS) time was 27 (range 11-42) months, mean ± SD was 26.1±9 months and the 2-year DMFS rate was 71% (figure 4).
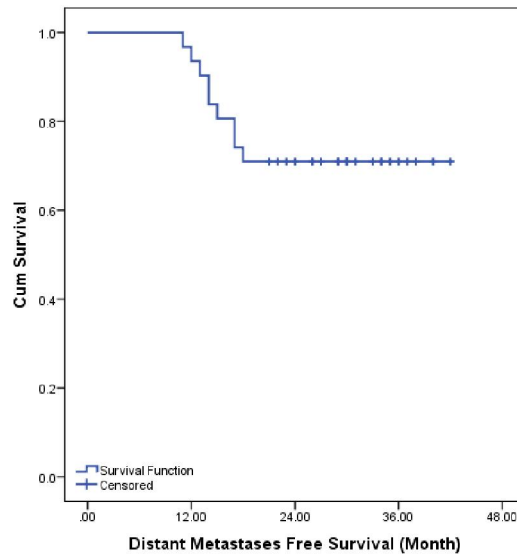

Figure (3): Local recurrence free survival of all patients.

Figure (4): Distant metastases free survival of all patients.

4. Discussion

Chemoradiation and surgical resection are important elements of multimodality treatment for patients with rectal cancer. The optimum sequence of these modalities had been addressed in several randomized trials. Preoperative RT/CRT has been shown to be superior to adjuvant treatment for a variety of endpoints in locally advanced rectal cancer with local recurrence rates were less than 10% [3, 4, 17]. The development of distant metastases recorded to be the predominant mode of failure in rectal cancer (30–35%). So, integrating more effective systemic chemotherapy into combined modality programs in rectal cancer patients is a matter of debate primarily because satisfactory local control rates can be achieved with preoperative CRT alone [10, 18].

In the present study out of the 31 patients treated with surgery, 29 (93.5%) patients had a radical R0 resection and this result was nearly similar to that reported by Schou et al. (94%) [19]. It was slightly lower than reported by Koeberle et al. [20] who reported that, 98% of the patients who underwent surgery had achieved R0 resection. On the other hand,

our result was higher than findings reported by Fernandez-Martos et al. (86%) [21].

Sphincter preservation had achieved in 64.5% of our patients. In Koeberle et al. [20] study, sphincter preservation had achieved in 84% of patients. This may be explained by that 61.3% of our patients had low-lying tumors (≤5 cm from anal verge) versus 37% in Koeberle et al. [20] study.

In this study, the objective response rate had achieved in 54.8% of all patients that was lower than that reported by Fernandez-Martos et al. [21] who reported 89%, making in consideration that CAPOX induction CT had administered for 4 cycles versus 2 cycles in our study.

Tumor and nodal downstaging were observed in 61.3% and 51.6% of all our patients respectively and this was comparable with the percent of tumor or nodal downstaging that ranged between 43% to 69% in other trials used CAPOX regimen as induction CT before neoadjuvant concomitant CRT for rectal cancer patients [19, 20, 21].

Chau et al. [11] questioned the advantage of using induction CT prior to preoperative concomitant CRT in rectal cancer patients by adding four cycles of

induction CAPOX before concomitant CRT. Pathological complete tumor response was achieved in 24% of patients, which was superior to the 19.4% pCR recorded in our trial. Also, Schou et al. **[19]** reported a pCR rate of 23%. On the other hand, Fernandez-Martos et al. **[21]** reported a pCR rate of 14.3%.

Patients in our study had 2-year OS and DFS rates, 83% and 67.4% respectively and this result was comparable with results from Chua et al. **[12].** Schou et al. **[19]** reported 5-year OS and DFS were 67% and 63%, respectively. Fernandez-Martos et al. **[21]** reported that the 18-month OS and FFS rates were 91% and 76% respectively in the studied arm treated with induction CAPOX followed by CRT and surgery.

Overall survival is the gold standard primary end point in most trials, but the real evaluation of OS may require a long follow-up time. To overcome this drawback, a surrogate end point has been proposed such as pCR. Although a better outcome for patients with pCR has been suggested, in randomized trials, the addition of CT produced higher rates of pCR with no impact on OS **[5, 6]** with controversial conclusions about the use of pCR as a surrogate end point for outcome. In the present study, pCR did not significantly improve the OS and this may be explained by the small number of patients and the short follow-up period. However, none of the 6 patients who achieved pCR had local or distant recurrences nor died during the follow-up period. Maas et al. **[22]** did a pooled analysis of 3105 patients from 14 study datasets to explore the long-term outcome in patients with pCR after concomitant CRT. The datasets were widely variable in tumor stages and treatment regimens. They suggested a better outcome for patients achieved pCR with a 5-year DFS of 83.3% compared with 65.6% in those patients without pCR. Also, Valentini et al. **[23]** supported a lower risk for metastatic disease in patients with pCR.

It has also been suggested that small tumors ≤5 cm are more prone to achieve pCR **[24].** In our study out of the 6 patients with pCR, one (8.3% of all large tumors) patient initially had a tumor size >5 cm and five pCR patients had small tumor size (26.3% of all small tumors).

In our study, no treatment-related death had been recorded. Grade 3/4 toxicity was seen in 19.4% of patients and the most common non-hematological toxicity was grade 3 diarrhea (9.7% during CAPOX and 16.1% during concomitant CRT). Fernandez-Martos et al. **[21]** reported that 23% of patients experienced grades 3-4 toxicity, with 5% grade 3 diarrheas. Koeberle et al. **[20]** recorded the most common non-hematological toxicity were grade 3 or 4 diarrhea (20%) (10% during induction CAPOX and 10% during CAPOX-RT) and suggested that the

additional cycle of CAPOX increased the toxicity of preoperative CRT. Schou et al. **[19]** found that grade 3/4 toxicity was seen in 18% of patients, and grade 3 or 4 diarrhea was seen in 7% of patients during induction CT and in 5% during CRT.

In conclusion, our results demonstrated that induction CAPOX followed by concomitant capecitabine-RT is feasible with tolerable toxicity. Greater exposure to systemic treatment results in high rates of R0 resection, sphincter preservation and tumor downstaging with encouragingly pCR rate in patients with locally advanced rectal cancer. Further studies of this approach to examine more optimal regimens are warranted.

5. Conflict of Interest: None

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References
1. Brown G: Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ, 2006; 333(7572): 779–82.
2. Rödel C, Arnold D, Becker H, Fietkau R, Ghadimi M, Graeven U, et al.: Induction chemotherapy before chemoradiotherapy and surgery for locally advanced rectal cancer: Is it time for a randomized phase III trial? Strahlenther Onkol, 2010; 186(12): 658-64.
3. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med, 2004; 351(17): 1731–40.
4. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al.: Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol, 2009; 27(31): 5124–30.
5. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al.: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. J Clin Oncol 2006; 24(28): 4620–5.
6. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al.: Chemotherapy with preoperative radiotherapy in

rectal cancer. N Engl J Med, 2006; 355(11): 1114–23.

7. Rödel C, Liersch T, Hermann RM, Arnold D, Reese T, Hipp M, et al.: Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 2007; 25(1): 110–7.

8. Milas L, Hunter NR, Mason KA, Milross CG, Saito Y, Peters LJ: Role of reoxygenation in induction of enhancement of tumor radioresponse by paclitaxel. Cancer Res, 1995; 55(16): 3564–8.

9. Taghian AG, Abi-Raad R, Assaad SI, Casty A, Ancukiewicz M, Yeh E, et al.: Paclitaxel decreases the interstitial fluid pressure and improves oxygenation in breast cancers in patients treated with neoadjuvant chemotherapy: Clinical implications. J Clin Oncol 2005; 23(9): 1951–61.

10. Glynne-Jones R, Grainger J, Harrison M, Ostler P, Makris A: Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: Should we be more cautious? Br J Cancer, 2006; 94(3): 363–71.

11. Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, et al.: Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging–defined poor-risk rectal cancer. J Clin Oncol, 2006; 24(4): 668-74.

12. Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al.: Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol, 2010; 11(3): 241–8.

13. Edge SB, Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol, 2010; 17(6): 1471-4.

14. Hamilton SR, Aaltonen LA.: Pathology and genetics; tumors of the digestive system. IARC 2000; 110-111.

15. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al.: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol, 2003; 13(3): 176-81.

16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009; 45(2): 228-47.

17. Pahlman L, Glimelius B: Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. Ann Surg, 1990; 211(2): 187–95.

18. Glynne-Jones R, Sebag-Montefiore D: Role of neoadjuvant chemotherapy in rectal cancer: interpretation of the EXPERT study. J Clin Oncol, 2006; 24(28): 4664–5.

19. Schou JV, Larsen FO, Rasch L, Linnemann D, Langhoff J, Høgdall E, et al.: Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol 2012; 23(10): 2627-33.

20. Koeberle D, Burkhard R, von Moos R, Winterhalder R, Hess V, Heitzmann F, et al.: Phase II study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advanced rectal cancer. Br J Cancer, 2008; 98(7): 1204–9.

21. Fernández-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, et al.: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer derecto 3 study. J Clin Oncol, 2010; 28(5): 859–65.

22. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al.: Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol, 2010; 11(9): 835–44.

23. Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, et al.: Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol, 2011; 29(23): 3163–72.

24. Kim C, Anne PR, Mitchell E, Pequignot E, Palazzo J, Goldstein S, et al.: Impact of pretreatment size and lymph nodes on pathological complete response and survival in a prospective trial of chemoradiation. Int J Radiat Oncol Biol Phys 2005; 63(Suppl 1): S164-5.

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