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: Aim: The aim was to analyze the safety and efficacy of induction chemotherapy (CT) with capecitabine plus oxaliplatin (CAPOX) followed by concomitant chemoradiotherapy (CRT) before surgical resection in locally advanced rectal cancer (LARC) patients. **Patients and Methods:** Thirty-one patients with LARC received induction CAPOX followed by concomitant RT plus capecitabine and surgery, then the patients received an additional 4 cycles of adjuvant capecitabine. The primary end point was an assessment of pathological complete response (pCR) and the feasibility of surgical resection with sphincter preservation. **Results:** All patients underwent surgery and 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% of patients. Pathological CR was recorded in 19.4% of patients. The 2-year overall survival (OS) and disease free survival (DFS) rates were 83% and 67.4%, respectively. Diarrhea was the most common grade 3/4 toxicity seen during the induction (9.7%) and concomitant CRT (16.1%) phases. **Conclusions:** Our results demonstrated that, induction CT with CAPOX followed by concomitant RT plus capecitabine is effective with tolerable side effects. Greater exposure to systemic treatment results in high rates of tumor downstaging, pCR, R0 resection, and anal sphincter sparing in LARC patients.
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1. Introduction

Generally, LARC treatment includes RT, CT, CRT, surgery, and targeted therapy. Multimodality treatment resulting in decreased incidence of local recurrence (LR) to be <10% but the incidence of distant failure still high (30%–35%). So, the main purpose of addition of induction CT is to obtain better distant disease control rather than to improve LR rate **[1, 2].**

The neoadjuvant treatment with RT or CRT for rectal cancer patients is more effective than adjuvant treatment **[3, 4].** About 50% of patients did not administer the full adjuvant CT dose as planned most commonly due to its side effects or patient refusal **[5-7].**

The advantages of induction CT for rectal cancer include better treatment compliance, delivering full CT doses with tumor downstaging that potentiate the effect of the local treatment. The shrinkage of the tumor improves its vascularity, oxygenation, and may increase cytotoxic agent's concentration intratumorally **[8, 9].**

Also, induction CT aid in early eradication of distant micrometastases. On the other hand, it may cause a delayment of surgical interference, may reduce CRT compliance, and may induce an accelerated repopulation **[10]**.

Chau et al. **[11]** reported that, induction CAPOX before concomitant CRT (capecitabine/RT) and total mesorectal excision (TME) in patients with LARC results in rapid symptomatic response, significant tumor regression, 24% pCR rate and 99% R0**.**

Chua et al. **[12]** assessed the use of induction CAPOX every 3 weeks for 4 cycles, followed by capecitabine concomitant with RT (54 Gy/6 weeks), and followed by TME and adjuvant capecitabine for 12 weeks. After induction phase and concomitant phase the radiological response rates (RR) were 74% and 89%, respectively. The overall survival (OS) and progression free survival (PFS) rates at 3-years were 83% and 68%, respectively with 20% pCR rate**.**

Based on these encouraging results, we aimed to evaluate the safety and efficacy of CAPOX as induction CT with preoperative concomitant CRT with capecitabine followed by surgery and adjuvant CT in treating LARC 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. An informed consent was obtained from all patients.

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, liver, and renal functions.

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 gastrointestinal 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 distance from the caudal edge of the tumor to the anal verge was estimated via sigmoidoproctoscopy. The longest diameter of the tumor in any dimension was defined as the pretherapy tumor size. Assessment of the tumor radiologically by abdominopelvic computed tomography (CT) scan and/or magnetic resonance imaging (MRI). All patients were subjected to chest X-ray or CT scan and additional studies were done if metastatic disease was suspected.

The disease was staged according to the TNM staging system (7th edition) **[13]** and graded according to the World Health Organization (WHO) classification **[14].**

Complete blood count (CBC), serum blood chemistry including liver and renal function tests, 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

Induction CT include 2 cycles of CAPOX regimen as oral capecitabine (1000 mg/m^2 twice daily) for 14 days followed by 7 days off and intravenous infusion of oxaliplatin (130 mg/m^2) every 3 weeks.

Concomitant CRT

Patients began concomitant CRT three weeks after the last induction CT cycle. Oral capecitabine (825 mg/m^2 twice daily) was received during the RT days. The first capecitabine dose received 2 hours before RT and the second dose received after 12 hours.

A CT slices at a distance of 0.5 cm in treatment position was obtained. Linear accelerator (6 MV) was used to deliver three-dimensional conformal RT (3-DCRT) to the tumor and pelvic lymph nodes (LNs). 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 2 weeks and the cycles repeated, every 3 weeks.

Toxicity Evaluation

Acute toxicity was assessed during the course of concomitant therapy weekly and CBC was tested each time. The intensity of side effects was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 **[15]**.

Dose Modification

Chemotherapy and RT were discontinued if ≥grade 3 toxicity developed. When toxicity improved to ≤grade 1, the treatment was resumed with reduction of CT dose to 75% of the planned dose for the first toxicity event and to 50% for the second toxicity event.

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]**.

Pathological CR was defined as; no viable malignant cells in the primary tumor surgical specimen and in the LNs (pT0N0). Potential predictive factors for pCR were evaluated using a chi-square test. The lowering of the clinical T or N stage in the postoperative pathologic stage was defined as T or N downstaging.

The OS was estimated from the date of diagnosis to the date of death or last follow-up. The DFS was estimated from the date of start treatment to the date of documented loco-regional (pelvis, perineum or at the anastomotic site) or distant recurrence.

Survival rates were calculated by the Kaplan-Meier method. All analyses were performed using SPSS version 21.0. A *p*-value <0.05 was considered statistically significant.

3. Results

Patients and tumor characteristics

The age of the studied patients ranged between 28 and 64 (median, 51) years with male represented 58.1% and male to female ratio were 1.4:1. The median distance from the verge to the caudal edge of the tumor 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 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 elapsed from preoperative concomitant CRT to 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 (Table 1).

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).

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

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.

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 commonest ≥grade 3 toxicity 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).

Table 2: Clinical response, pathologic response and disease downstaging

Characteristics	No.	%
Clinical response		
Complete response	2	6.5
Partial response	15	48.4
Overall response	17	54.8
Stable disease	14	45.2
Progressive disease	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

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

Early postoperative complication included; infection of the wound (6 events), delayed wound healing (5 events), leak at anastomotic site (3 events), intra-abdominal infections (3 events) and stoma complications (1 event).

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 received ≥3 CT cycles and about 80% of all cycles were given with full planned dose.

Table 4: Treatment toxicities

Toxicity	During induction CT		During concomitant CRT	
	G 3 No, (%)	G 4 No, (%)	G 3 No, (%)	G 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

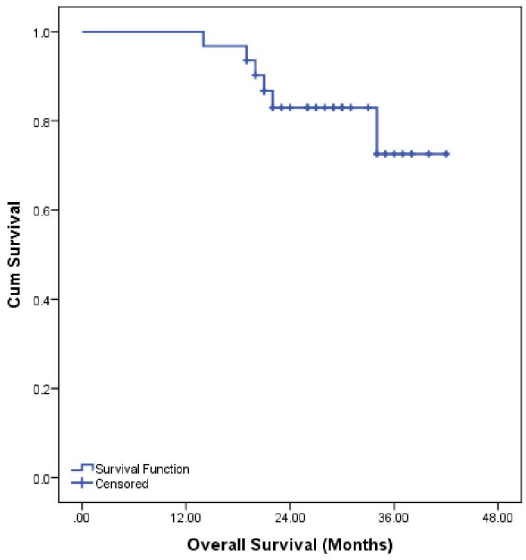

Figure (1): Overall survival of all patients.

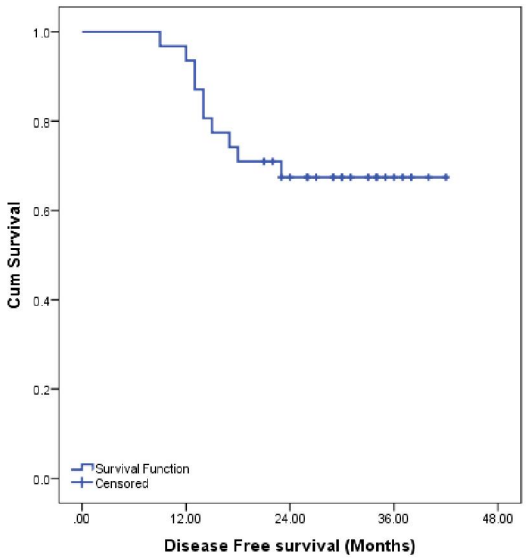

Figure (2): Disease free survival of all patients.

Survival

As regard the survival outcome for all patients, the mean OS time was 37.3 months (95% CI, 33.9-40.6) and the 2-year OS rate was 83% (figure 1).

The mean DFS time was 33.2 months (95% CI, 28.6-37.7) and the 2-year DFS rate was 67.4% (figure 2).

Local failure had occurred in 4 (12.9%) patients, 1 (3.2%) of them had local failure alone and 3 (9.7%)

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 mean local recurrence free survival (LRFS) time was 38.3 months (95%CI, 34.9-41.7) and the 2-year LRFS rate was 86% (figure 3).

Distant failure had occurred in 9 (29%) patients, 6 (19.4%) of them had distant failure alone and 3 (9.7%) 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 LNs (3.2%). The mean distant metastases free survival (DMFS) time was 34 months (95% CI, 29.6-38.4) and the 2-year DMFS rate was 71% (figure 4).

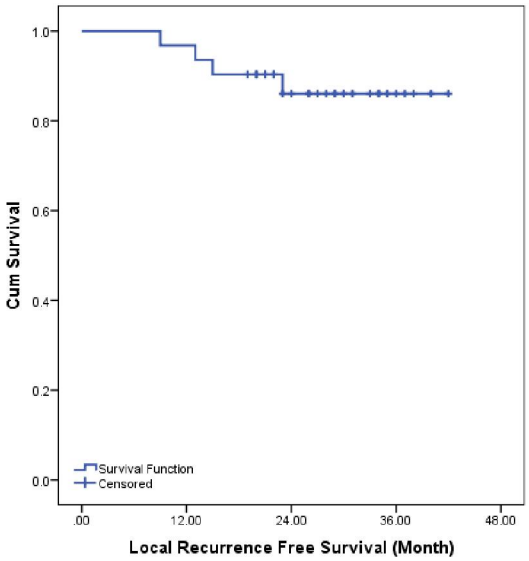

Figure (3): Local recurrence free survival of all patients.

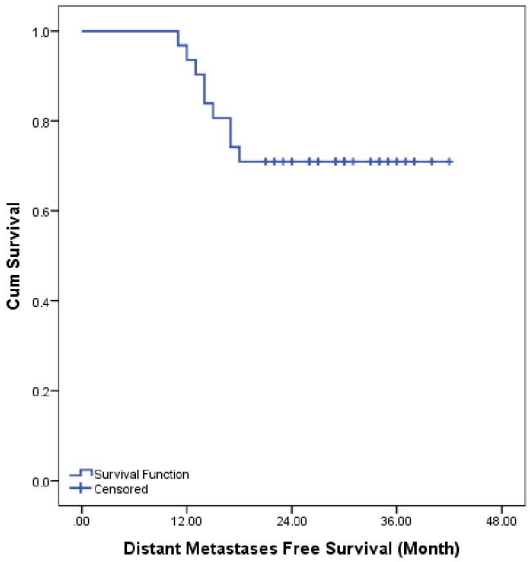

Figure (4): Distant metastases free survival of all patients.

4. Discussion

Preoperative chemoradiation followed by surgery are the main components of multimodality treatment for rectal cancer patients. Several randomized trials addressed these multimodality approaches to search for the optimal sequence of treatment **[3, 4, 17]**. In rectal cancer the distant failure is the commonest mode of treatment failure **[2]**. So, using more effective systemic CT into multimodality treatment protocols in rectal cancer patients is a matter of debate because preoperative CRT alone can results in good local control rates **[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. **[19]** (94%)**.** 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. **[21]** (86%)**.**

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 the tumor of the majority (61.3%) of the studied patients were at ≤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.

In this study, tumor and LNs downstaging had achieved in 61.3% and 51.6% of 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. Tumor pCR was recorded in 24% of cases and that was higher (19.4%) than recorded among our patients. Also, Schou et al. **[19]** reported a pCR rate of 23%. While, Fernandez-Martos et al. **[21]** recorded 14.3% pCR rate.

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 that the OS and DFS rates at 5-years were 67% and 63%, respectively. Fernandez-Martos et al. **[21]** reported that the 18-month OS and DFS rates were 91% and 76% respectively in the studied arm treated with induction CAPOX followed by CRT and surgery.

Overall survival is the main end point in most trials, but the exact evaluation of OS may require prolonged follow-up. To resolve this problem, an alternate parameter such as pCR was suggested. However, there is a controversy about the use of pCR for outcome evaluation as the addition of CT in many trials had no good impact on OS although it produced higher rate of pCR **[5, 6]**. In the present study, pCR did not significantly improve the OS and this may be explained by the relatively short duration of patients follow and the small number of patients. However, among 6 patients who achieved pCR, none of them had failed locally or distantly nor died during the follow-up period. Maas et al. **[22]** reported a better 5-year DFS (83.3%) for patients who achieved pCR after concomitant CRT compared with 65.6% for those who did not achieved pCR. In addition, Valentini et al. **[23]** reported that pCR is commonly associated with low rate of distant metastases.

It was proposed that pCR usually associated with tumors ≤5 cm **[24]** and our results was in agreement with this fact as out of the 6 patients who achieved pCR, 5 of them were presented with tumor size ≤5 cm.

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 an increased adverse effects of the neoadjuvant CRT with the addition of more cycles of CAPOX regimen. Schou et al. **[19]** found that ≥grade 3 toxicity was noticed in 18% of patients, and ≥grade 3 diarrhea was observed in 7% of patients during induction CT and in 5% during CRT.

In conclusion, our results demonstrated that induction CT with CAPOX followed by concomitant RT plus capecitabine is effective with tolerable side effects. Greater exposure to systemic treatment results in high rates of tumor downstaging, pCR, R0 resection, and anal sphincter sparing in LARC patients. Additional larger studies of this approach to investigate more optimal regimens are needed.

5. Conflict of Interest: None

6. References

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