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Neoadjuvant Chemotherapy and Concomitant Boost Radiotherapy in the Treatment of Locally Advanced Rectal Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Author MAA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author EAA managed the analyses of the study. Authors SME, EHE and EAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study aimed to examine the efficacy and toxicities of concomitant boost three-dimensional conformal radiotherapy along with multidrug chemotherapy (capecitabine and oxaliplatin) in neoadjuvant course for locally advanced rectal cancer (LARC).
Study Design: A phase II interventional nonrandomized study.
Place and Duration of Study: This Study was conducted at Clinical Oncology and nuclear medicine department of Mansoura University Hospitals (Egypt) between November 2016 and October 2019.

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Methodology: Thirty patients (18 women, 12 men; age range 18-75 years) with (cT3-T4 and/or cN+) histologically confirmed rectal adenocarcinoma located within 12 cm of the anal verge were included in this study. Patients received three-dimensional conformal radiotherapy (3DCRT) to the pelvis of 45 Gy and a concomitant boost of 10 Gy to the primary tumor in 25 fractions, and concurrent with oxaliplatin (50 mg/m2 d1 weekly) and capecitabine (625 mg/m2 bid d1–5 weekly). Radical surgery was scheduled six to eight weeks after chemoradiation. Acute toxicities were recorded according to Common Terminology Criteria for Adverse Event (CTCAE) v5.0. Potential prognostic factors were evaluated using a binomial logistic regression. Survival curves were estimated using the Kaplan-Meier method and compared with Log-rank test.
Results: All patients received chemoradiation. Twenty-seven patients underwent surgical resection. Twenty-five patients underwent sphincter-sparing surgery (92.6%) and nine patients (33.3%) achieved pathological complete response (pCR). The incidences of grade III neutropenia, diarrhea, and radiation dermatitis were 6.7%, 6.7%, 3.3% respectively. The three-year local recurrence (LR), disease-free survival (DFS) and overall survival (OS) rates were 7.4%, 63% and 74.1%, respectively. We found pre-surgical negative nodal status to be significantly associated with pCR (p=0.009). The pathological nodal stage was an independent prognostic factor to DFS.
Conclusion: The combination of oxaliplatin, capecitabine, and dose escalation using concomitant boost 3DCRT is safely administrated in patients with locally advanced rectal adenocarcinoma and it offers high pCR and sphincter preservation rate.

Keywords: Rectal Cancer; three-dimensional conformal radiation therapy; concomitant boost; neoadjuvant chemoradiotherapy.

ABBREVIATIONS

3DCRT: Three-dimensional conformal Radiotherapy; CTCAE: Common Terminology Criteria for Adverse Event; pCR: pathological complete response; LR: local recurrence; DFS: disease-free survival; OS: overall survival; CRT: chemoradiotherapy; TME: total mesorectal excision; IMRT: Intensified modulated radiotherapy; MRI: magnetic resonance imaging; RT: radiotherapy; ECOG: Eastern Cooperative Oncology Group; CT: computed tomography; PTV: planning target volume; CTV: clinical target volume; GTV: gross tumor volume; TRG: Tumor regression grade; cT: clinical tumor stage; cN: clinical nodal stage.; ypT: Pathological tumor stage; ypN0; pathological nodal stage; yN: after neoadjuvant nodal stage; yT: after neoadjuvant tumor stage.

1. INTRODUCTION

In patients with stage II or III rectal cancer, the National Comprehensive Cancer Network (NCCN) guidelines, 2020 recommended trimodal treatment with neoadjuvant chemoradiotherapy (CRT), surgical resection with total mesorectal excision (TME), plus chemotherapy. While this multimodal approach has led to improvement in the rates of LR and anal-sphincter preservation benefits [1], it has no significant impact on distant failure rates or OS [2].

The pathological complete response (pCR) after neoadjuvant CRT has been linked to a better prognosis and has a direct impact on LR and survival rates [3]. Moreover, complete response after neoadjuvant CRT provides a predictor of quality of life because of increasing sphincter preservation rate [4]. Therefore, pCR frequency should be a mandatory end point in any rectal cancer neoadjuvant trial [5]. However, even with validated neoadjuvant treatment regimens, only approximately 15% of patients benefit from pCR at the time of surgery [6].

To obtain a better tumor response, elevating treatment dose has been considered a feasible method [7]. Radiation therapy dose escalation using both external beam radiation therapy and brachytherapy techniques was investigated by Appelt et al. [8] & Burbach et al. [9]. A dose-response relationship for rectal cancer has been confirmed, and patients receiving boost doses have demonstrated increased rates of tumor response with acceptable rates of early toxicity [10].

Since both capecitabine and oxaliplatin have radio-sensitizing effects, and are synergistic in colorectal cancer, research efforts have focused on treatment schedules that include both drugs and radiotherapy (RT) as neoadjuvant CRT for rectal cancer patients [11]. Bajeta et al. [12] reported that capecitabine can safely replace 5-FU in combination with oxaliplatin and irinotecan with promising results in terms of activity. Until now, there are several randomized clinical trials that used conventional radiotherapy fractionation,

(1.8–2 Gy daily fractionation), in their treatment schedules, and oxaliplatin with a weekly dose ranging from 50 to 85mg/m2 and capecitabine dose ranging 800-1000 mg/m2 bid for neoadjuvant concurrent CRT in rectal cancer [13-16].

Meta-analysis of data from at least 10 randomized trials including previous trials of the addition of a platinum drug to fluoropyrimidine-based CRT provides good quality evidence that a general addition of a platinum derivative to neoadjuvant fluoropyrimidine-based CRT does result in statistically significant improved pCR and reduced the likelihood of distant recurrence but does not improve overall and disease-free survival. Only the CAO/ARO/AIO- 04 trial achieved a statistically significant result in favor of the oxaliplatin group regarding DFS [17].

The addition of more aggressive chemotherapy than 5-FU based concomitant to radiotherapy may increase acute and late toxicities especially acute and late bowel toxicity (8). So that there are preoperative capecitabine plus oxaliplatin neoadjuvant concurrent CRT randomized clinical trials that used intensified modulated radiotherapy (IMRT) aiming to reduction of toxicity [7,11,18]. Zhu et al., 2014 [7] examined the use of IMRT, escalating the primary lesion's dose to 55 Gy with simultaneous integrated boost along with adding capecitabine 625 mg/m2 twice daily throughout the entire course of IMRT and oxaliplatin 50 mg/m2 weekly during the five-week followed by one cycle of Xelox. It was demonstrated that a concomitant boost radiotherapy plus concurrent capecitabine and oxaliplatin, can be safely administered in patients with LARC, and produces a high rate of pCR.

In our hospital, clinical tumor (cT3/T4) stage or clinical nodal (N+) stage rectal cancer patients are treated by neoadjuvant CRT that was delivered using 3DCRT. Those patients might have more opportunities to benefit from a high intensity treatment, whether chemotherapy or radiotherapy. In 2016, we designed our study aiming to achieve better treatment response, higher pCR and increased sphincter preservation rate. We used 3DCRT to deliver radiation dose to the pelvis of 45 Gy and a concomitant boost of 10 Gy to the primary tumor in 25 fractions along with weekly capecitabine and oxaliplatin.

The feasibility of intensified dose conduction with diminishing the toxicity of normal tissue at the same time to achieve better response compared to conventional neoadjuvant treatment is our study hypothesis.

1.1 Literature Survey

It was concluded that the neoadjuvant-intensified CRT with addition of multidrug chemotherapy (oxaliplatin and fluoropyrimidine) achieved better OS in patients with LARC in view of an increase in local tumor control [19,20] investigated whether an intensified CRT using a concomitant boost (5 Gy) led to a better result in LARC, and it was found that a concomitant boost achieved a slightly higher pCR rate but delayed surgical wound healing. On the other hand, the effect of an external radiation boost to the tumor bed before standard conventional CRT with concurrent capecitabine on complete tumor response in LARC failed to achieve pathological or clinical response benefits [21]. Because Improve pCR rates after intensified neoadjuvant CRT may facilitate surgery-sparing approaches, a systematic review and meta-analysis of radiation neoadjuvant dose-escalation studies (54–60 Gy) using IMRT and VMAT was done. Radiotherapy dose above 54 Gy was associated with high rates of pCR, complete resection and acceptable acute grade ≥III toxicities [22]. Our study reported that dose escalation can be safely delivered by using 3DCRT and with addition of oxaliplatin. Our used intensified regimen was safe, tolerable and linked to high pCR rate and sphincter preservation rate. Our main limitation is the small sample size. Moreover, longer follow is needed to detect the impact of complete response on survival outcomes.

2. MATERIALS AND METHODS

2.1 Patients Selection

The eligibility criteria were: Patients with histologically confirmed diagnosis of rectal adenocarcinoma, localized <12 cm from anal verge by colonoscopy and rigid proctoscopy, II–III stage (cT3-T4 and/or cN+) disease were determined by pelvic magnetic resonance imaging (MRI) and or endorectal ultrasound, age > 18years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow function (ANC > 1800 /mL and platelet count > 100,000 /ml, Hg > 10 g/dl) and adequate renal and hepatic function (creatinine clearance > 50 mL/min and bilirubin ≤ 1.5 mg/mL). Patients were excluded if they were with any of the following exclusion criteria: Pregnancy or lactation, prior chemotherapy for colon or rectal

cancer or RT to the pelvis, distant metastasis, synchronous colon carcinomas or anal canal extension, severe active comorbidity, serious cardiac disease, evidence of grade II or greater peripheral neuropathy and lack of physical integrity of the gastrointestinal tract that would preclude feasibility of oral chemotherapy (capecitabine).

2.2 Pretreatment Evaluation

It included a complete history and physical examination, digital rectal examination (DRE), complete blood count, liver and renal function tests, carcinoembryonic antigen (CEA) and electrocardiography, colonoscopy, proctoscopy and biopsy, computed tomography (CT) of the chest and abdomen, pelvic MRI or endorectal ultrasound.

2.3 Chemoradiotherapy

2.3.1 Three-dimensional conformal RT

All Patients underwent CT-based simulation with 5 mm slice thickness over the region of interest in supine position or in prone position on an up-down table (UDT). The scan should extend from the L2 vertebral body to below the perineum. Intravenous contrast was injected in all patients. Patients were simulated in the “arms up” position whether prone or supine and with a full bladder (patients were instructed to empty the bladder and drink 300 cm3 of water one hour before CT-simulation and before daily treatment fraction).

Radiotherapy was planned up to 55 Gy in 25 fractions (5 fractions per week) as 45 Gy at 1.8 Gy per fraction to pelvis with 4-field technique and additional 0.4 Gy per fraction given as second daily dose to primary tumor with 4-field technique during all entire course of radiotherapy at tumor with margins (1.5 cm radially +2.5 cm craniocaudally). So, dose delivered to planning target volume2 (PTV2) (pelvis) will be 45 Gy (1.8 Gy/fraction). A concomitant boost dose of 10.0 Gy with accelerated fractionation at 2.2 Gy/fraction, five sessions weekly, will be delivered to the PTV1 (tumor with margins) during the same fraction of PTV2. The minimum dose in the PTV is ≥ 93% of the prescribed dose; the highest dose in the PTV is < 115% of the prescribed dose, ≤ 5% of the PTV volume receives ≥ 110% of the prescribed dose.

PTV1 was clinical target volume1 (CTV1) + 1 cm margin. In CTV1, Rectal gross tumor volume (GTV) (tumor) +1.5 cm radially, +2.5 cm craniocaudally were included. PTV 2 was CTV2 + 1cm margin. In CTV2, the CTV1 plus the entire mesorectum, perirectal lymphatics, the entire pre-sacral space, iliac lymphatics (external iliac only if T4) were included.

The organs at risk (OAR) that were contoured on the planning CT were the following: bladder, femur head, and bowel bag). They were delineated as follows: 1) the small intestine was defined as all intestinal loops below the sacral promontory (excluding rectosigmoid junction); 2) femoral heads from the cranial extremity to the level of the lower margin of ischial tuberosities; and 3) the bladder was contoured entirely with no distinction between the wall and its content).

The dose–volume histogram (DVH) will be in accordance with the accepted tolerance dose for OAR. The doses of the OARs had to meet the following constraints: bladder, maximum dose < 50Gy, V40 Gy ≤ 40% volume; femoral heads, D-max < 50 Gy in whole volume and V40 Gy ≤ 40%; and small bowel, D-max < 50 Gy in whole volume and V45 Gy < 195 cc volume.

Radiotherapy was delivered with X-ray from linear accelerator with 15 MV photon energy. 3DCRT planning will be used.

2.3.2 Concurrent chemotherapy

Patients were treated with neoadjuvant chemoradiotherapy with Capecitabine at dose 625mg/m2 twice daily (two administrations, each 12 h apart) orally from Saturday to Wednesday throughout the whole course of radiotherapy, Oxaliplatin at a dose of 50 mg/m2 D1 intravenous administration, it will be administered weekly during the five-weeks course of radiotherapy. Radiotherapy was given between 2-6 h after chemotherapy administration. Adequate hematological, renal and hepatic function parameters were required before each chemotherapy infusion.

2.4 Toxicity Measurement

Patients were evaluated five times during the course of chemoradiation to assess acute toxicity. Toxicities were assessed and recorded weekly according to CTCAE v5.0. If grade 3/4 hematologic toxicities occurred, concurrent CRT would be interrupted until toxicity resolved to Grade 1/2, then CRT would resume with 25% a dose reduction of Oxaliplatin dose. If grade 2 neurotoxicity occurred, the oxaliplatin dose would be reduced by 25% in subsequent cycles. For

grade 3 non hematological toxicity, grade 2 capecitabine induced hyperbilirubinemia and grade 2 hand-foot syndrome, the capecitabine dose would be reduced by 25% also. If grade 3 hand-foot syndrome occurred, the capecitabine would be reduced by 50%. If grade 4 non-hematologic toxicities except diarrhea occurred, chemotherapy would be omitted, with radiotherapy continuing alone. If grade 4 diarrhea occurred, concurrent CRT would be interrupted until toxicity resolves to Grade 2/3, and then radiotherapy would be restarted without chemotherapy (capecitabine).

2.5 Surgical Operation Protocol

After 4-6 weeks, all patients were evaluated again. Surgical resection was performed 6-8 weeks after completion CRT. TME was mandatory. Type of operative procedure was abdominoperineal resection or low anterior resection. Then the surgeon decided whether a temporary colostomy should be performed.

2.6 Adjuvant Chemotherapy and Follow-up

After surgical resection, patients received adjuvant chemotherapy regardless of pathological stage. Adjuvant chemotherapy consisting of six to nine injections of FOLFOX-6 (every 14 days). Follow up evaluation included DRE, CEA and abdomen-pelvis ultrasound every 3-6 months with CXR and CT or MRI abdomen and pelvis every 6-12 months for about 2 years at least one year after enrollment of the last patient. Recurrence was defined as local (within the rectum near anastomosis), regional (within the pelvis) or distant (outside the pelvis).

2.7 Study End Points and Statistical Analysis

The primary end point of this phase II trial was pCR rate to assess efficacy of concomitant boost neoadjuvant radiotherapy (55 Gy/5 weeks, total dose) plus concurrent chemotherapy (capecitabine plus oxaliplatin) in the treatment of LARC. pCR was defined as the complete disappearance of the infiltrative primary tumor and the absence of malignant deposits in the locally resected lymph nodes.

Secondary endpoints include evaluation of sphincter preservation rate, clinical response, toxicity (acute), disease free survival and overall survival. Sphincter preservation was defined as any procedure in which the rectal tumor was removed while leaving behind the ana sphincter intact. Distant metastases free survival was defined as the time from the assignment to the date of distant metastases. DFS was defined as the time from surgical resection to the date of local recurrence, distant metastases or death whatever came first. OS was defined as the time from assignment to death.

Data were entered and analyzed using IBM-SPSS software. Qualitative data were expressed as frequency and percentage. For data comparison, qualitative data: Chi-Square test or Fisher's exact test according to sample size of cells was used. Standard logistic regression: To predict the likelihood of a diagnosis using only one predictor, standard logistic regression analysis was used to calculate the odds ratio (OR) with its 95% Confidence Interval (95% CI). Multi-variable logistic regression was used to create a prediction model of the likelihood of a diagnosis to detect the significant "independent" predictors with their OR (95% CI). Survival curves were estimated using the Kaplan-Meier method and compared with Log-rank test. For any of the used tests, results were considered as statistically significant if p value ≤ 0.050.

3. RESULTS

3.1 Clinical Characteristics

Between October 2016 and May 2019, 30 patients were enrolled in the study. All patients were diagnosed with LARC: of total 30 patients, 12 were men and 18 were women, 53.5% of patients were 18-50 years old and 46.7% were >50 years old. 23.3% of patients were ECOG score 2. Twelve patients (40%) had tumor locate >5 cm from anal verge and eighteen patients (60%) had tumor locate ≤ 5 cm from anal verge. By MRI, nineteen patients (63.3%) were considered as having cT3 and eleven patients (36.7%) were considered as having cT4. Eleven patients (36.7%) were considered as having cN0 and nineteen patients (63.75%) were considered as having cN1-2 (Table 1).

3.2 Treatment Compliance & Acute Toxicity during Entire Course of CRT

All thirty patients completed the targeted radiation treatment to a total dose of 55 Gy in 25 fractions and completed five weeks of capecitabine and five cycles of oxaliplatin. Twenty-eight patients finished the planned

treatment program without any interruption. Two patients didn't complete the planned chemoradiotherapy at planned time (postpone chemoradiotherapy for one week) because of treatment toxicity. Both of them had grade III neutropenia. After the toxicities were resolved, CRT continued with 25% dose reduction of chemotherapy. Most of the adverse events during CRT were mild (grade I or II). No grade IV–V toxicities were recorded. Frequency of grade III acute toxicities was 16.6%. Grade III neutropenia, diarrhea and radiation induced dermatitis were 6.7%, 6.7%, 3.3% respectively (Table 2).

3.3 Presurgical Radiological Response Assessment

Pretreatment and post treatment MRI evaluation was done to all patients. Clinical downstaging percentage recorded in seventeen patients (56.7%). cT-downstaging (Table 3) and cN-downstaging percentage was 50% and 36.7% respectively.

3.4 Operative Findings

Twenty-seven patients underwent surgical resection according to the schedule. Three patients refused the surgical resection due to good response and subjective improvement. The median time from the last radiotherapy session to day of the operation was 7.5 week (6-9 weeks). Twenty-five patients (92.9%) underwent sphincter-sparing low anterior resection. For tumor of the lower third, sphincter preservation was achieved in 16 of 18 patients, which represent (89%). Pathological tumor (ypT0) stage and pathological nodal (ypN0) stage were detected in 9 (33.3%) and 21(77.8%) patients respectively. Tumor regression grade (TRG) information according to AJCC/CAP TRG was available in pathological examination. TRG was Grade 0(complete response) in 9 (33.3%) patients, grade 1(moderate response) in 13 (48.1%) patients, grade 2(minimal response) in 3(11.1%) patients and grade 3(poor response) in 2(7.4%) patients. Twenty-four patients of assumed to be Ro at time of surgery. All operative finding and pathological features are listed in Table 4. Pathological downstaging was achieved in 74% (20/27) of cases. Pathological T down-staging percentage is 77.8% (21/27) cases. Pathological N downstaging percentage is (44.4%) 12/27 cases.

Acute surgical complications included abdominal wound infection in seven patients (25.9%). Urine retention, anastomotic leak and presacral infection occurred in one patient (3.7%), two patients (7.4%), two patients (7.4%) respectively (Table 5).

3.5 Pathological Complete Response Predictors

Pathological complete response (pCR) was achieved in 9/27 operated cases (33.3%). Possible predictive factors for pCR are listed in Table 6. Patients with cT3 (88.9%) had higher pCR than patient with cT4 (11.1%) with p-value tended to approach significance (p=.091) by Fisher's exact test. It was found that all patients with after neoadjuvant nodal (yN0) stage achieved pCR (100%) versus no patients with yN1-2 and this difference was highly significant (p=.009). One-third of those who achieved pCR (n=9) were after neoadjuvant tumor (yT0) stage while two-thirds were yT2-4 in equal proportions and the difference was trend bordering on statistical significance (p= 0.067) by Fisher's exact test.

3.6 Univariable and Multivariable Analysis of Predictors of the Likelihood of Achievement of pCR:

A binomial logistic regression was run to ascertain the effects of clinical T, Clinical downstaging, post chemoradiotherapy CEA nadir<5ng/ml, tumor location and MRF involvement on the likelihood that participants achieve pCR. None of the examined predictors achieved statistical significance with marginally significant p value was that for low rectal tumor location versus mid rectal tumor location (p=.061) and cT3 vs cT4 (p = .082). A major weakness in this model is the small sample size (Table 7).

3.6.1 Follow up and treatment outcomes

With median follow up of 20 months (range, 12-42 months), two patients presented with LR. One of two patients with pCR and another patient without. Three-year LR rate was 7.4%. DFS was defined from surgical resection to the date of LR, distant metastases or death. The median time for DFS was more than study period. Seven patients were died. One patient developed distant lung metastases 10 months and died 24 months after CRT. Four patients didn't present any evidence of tumor failure at their last visits. Two patients were died after surgery because of sever operative infection. The median time for OS was more than study period. Three-year DFS, OS

rates were 63% and 74.1% respectively (Figs. 1& 2).

3.6.2 Univariate and multivariate analysis for OS & DFS

All potential prognostic factors of OS & DSF, including age, gender, distance from anal verge, cT stage, cN stage, ypT and ypN stage, pCR and pathological downstaging were evaluated using A binomial logistic regression to ascertain the effects of these predictors. On univariable analysis and next multivariate Cox regression analysis, the ypN0 was statistically significant predictors of DFS (p=0.020). Univariable analysis showed that younger age, ypN1-2, absent pathological downstaging, and TRG (G2-G3) were statistically significant predictors of mortality. On next multivariable analysis, none of the examined predictors achieved statistical significance A major weakness in this model is the small sample size.

The three-year DFS rate was significantly different among the patients with ypN0 versus patient with ypN1-2 (76.2% versus 16.7%) (p=.004) by log Rank test (Fig. 3).

The three-year OS in the patients with ypN0 was significantly higher than OS in patients with ypN1-2 (85.7% versus 33.3%) (p=.008) by log Rank test. The three-year OS rate was significantly different in patients who achieved pathological downstaging than patients who didn't achieve pathological downstaging (85% versus 42.9%) (p=.012). Patients with TRG 0 or 1 achieved three-year OS significantly higher than that was achieved in patients with TRG 2 or 3 (86.4% versus 20%) (p=.001) by log Rank test. Younger age (<50) patients achieved three-year OS higher than that was achieved in older age patients with marginally significant difference (86.4% versus 58.3%) (p=.069) by log Rank test (Figs. 4,5).

Table 1. Patients' characteristics

Characteristics	Number (N)=30	%
Gender		
Male	12	40
Female	18	60
Age		
18-50	16	53.3
>50	14	46.7
Comorbidities		
No	22	73.3
Yes	8	26.7
ECOG		
0-1	23	76.7
=2	7	23.3
Tumor location		
Mid (>5 cm from anal verge)	12	40
Low (<5 cm from anal verge)	18	60
Clinical T		
T3	19	63.3
T4	11	36.7
Clinical N		
N0	11	36.7
N1-2	19	63.3
CEA		
Normal (<5ng/ml)	19	36.7
High (>or = 5 ng/ml)	11	63.3

ECOG: Eastern Cooperative Oncology Group, CEA: carcinoembryonic antigen

Table 2. Acute toxicities

Toxicities	Total (%)	Grade1(%)	Grade2(%)	Grade3(%)
Radiation induced proctitis	30(100%)	8(26.7%)	22(73.3%)	0(0%)
Radiation induced dermatitis	23(76.6%)	21(70%)	1(3.3%)	1(3.3%)
Fatigue	23(76.7%)	21(70%)	2(2.6%)	0(0%)
Diarrhea	15(50%)	5(16.7%)	8(26.6%)	2(6.7%)
Dysuria	11(36.7%)	11(36.7%)	0(0%)	0(0%)
Capecitabine-induced hyperbilirubinemia	2(6.6%)	1(3.3%)	1(3.3%)	0(0%)
Oxaliplatin-induced sensory Peripheral neuropathy	18(60%)	15(50%)	3(10%)	0(0%)
Anemia	16(53.3%)	9(30%)	7(23.3%)	0(0%)
Neutropenia	5(16.7%)	0(0%)	3(10%)	2(6.7%)

Table 3. Clinical T down staging

cT stage	yT stage					Total
	yT0	yT1	yT2	yT3	yT4	
cT3	3	0	5	8	3	19
cT4	0	0	1	6	4	11
Total	3	0	6	14	7	30

Table 4. Operative findings

Operative findings	N=27	%
Surgery type:		
Low anterior resection	25	92.6
abdominoperineal resection	2	7.4
lymph-vascular invasion:		
No	25	92.6
Yes	2	7.4
perineural invasion:		
No	24	88.9
Yes	3	11.1
CRM:		
Negative	26	96.3
Positive	1	3.7
ypT		
T0:	9	33.33
T1	0	0
T2	9	33.33
T3	9	33.33
ypN		
ypN0	21	77.8
ypN1	3	11.1
ypN2	3	11.1
other margins:		
Negative:	25	92.6
positive:	1	3.7
Inadequate:	1	3.7
Tumor regression grade:		
Grade 0	9	33.33%
Grade 1	13	48.1%
Grade 2	3	11.1
Grade 3	2	7.4

CRM: circumferential radial margin

Table 5. Acute surgical complications

Toxic manifestation	Total (%)	Grade 1(%)	Grade 2(%)	Grade 3(%)	Grade 4(%)
Abdominal Wound sepsis	7(25.9)	0	4(14.8)	2(7.4)	1(3.7)
Urine retention	1(3.7)	1(3.7)	0	0	0
Presacral (pelvic infection)	2(7.4)	0	1(3.7)	1(3.7)	0
Anastomotic leak	2(7.4)	2(7.4)	0	0	0

Table 6. Pathological complete response predictors

Characteristic	pCR achieved (n=9)	pCR not achieved (n=18)	P value (Fisher's exact test)
Tumor location			
Mid rectum:	1 (11.1%)	8(44.4%)	0.193
Low rectum:	8 (88.9%)	10 (55.6%)	
MRF involvement:			
Absent:	5(55.6%)	5(27.8%)	
Present:	4(44.4%)	13(72.2%)	0.219
Clinical T:			
T3	8(88.9%)	9(50%)	**0.091**
T4	1(11.1%)	9(50%)	
CEA post chemoradiotherapy			
nadir	8(88.9%)	14(77.8%)	0.636
Normal	1(11.1%)	4(22.2%)	
High			
Clinical downstaging:			
Yes:	7(77.8%)	9(50%)	0.231
No	2(22.2%)	9(50%)	
yT:			
T0:	3(33.3%)	0(0.0%)	
T2	2(22.2%)	4(22.2%)	**0.067**
T3	2(22.2%)	10(55.6%)	
T4	2(22.2%)	4(22.2%)	
yN			
N0:	9(100.0%)	8(44.4%)	**0.009**
N1-3:	0(0.0%)	10(55.6%)	

pCR: pathological complete response, MRF: mesorectal facial, CEA: carcinoembryonic antigen

Table 7. Univariable and multivariable analysis of pCR Predictors

Predictors	Univariable			Multivariable		
	P-Value	COR	95% CI	P-Value	OR	95% CI
Clinical T	**0.073**	8.0	0.8-77.8	**0.082**	9.3	0.8-115.9
Clinical downstaging	0.178	3.5	0.6-21.7	0.103	10.2	0.6-164.6
Post chemoradiotherapy CEA nadir	0.492	2.3	0.2-24.1	0.891	1.5	0.007-310.8
Tumor location	0.110	6.4	0.7-62.4	**0.061**	17.0	0.9-330.8
Mesorectal facia involvement	0.167	3.3	0.6-17.3	0.130	7.9	0.5-115.2

COR: crude odds ratio, CI: confidence interval, OR: odds ratio

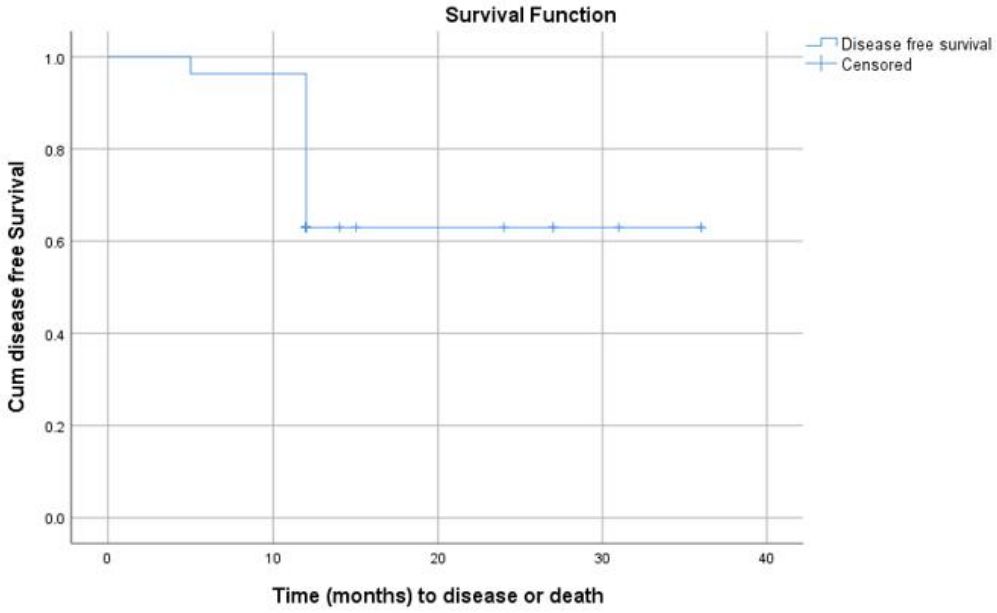

Fig. 1. Survival curve of disease-free survival (DFS)

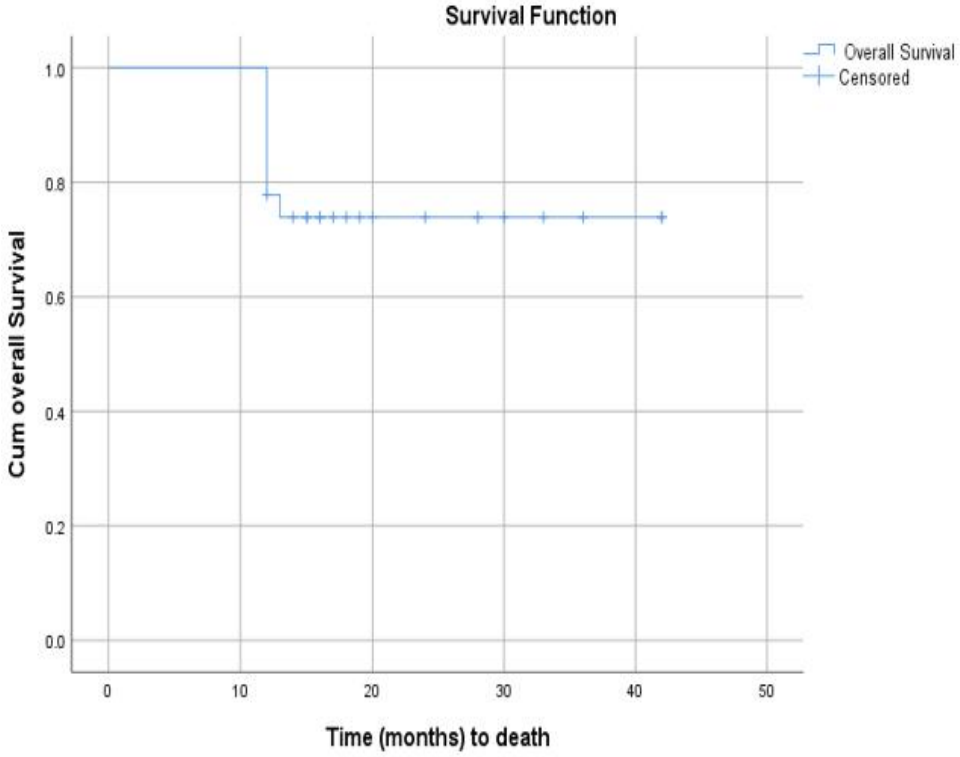

Fig. 2. Survival curve of Overall survival (OS)

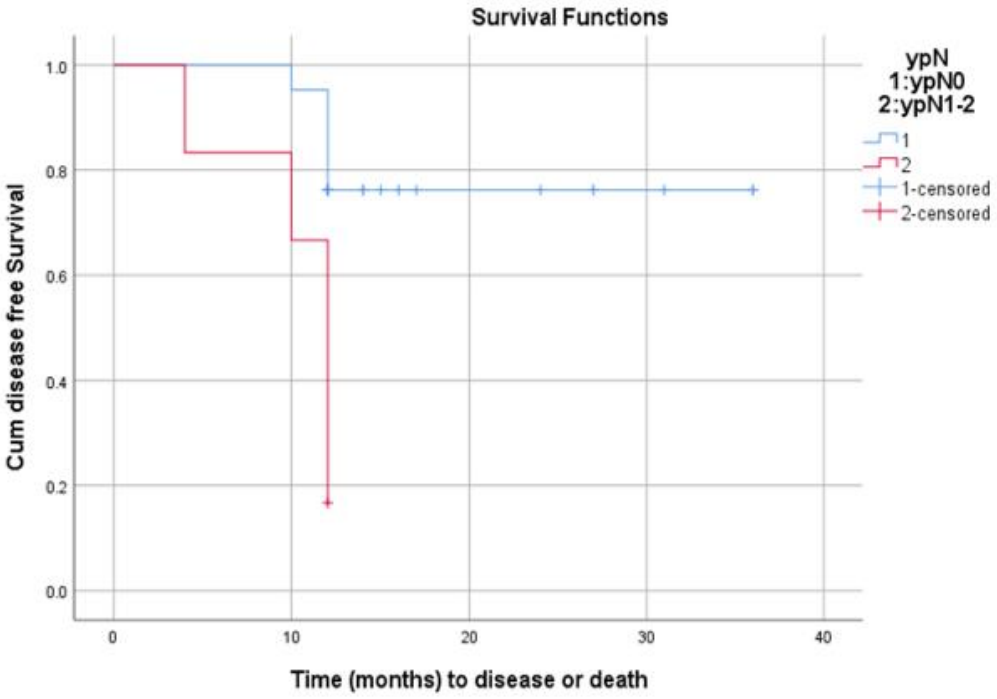

Fig. 3. DFS rate by ypN

4. DISCUSSION

Neoadjuvant treatment approaches either as short-course hypo-fractionated radiotherapy (SCRT) or as long course chemo radiotherapy (LCRT), usually with fluorouracil-based chemotherapy, are recommended by national and international guidelines [23]. RAPIDO trial compared neoadjuvant LCRT versus SCRT with subsequent CAPOX or FOLFOX chemotherapy, in patients with cT3 or cT4, N+ve. There was no recorded significant difference in local control, OS, surgical procedure or postoperative complication between two arms. So that, SCRT, followed by neoadjuvant chemotherapy, is an acceptable option for those patients [24].

Our study used an intensified regimen of concomitant boost radiotherapy (55 Gy) plus concurrent capecitabine with oxaliplatin in treatment of T3, T4 and or N+ve rectal cancer patients. We delivered radiotherapy by using 3DCRT technique. Our work mainly aimed to examine the efficacy and safety of this intensified regimen. The primary end point was pCR.

The benefits of pCR after neoadjuvant CRT in rectal cancer were well clarified by data from 16 different datasets. The complete responder patients had a 3·3 and 4.3-fold OS and DFS advantages respectively compared with incomplete responders. Patients with pCR were associated with four times less likely to develop local and distant failure compared with patients without pCR [25].

Oxaliplatin is an effective drug for CRC when combined with 5-FU [8]. A systematic review and meta-analysis of at least 10 randomized trials of the addition of a platinum drug to fluoropyrimidine-based CRT using conventional fractionation reported that the addition of a platinum derivative significantly increased the likelihood of a pCR at the time of surgery [17].

Our study resulted in pCR rate of 33.3%. It was higher in comparison to nearly almost other randomized studies used conventional conformal radiotherapy with concurrent platinum agent plus fluoropyrimidine-based chemotherapy. These trials reported that achieved pCR percentage ranged from 13.5 to 27.5% [13,14,26-28]. Our achieved pCR rate was comparable to that achieved in only one previous trial performed by Haddad et al., 2017 (pCR rate 34%) [15].

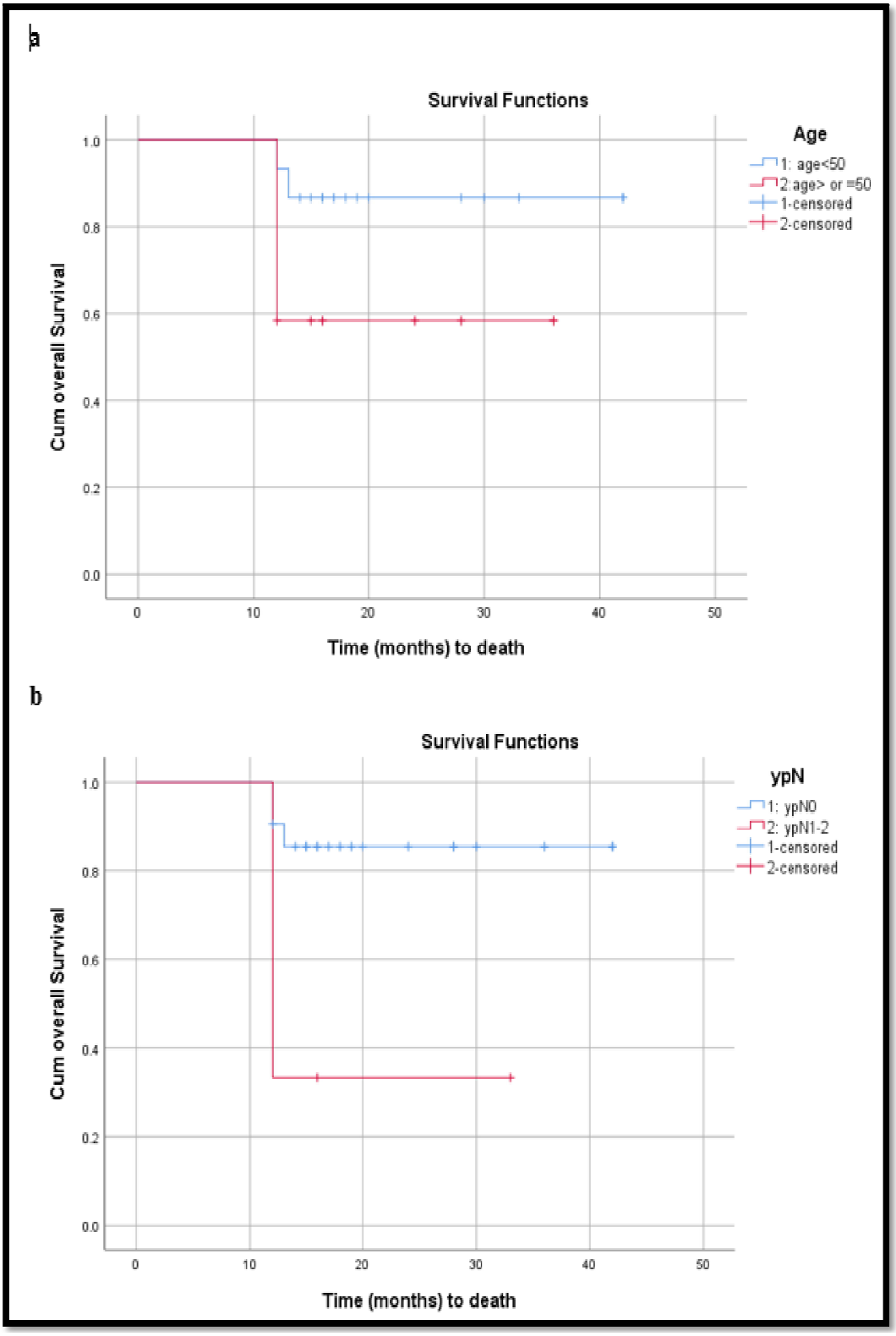

Fig. 4. a: OS rate by Age b: OS rate by pathological lymph node stage (ypN)

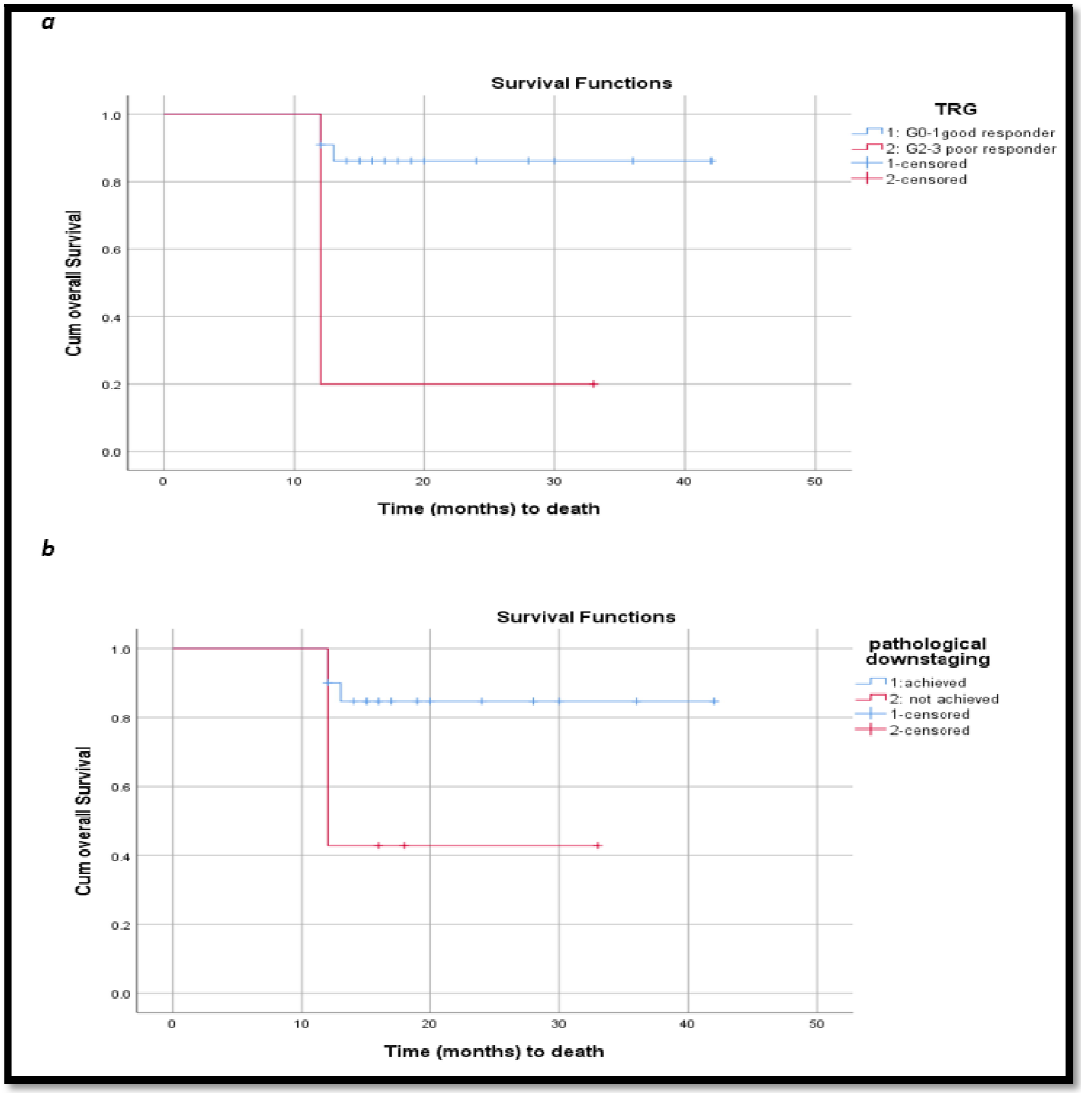

Fig. 5. a: OS rate by TRG b: OS rate by pathological lymph downstaging

The achieved pCR rate in our study was comparable with those of preoperative IMRT studies that used intensified CRT regimens. In the studies that used IMRT with variable radiation doses and with or without oxaliplatin, the pCR ranged from 0% to 50 %. This wide range of pCR among IMRT studies might be due to varying radiation doses, dose per fraction and chemotherapy regimens [29].

In our study, the predictors to achieve pCR have been extensively studied. Low rectal tumor location predicted a greater likelihood of pCR in comparison to mid rectal tumor location with marginally significant p-value (p=0.061). Some previous studies also suggested that the distance from anal verge ≤ 6 cm was correlated with higher pCR and favorable response [30,31]. This may be explained by that relative lack of organ mobility in tumors close to anal verge in comparison with mid and high tumors. So, tumors with lower location may have a greater possibility of delivering the prescribed dose to RT volumes compared to the rectal tumors with higher location [31]. Nevertheless, other studies showed that no association was found between tumor location and pathologic response [32]. Still further investigation is needed to determine the relationship between tumor distance from anal verge and response to neoadjuvant CRT [33].

A smaller tumor size has been found to be the most common factor related to an increased rate of pCR [32]. Letaief et al., 2017 [34] found that pCR rate was significantly higher in patients with the cT2 stage. We reported that cT3 (47%) achieved higher pCR in comparison cT4 (10%) to, however the difference approaching although not reaching a statistically significant level (p = .082).

In a case series study, lower yT was significantly associated with increased pCR [35]. We reported that one-third of those who achieved pCR in our study were yT0 while two-thirds were yT2-4 in equal proportions and the difference was marginally significant (p= 0.067). A recent retrospective analysis that done by Engel et al., 2020 [35] reported a significant association between preoperative N stage and pCR. In that analysis, 24.8% of patients who had no preoperative nodal involvement achieved a pCR, compared with just 15.5% of the patients who had positive preoperative nodal involvement (p = .031). Likewise, we found that achieved pCR in yN0 patients versus yN+ve patients (52.9% vs 0%) respectively, and this difference was highly statistically significant (p=0.009).

When a pCR is attained, anal-sphincter preservation rate increases [4]. Park et al., 2018 [36] retrospectively reviewed patients with stage II/III mid-to-lower rectal cancer following neoadjuvant CRT and reported that a sphincter-saving procedure was 89.9%. In randomized trials that added platinum agents to fluoropyrimidine-based CRT using conventional fractionation, sphincter-preserving surgery rate was ranging from 57.7% to 87.2% [17]. Our study achieved 92.6% sphincter preservation rate. For tumors of the lower third, sphincter preservation was achieved in 16 of 18 patients, which represent (89%). This relatively high sphincter preservation rate may be owing to intensified regimen of radiotherapy and small sample size.

Three-year LR that be recorded by seven phase III trials adding oxaliplatin to neoadjuvant CRT for rectal cancer ranged from 1.3% to 11.2% [13-16]. Metanalysis of these trials reported that adding oxaliplatin did not translate into improvements in LR [17]. Our study achieved (7.4%) 3-year LR. Park et al, 2018 [22] study reported significant difference in LR between complete responder and non-complete responder groups. Whereas, in our study there is no significant difference between who achieved pCR and who didn't achieve pCR. Longer follow up may be needed.

Three-year DFS that was recorded by seven phase III trials adding oxaliplatin to neoadjuvant CRT for rectal cancer ranged from 69.2% to 92.0% [13-16]. However, Hüttner et al., 2019 [17] noticed that addition of a platinum drug to fluoropyrimidine-based CRT did not translate into improvements in DFS. Our study achieved 63% three-year DFS and this is consistent with a similar trial performed by Zhu et al, 2014 [13] who reported 63.8% three-year DFS. We reported that patients who achieved pathological downstaging had a three-year DFS of 80%, but for those who didn't achieve pathological downstaging the three-year DFS decreased to 14.3% (p= .001). Patients with ypN0 had a three-year DFS of 76.2%, but for those with positive ypN it declined to 16.7%(p=.004).

Three-year OS have been recorded by seven phase III trials adding oxaliplatin to neoadjuvant CRT for rectal cancer and ranged from 77.8 ± 3.5% to 88.7% [13-16]. However, Hüttner et al, 2019 [18] proved that the addition of a platinum drug to fluoropyrimidine-based CRT did not have significant impact on OS. An IMRT study using an intensified regimen of concomitant boost radiotherapy plus concurrent capecitabine and oxaliplatin achieved 77.4% three-year OS [7]. Our study with similar intensified regimen using conformal radiotherapy reported 74.1% three-year OS.

In our study, univariate and multivariate analysis for DFS & OS were done. All potential prognostic factors, including age, tumor location, cT stage, cN stage, ypT stage, ypN stage, pathological downstaging and TRG score were evaluated using the binomial logistic regression. On univariate analysis, our study also showed that negative ypN, and achieved pathological downstaging were statistically significant predictors of DFS. In the multivariate analysis, only ypN was found independently associated with DFS (only ypN0 achieved statistical significance (p=0.020). These results were in accordance with the results of other trials that showed that tumor downstaging [37] and pathological N status [38] were independently associated with DFS in LARC patients treated with preoperative CRT and TME.

In the univariate analysis, age, ypN stage, pathological downstaging and TRG score exhibit a correlation with OS. Older age (>50), positive ypN, absent pathological downstaging, and advanced TRG (G2-G3) were statistically significant predictors of mortality. In multivariate analysis, none of the examined predictors

achieved statistical significance. A major weakness in this model is the small sample size. We reported that younger age associated with 86.7% three-year OS and older age associated with 58.3% three-year OS (P=.069). Langrand-Escure et al., 2018 [39] approved that age influenced OS independently. The old age was correlated with a lower rate of concurrent chemotherapy and a poorer ECOG performance status, which can partly explain the poor outcome of elderly patients.

It was reported that node involvement was identified as major predictive factor of poor OS [39], and the poor outcomes were seen in patients with ypN2 disease [19]. Our study reported that patients with ypN0 also achieved 85.7% three-year OS, while patients with positive pathological LN achieved 33.3% three-year OS (p=.008). These reports suggested that these patients are good candidates for novel treatment approaches, such as expanded postoperative chemotherapy.

It was found that prognosis has also correlated with TRG, and the better prognosis with lower TRG was maintained with long-term follow-up [40]. In our study, TRG (0-1) patients' three-year OS was 86.4%, but TRG (2-3) patients' three-year OS dropped to 20% (p=.001).

Some clinical trials suggested that tumor-downstaging improved OS rates [37,41]. We reported also that patients who achieved pathological downstaging had a three-year OS of higher than who didn't achieve pathological downstaging (85.0% vs 42.9%) (p=0.026). Gunther et al., 2017 [41] reported that the achieved rate of tumor downstaging after adding of a concomitant boost radiotherapy was higher than the same achieved after standard dose radiotherapy (76% vs 51%). Our study achieved that pathological Tumor downstaging percentage was 77.8%.

The complete remission following neoadjuvant CRT was considered a significant prognostic factor for DFS and OS [40]. In meta-Analysis of twelve studies, pCR patients had OS and DFS of 92.9% and 86.9% respectively versus 73.4% and 63.9% respectively for partial or no response patients [22]. We reported that patients who achieved pCR had three-year DFS and three-year OS of 66.7% and 88.9% respectively, while who didn't achieve pCR had 61.1% and 66.7% respectively with no statistically significant difference. The high rate of pCR did not translate into high DFS or OS compared to some other trials adding oxaliplatin to CRT. This may be attributed to two factors, First, our study had a small sample size. Second, the percentage of cT4 and ECOG 2 patients in our study were significantly higher than these trials (cT4: 36.7% vs. 5.5-13%) (ECOG 2:23.3% vs. 0-4.8%) [16,32,33,39].

Regarding the toxicity, we reported that the incidence of grade III neutropenia, diarrhea and radiation dermatitis were 6.7%, 6.7% and 3.3% respectively, and no grade IV toxicities were recorded. So that all grade III toxicities were 16.7%. The incidence of Grade III-IV toxicities of our study were comparable with those of phase III trials adding oxaliplatin to neoadjuvant CRT using conventional fractionation. In these trials, the incidence of grade III-IV toxicities was 15.4-36.7% with oxaliplatin and fluoropyrimidines CRT arm, while it was 6.8-15.2% with fluoropyrimidines alone CRT arm [13,16,26].

The randomized studies used conventional radiotherapy plus concurrent oxaliplatin with capecitabine chemotherapy reported that the incidence of grade III diarrhea or more ranged from 6% to 19% [14,15,27,28]. The incidence of grade III diarrhea in our study was comparable to most of these studies. The incidence of grade III neutropenia and radiation dermatitis was compared with other reported trials that used conventional radiotherapy plus concurrent oxaliplatin with fluoropyrimidines based-chemotherapy. CAO/ARO/AIO-04 trial [27] and Jaio et al., 2015 [42] reported 4.8% and 5% grade III hematological toxicities respectively. Apart from two cases (6.7%) of neutropenia, no other grade III hematological toxicities were observed in our study. STAR-01 trial [26], Allegra et al., 2015 [14] and Haddad et al., 2017 [15] reported 5%, 3.4% and 1% Grade III radiation dermatitis respectively. Our study reported 3.3% Grade III radiation dermatitis.

As regard toxicity, our results using 3DCRT were compared to those of preoperative intensified CRT trials using IMRT. One of the advantages of IMRT over 3DCRT was its ability to spare the small bowel [29]. In Yang et al, 2013 [43], the cases with grade ≥2 diarrhea were higher in patients who were treated with 3DCRT as part of CRT in contrast to IMRT (32% vs 11%). Grade II diarrhea or more was 33.3% in our study. Grade III diarrhea was experienced by 6.7% in our study, while it was between 1% and 18% among different IMRT studies. This difference in the

values could be explained as a result of the variations in contouring, planning, beam angles, and diets among there trials [29]. It was noticed that grade III radiation dermatitis varied from 0.03% to 21% among different IMRT studies [5,29]. As previously mentioned, grade III radiation dermatitis in our study was 3.3%. The incidence of grade III neutropenia in our study was compared to the upper limit of grade III hematological toxicities' range (0%–6%). among almost the IMRT studies [5,29].

CAO/ARO/AIO-04 trial (22), PETACC-6 trial [16], STAR-01 trial [26], ACCORD 12/0405 PRODIGE 2 [13], FOWARC trial [44] reported that neither postoperative morbidity, nor anastomotic leakage demonstrated a statistically significant difference with the addition a platinum agent with CRT. STAR-01 trial [26] and CAO/ARO/AIO-04 [27] trial reported that grade III/IV acute surgical complications in fluorouracil and oxaliplatin group were 17% and 13% respectively versus 15% and 10% in fluorouracil only group. In our study, we reported that grade III/IV acute surgical complications were 14.8%.

Gunther et al, 2017 [41] performed a phase II study examined patients who received CRT with concomitant boost radiation therapy versus patients who received standard dose CRT. It reported that surgical wound complications that required treatment did not differ between both groups. Concomitant boost group reported that anastomotic leak, wound complications, urine retention and peri-sacral infection were 6.6%, 25%, 1.3% and 22.3% respectively, while standard dose group reported 9.2%, 17%, 22.3%, 10.5% respectively. In our study, the incidence of anastomotic leak, wound complication, urine retention and peri-sacral infection were 7.4%, 25.9%, 3.7% and 14.8%. Apart from three cases (11.1%) of abdominal wound sepsis and one case (3.7%) of pelvic sepsis, no other grade III/IV acute operative complications were recorded.

5. CONCLUSION

Overall, this phase II trial agreed that the combination of oxaliplatin, capecitabine, and radiotherapy is safe and offers an appealing percentage of pCR (33.3%) and high sphincter preservation rate (92.6%). Moreover, Dose escalation may have important implications for novel treatment strategies for rectal cancer that rely on pCR, such as nonoperative management. Therefore, strategies to enhance radiation therapy response through dose optimization should be further pursued.

CONSENT AND ETHICS APPROVAL

The study was approved by the Ethics Committee of institutional research Board of Mansoura University Faculty of medicine (2016-10-06]. All patients entered the informed consent form. All patients provided written informed consent, and study was approved by local ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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