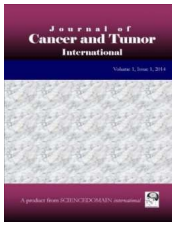

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Neoadjuvant Chemoradiotherapy and Chemotherapy in Patients with Locally Advanced Rectal Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AMA and MIA gave the concept and designed the study. Authors AMA, MIA, HF, AS and NMA did the study materials. Authors AMA and MIA collected the assembly of data. Authors AMA and MIA managed interpretation and data analysis. Author AMA wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Evaluate the role of neoadjuvant chemoradiotherapy (CRT) followed by an additional cycle of chemotherapy and total mesorectal excision (TME) in patients with locally advanced rectal cancer on the rate of pathologic complete response (pCR) and tumor downstaging, their impact on survival and evaluation of treatment related toxicity and surgical complications.
Patients and Methods: This prospective phase II trial included 73 patients with histopathologically proven non metastatic rectal adenocarcinoma referred from or admitted at Surgical Oncology Department, Radiotherapy Department, South Egypt Cancer Institute, and Clinical Oncology Department, Assiut University, Egypt, from March 2012 to September 2013. Radiotherapy (1.8 Gy, 5 days a week over 5 weeks, total dose 50.4 Gy, 3 D conformational technique) was given in combination with intravenous oxaliplatin 50 mg/m^2 once weekly for 5 weeks and oral capecitabine

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825 mg/m^2 twice daily on each day of radiation. After completion of CRT, patients received an additional cycle of chemotherapy consisted of oxaliplatin (130 mg/m^2 on day 1) and capecitabine (825 mg/m^2, twice per day from day 1 to day 14). Surgery was performed 6–8 weeks after completion of chemoradiotherapy.

Results: Seventy patients (95.9%) underwent surgery. Postoperative pathologic assessment showed an overall downstaging rate of 78.1%, while 16 patients (21.9%) had stationary disease. Complete pathologic response was achieved in 11 patients (15.1%). No tumor progression has been observed. After median follow up period of 26 months (7-30 months), the 2-year overall survival (OS) was 88%, recurrence free survival was 88.7% and distant metastasis free survival was 93.9%. Lower pathologic tumor stage was significantly associated with better OS (*P* = .002) and recurrence-free survival (*P* = .001), while pathologic nodal stage and TRG had no significant difference in overall survival, recurrence free survival or distant metastasis free survival. Forty-one patients (56.2%) experienced grade 1-2 toxicity and 5 patients (6.8%) experienced grade 3 toxicity.

Conclusion: Neoadjuvant CRT and one cycle of chemotherapy followed by TME is effective with pCR of 15.1% and overall downstaging rate of 78.1%. In addition to favorable toxicity profile (lower grade 3 and 4 toxic effects as 3 patients developed grade 3 diarrhea and 2 patients developed grade 3 hematological toxicity and lower rate of Grade 1 – 2 diarrhea ; 28.8%) and outcome.

Keywords: Neoadjuvant; radiotherapy; chemotherapy; surgical operation; rectal cancer.

1. INTRODUCTION

Local recurrence and distant metastasis are serious problems in locally advanced rectal cancer (LARC). The local recurrence rate with conventional surgery alone was 20–45% and to <10% by total mesorectal excision (TME) [1,2]. The high local recurrence rate after surgical resection, necessitate multimodal management of surgery, chemotherapy and radiotherapy to achieve the optimal outcome [3]. The aims of preoperative treatment in LARC are improvement of survival, reduce local recurrence and increase sphincter saving surgery [4–7]. Efforts to improve such results have focused on preoperative combined chemoradiotherapy (CRT) treatment regimens [8–10]. Several trials have also explored the role of induction of oxaliplatin and capecitabine before CRT aiming at reducing the rate of distant metastasis [11-13].

The advances in preoperative therapies have led to the need for an accurate preoperative staging technique to select those patients who are most likely to benefit from these interventions without subjecting others to unnecessary treatment. Magnetic resonance imaging (MRI) scans are the gold standard for assessing the involvement of mesorectal fascia by tumor. Patients with involvement of mesorectal fascia by tumor, have high risk of positive circumferential margin (CRM) and require downstaging before surgery.

In our study, we evaluated the role of neoadjuvant CRT (capecitabine and oxaliplatin) followed by an additional cycle of chemotherapy and TME in subgroup of patients with locally advanced rectal cancer on the rate of pathologic complete response (pCR) and tumor downstaging, their impact on survival and evaluation of treatment related toxicity and surgical complications.

2. PATIENTS AND METHODS

This prospective phase II trial included all new cases with locally advanced rectal cancer referred from or admitted at Surgical Oncology Department, Radiotherapy Department, South Egypt Cancer Institute, and Clinical Oncology Department, Assiut University, Egypt from March 2012 to September 2013.

Pre-therapeutic evaluations included a complete history and physical examination, digital rectal examination, complete blood count, liver and renal function tests, proctosigmoidoscopy with biopsy, colonoscopy, contrast-enhanced pelvic MRI and endorectal ultrasound before treatment and after chemoradiotherapy, computed tomography (CT) scan of the chest and abdomen.

All patients enrolled in the study were newly diagnosed and histopathologically proven T3/4, and N- / N+ non metastatic rectal adenocarcinoma according to the criteria of the 7th edition of the AJCC Cancer Staging Manual [14]. Inclusion criteria were: on MRI, patients had T3/4, and N- / N+, age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 [15] and adequate liver,

renal and hematological functions (granulocytes >1500/mm^3, platelets >100 000/mm^3, bilirubin ≤ 1 upper limit of normal, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 ULN, creatinine ≤ 1.5 mg/dl or creatinine clearance at least 60 ml/min). Patients with history of previous malignancy, previous treatment with chemotherapy or radiotherapy, major organ dysfunction, pregnancy or breast-feeding and chronic diseases such as diabetes, hypercholesterolemia and hypertension, were excluded from enrollment in the trial.

Informed consent was taken from the patients and the study was approved by the institutional ethics committee.

2.1 Preoperative Combined Chemoradiation

2.1.1 Radiotherapy

Conformal three dimentional radiotherapy was used for all patients based on a contrast CT scan of the pelvis.

2.1.1.1 Target volume

Included the rectum, mesorectum and the draining lymph node chains (pararectal, hypogastric, presacral lymph nodes). CT was performed in the treatment position, with 5-mm thick slices and a 5-mm spacing between images. Gross tumor volume encompassing the tumor and involved pelvic lymph nodes. After careful review with the radiologist and surgeon, the clinical target volume (CTV) was delineated. The CTV encompassing the entire rectum, mesorectum, pararectal nodes, the presacral and promontory nodes (limit S1/S2), and the internal iliac nodes up to the venous bifurcation. The planning target volume was an expansion of the CTV (10 mm). Organs at risk were also contoured: bladder and femoral heads.

2.1.1.2 Field arrangement

Three field techniques were used (one posterior and two opposing wedged lateral fields) to give a homogeneous distribution to the target volume.

2.1.1.3 Dose and energy

All patients were treated by a photon beam of either 6 or 15 MeV. The total dose of 50.4 Gy (pelvis dose of 45 Gy/25 fractions and 5.4 Gy/3 fractions boosted to the primary tumor plus 2 cm margin) was prescribed at the isocenter of the plan according to ICRU report No. 50.

2.1.2 Chemotherapy

Capecitabine was administered at 825 $mg/m^{(2)}$ twice daily for 5 days/week and oxaliplatin at 50 $mg/m^{(2)}$ on day 1 weekly for 5 weeks starting the first day of RT (before RT). After completion of CRT, patients received an additional cycle of chemotherapy consisted of oxaliplatin (130 mg/m2 on day 1) and capecitabine (825 mg/m2, twice per day from day 1 to day 14) for 21 days.

2.2 Toxicity

Clinical examination and laboratory tests (including renal, liver and hematological evaluations) were performed weekly during chemoradiation using National Cancer Institute Common Toxicity Criteria CTCAE, v 3.0 [16]. A 25% dose reduction of chemotherapy consisted of was planned in case of grade 3 or 4 toxicity.

2.3 Surgery

TME (R0 resection) was performed 6-8 weeks after the completion of chemoradiation. TME involves en-bloc resection of the rectum, perirectal fat and lymphoid tissue.

Evaluation of tumor and nodal downstaging was done through comparison between baseline MRI and histopathological specimen; the absence of tumor cells in the resected specimen and lymph nodes was defined as (pCR). Tumor regression grade (TRG) was quantified according to a five-point scale of Dworak et al. [17]: TRG 0: no regression; TRG 1: dominant tumor mass with obvious fibrosis and/or vasculopathy; TRG 2: dominantly fibrotic changes with few tumor cells or groups (easy to find); TRG 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; TRG 4: no tumor cells, only a fibrotic mass (total regression or response). Three cycles of adjuvant chemotherapy consisted of oxaliplatin (130 mg/m2 on day 1) and capecitabine (825 mg/m2, twice per day from day 1 to day 14) was recommended for patients with T3/ T4 or positive nodes at pathologic examination.

2.4 Statistical Analysis

Recurrence-free survival time was defined as the date of entry to the date of recurrence. Overall survival time was defined as the date of entry to

the date of death from any cause. Patients who did not experience recurrence, metastasis, or death at the time of the analysis were censored. Recurrence-free survival, metastasis free survival and overall survival were calculated by the Kaplan-Meier method [18] and the differences between the survival curves were determined by the log-rank test. The p-values were double-sided with $p < 0.05$ considered statistically significant. All analyses were performed using the Statistical package for Social Sciences software (version 18.0, SPSS, Chicago, IL).

3. RESULTS

3.1 Patient Characteristics

From March 2012 to September 2013, 73 patients were included onto the study. Patients and tumor characteristics are summarized in Table 1. Median age was 56 years (range 34–68). The majority (60.3%) of the tumors were located in the middle rectum. Eighteen patients (24.7%) presented with T4N+ve disease where inoperable due to infiltration of vagina (5 patients), sacrum (3 patients) and bladder neck (10 patients).

3.2 Toxcicity

Toxic effects during neoadjuvant chemoradio-therapy and chemotherapy are listed in Table 2. Forty-one patients (56.2%) experienced grade 1-2 toxicity and 5 patients (6.8%) experienced grade 3 toxicity. The most common adverse events were grade 1-2 neuropathy and diarrhea which were experienced in 26 patients (35.5%) and 21 patients (28.8%) respectively. Three patients developed grade 3 diarrhea and 2 patients developed grade 3 hematological toxicity (leukopenia and neutropenia) which required delay in the treatment. No treatment related deaths occurred.

3.3 Surgery

Six to 8 weeks after surgical exploration, 42 patients (57.5%); underwent low anterior resection (using handsewn technique in 30 patients and staplers in 12 patients due to short distal segment in 9 patients with lesions < 5cm from anal verge and narrow pelvis in 3 patients with lesions located >5 cm from anal verge) and 28 patients (38.4%) underwent abdominoperineal resection. The circumferential resection margin was free in all cases. Three patients (4.1%) remained inoperable due to sacral infiltration. In those patients with unresectable rectal cancer during surgical exploration, palliative colostomy was done and biopsies from primary tumor and perirectal lymph nodes were taken. The postoperative 30 days mortality was not observed. Postoperative complications were in the form of chest infection (one out of 70 patients; 1.4%) and was treated with antibiotics, acute urinary infection (2 out of 70 patients; 2.9%) and were treated conservatively and anastomotic leakage (one out of 70 patients; 1.4%) which healed conservatively.

Table 1. Patients and tumor characteristics

Variable	Number	Percent
Age (years)		
Median	56	
Range	34-68	
Sex		
Male	51	69.9
Female	22	30.1
Performance status		
0	58	79.5
1	15	20.5
Location of the tumor from anal verge		
0- < 5 cm	22	30.1
5- < 10 cm	44	60.3
10 – 15 cm	7	9.6
Clinical stage (MRI)		
cT stage		
T3	34	46.6
T4	39	53.4
cN stage		
Negative	30	41.1
Positive	43	58.9

Abbreviations: MRI, magnetic resonance imaging; +ve, positive; cT, clinical tumor; cN, clinical nodal

3.4 Pathologic Response and Downstaging

Comparison of pre-CRT MRI scans with histology of the resected specimen showed an overall downstaging rate of 78.1% (57 out of 73 patients), while 16 patients (21.9%) had stationary disease. Complete pathologic response was achieved in 11 patients (15.1%). No tumor progression has been observed (Table 3). In subgroup of patients with unresectable rectal cancer (15 out of 18 patients) became resectable. Sphincter preservation rate was achieved in the majority of patients whose tumor were located > 5 cm from the anal verge (34 out of 51 patients; 66.7%) and in 8 out of 22 patients (36.4%) with tumor < 5 cm from the anal verge.

Table 2. Toxicity of neoadjuvant chemoradiation and chemotherapy

Toxicity	Grade 1 No (%)	Grade 2 No (%)	Grade 3 No (%)	Grade 4 No (%)
Diarrhea	12 (16.4)	9 (12.3)	3 (4.1)	0
Nausea	9 (12.3)	8 (11)	0	0
Vomiting	7 (9.6)	9 (12.3)	0	0
Stomatitis	6 (8.2)	0	0	0
Liver	11 (15.1)	5 (6.8)	0	0
Urinary inflammation	7 (9.6)	2 (2.7)	0	0
Neuropathy	23 (31.5)	3 (4.1)	0	0
Anemia	10 (13.7)	7 (9.6)	0	0
Neutropenia	7 (9.6)	3 (4.1)	1 (1.4)	0
Thrombocytopenia	6 (8.2)	5 (6.8)	0	0
Leukopenia	7 (9.6)	3 (4.1)	1 (1.4)	0
Handfoot syndrome	1 (1.4)	0	0	0

According to the Dworak classification, the majority of the patients (41 patients; 56.2%) were classified as TRG 3 (Table 4).

3.5 Pattern of Treatment Failure

After median follow up time of 26 months (range, 7-30), 6 patients (8.2%) had local recurrence and 3 patients (4.1%) had distant recurrence to the liver (2 patients) and peritoneal cavity (1 patient).

3.6 Survival

After median follow up period of 26 months (7-30 months), the 2-year OS was 88%, recurrence free survival was 88.7% and metastasis free survival was 93.9% (Figs. 1-3). Lower pathologic tumor stage was significantly associated with better OS (*P* = .002) (Fig. 4) and recurrence-free survival (*P* = .001) (Fig. 5), but no significant difference in metastasis-free survival (*P* = .314). In contrast, pathologic nodal stage and TRG had no significant difference in OS, recurrence free survival or metastasis free survival.

4. DISCUSSION

Several phase I and II studies have evaluated oxaliplatin, FU/LV, and capecitabine in rectal cancer, with pCR rates of 15% to 28% [19-31]. These results were promising compared to what was reported by German [32] and Fédération Francophone de Cancérologie Digestive studies [33]; preoperative FU-based CRT resulted in pCR rates of 8% and 11.7% respectively. Therefore, in our current protocol, we used oxaliplatin and capecitabine during CRT plus an additional cycle of oxaliplatin and capecitabine with implementation of this preoperative treatment strategy based of MRI assessment for comparison between clinical and pathological down staging of the tumor and lymph nodes and on the potential resection margin.

In our study, the overall pathological downstaging rate was 78.1% (57 out of 73 patients) with pathologically determined complete response rate of 15.1% (ypT0No). Our result is comparable to Garcia-Aguilar et al. [34] who reported pCR rate of 17% after CRT plus 2 cycles of chemotherapy (5-FU + leucovorin + oxaliplatin). However, Xu et al. reported higher rate of pCR (19%) and downstaging rate of 54% after CRT (Capecitbine + Oxaliplatin + radiation) plus one additional cycle of chemotherapy (Capecitabine + Oxaliplatin). This is might probably due to inclusion of patients with lower stage (T1/T2) disease. Caravatta et al. [35] reported higher rate of pCR (32%) and a tumor down-staging rate of 76% in patients with T3/T4 and/or N≥1 rectal cancer. This might attributed to inclusion of radiotherapy boost (55 Gy/5 weeks) plus concurrent chemotherapy (raltitrexed + oxaliplatin). In our study, the pCR and the overall pathological downstaging rate was better than the study reported by Hosper et al. (pCR of 10% and downstaging to T0/T2: 33%) [36] and another study reported by Machiels et al., (pCR of 14% and downstaging rate of 53%) [37]. The previous 2 study used neoadjuvant CRT (capecitabine plus oxaliplatin). This is might be due to the addition one cycle of chemotherapy (oxaliplatin + capecitabine) after CRT in our study.

After median follow up of 26 months, our study reported high rate of local relapse (n=6, 8.2%) compared to other studies [35,37,38]. The lower rates in the current study than that in the reported studies, may be due to higher radiotherapy dose (55 Gy/5 weeks) [35], the

more favorable distribution of T stage [37,38] and limited follow up period as in the study reported by Machiels et al. In this study there was no local recurrence and only 2 patients had distant metastasis [37]. Furthermore, in our study, 70% of patients with T3 tumors had tumors that extended more than 5 mm beyond the muscularis propria on diagnostic MRI which were shown to have a significantly higher locoregional recurrence rate and poorer 5-year cancer-specific survival [39]. We only had 3 patients with distant metastasis after median follow up period of 26 months. Xu et al., reported that 13 patients developed distant metastasis (7 cases in lung, 2 cases in liver, 2 cases in lung and liver, 1 case in brain, 1 case in bone marrow), and 8 patients died of rectal cancer [38]. The higher rate of distant metastasis in the reported study than that of our study due to longer follow up period (3 years). Chu et al. reported that 2 patients had local recurrence and 9 patients had distant metastasis after median follow up time of 23 months [12].

In our study, the 2-year overall survival was 88%, recurrence free survival was 88.7% and distant metastasis free survival was 93.9%. Our results were close to the results from Xu et al. the 2-year metastasis-free survival and overall survival were about 96.3%, 85% and 89% respectively. However he reported higher rate of recurrence free survival (96.3%), this is might probably due to inclusion of patients with lower T stage (T1 and T2) [38]. The 2- year OS reported by our study was comparable to that reported by Chau et al. (89%) however, he reported 2–year failure free survival rates of about 69% [12]. Our results (CRT plus one cycle of chemotherapy) yielded comparable survival to the addition of 2 or 3 cycles of chemotherapy which were administered in this trial [12].

Maas et al. analyzed 3105 patients with rectal cancer from 14 study datasets to explore the impact of pCR after CRT on the outcome. They reported better outcome and 5-year crude DFS of 83.3% in patients with pCR [40]. In our study, none of the 11 patients with pCR had local recurrence or distant metastasis with 100% OS rates during follow up period and there was significant difference in tumor stage before treatment and after surgery (P <0.0001). Belluco et al. found that, patients with pCR had significantly better 5-year overall survival, disease specific survival, disease-free survival, metastasis-free survival, and local recurrence-free survival following neoadjuvant CRT for T3 rectal cancer [41]. In contrast, Xu et al. reported similar overall survival, recurrence free survival and distant metastasis-free survival of those patients who achieved pCR and those who did not [38].

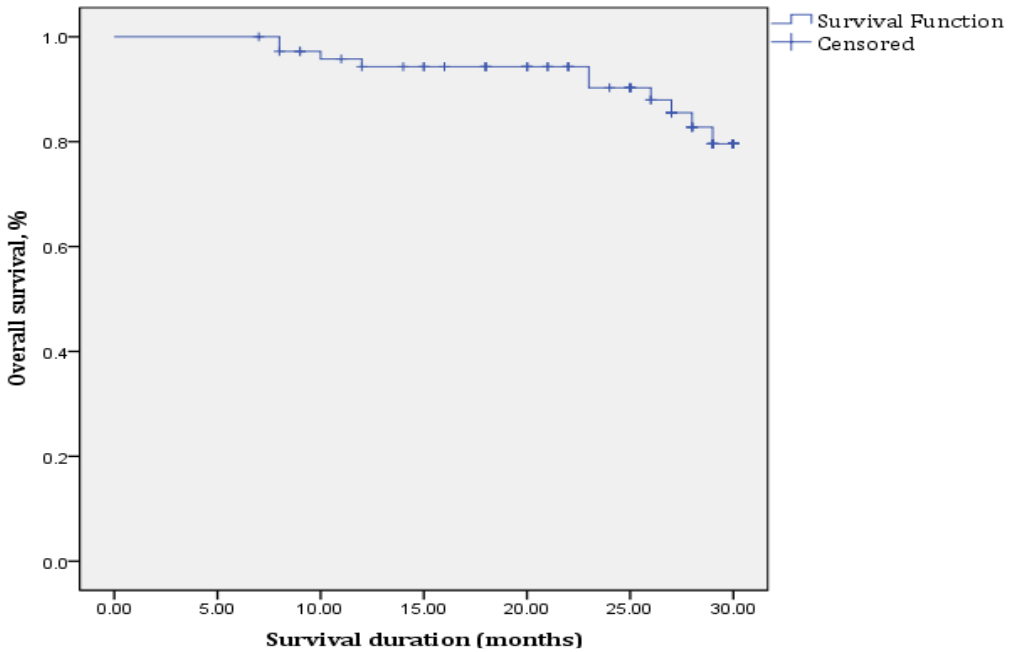

Fig. 1. Overall survival for 73 Patients with locally advanced rectal cancer
Kaplan- Meir analaysis illustrated 2-year overall survival of 88%

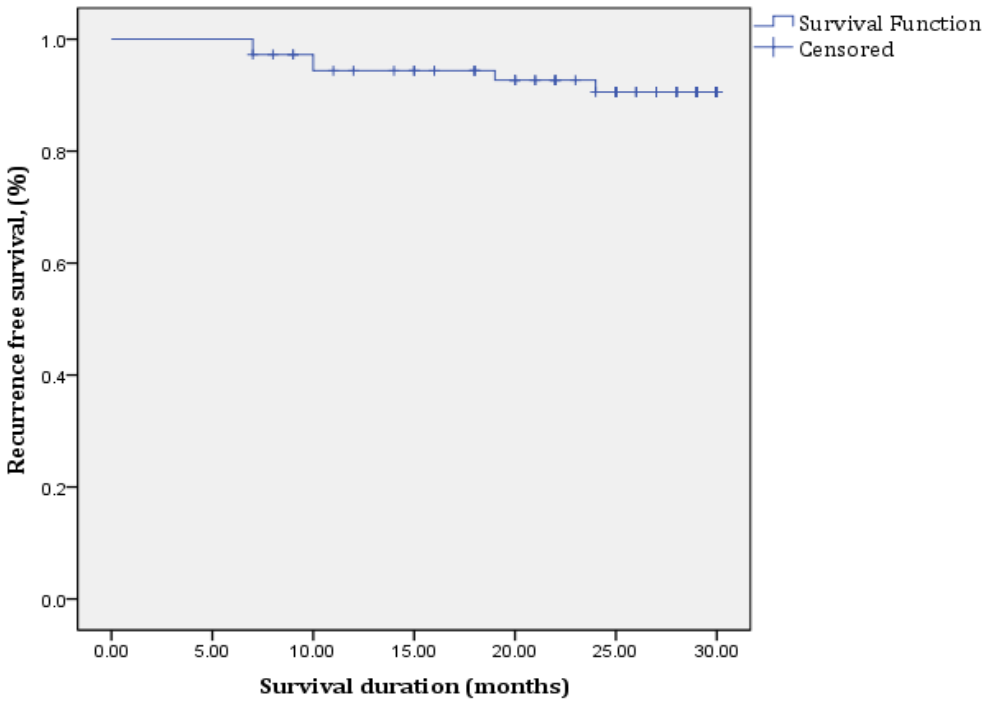

Fig. 2. Recurrence free survival for 73 patients with locally advanced rectal cancer

Kaplan- Meir analaysis illustrated 2-year recurrence free survival of 88.7%

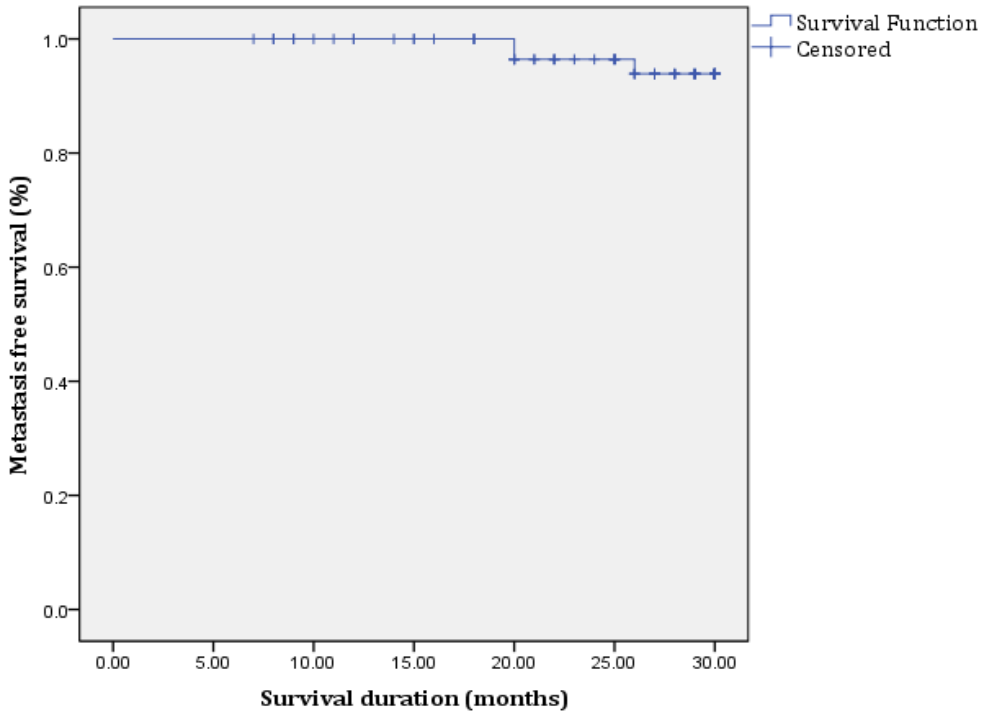

Fig. 3. Metastasis free survival for 73 patients with locally advanced rectal cancer

Kaplan- Meir analaysis illustrated 2-year metastasis free survival of 93.9%

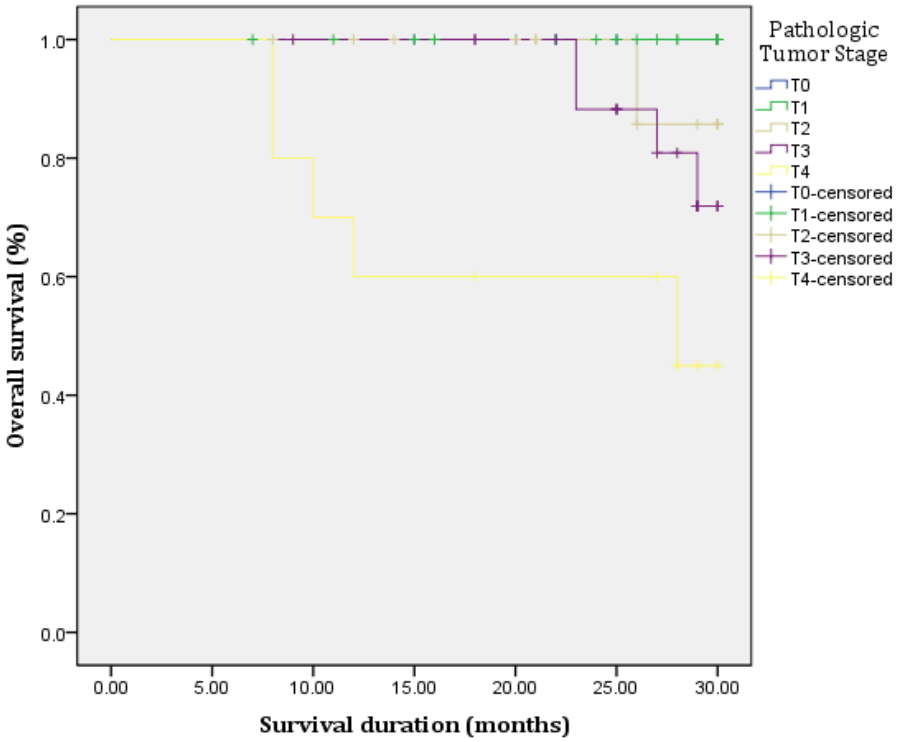

Fig. 4. Survival analysis for overall survival with different pathologic tumor stage
Log rank test for overall survival illustrated, significant difference between pathologic tumor stage (P = .002)

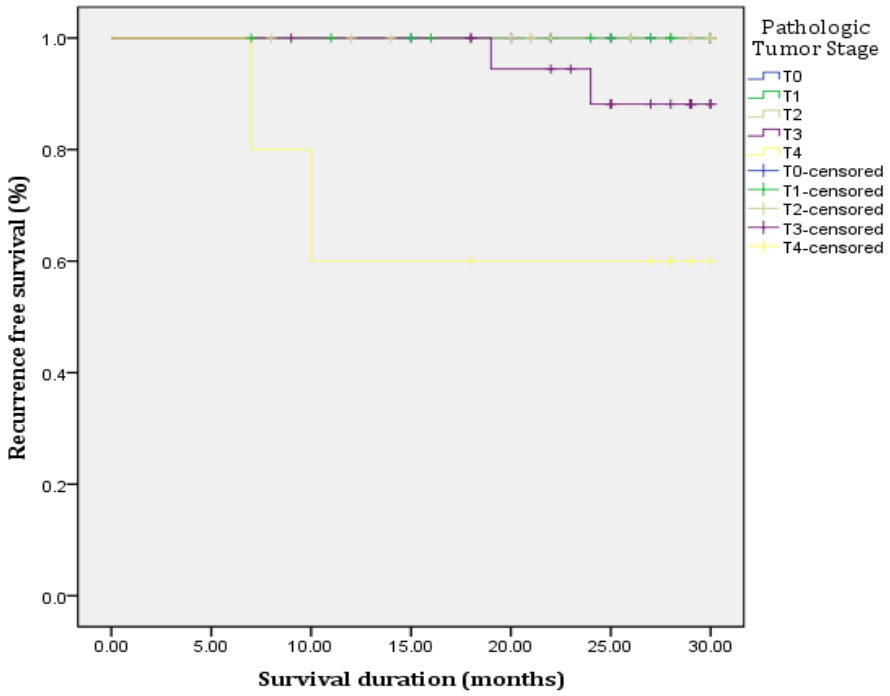

Fig. 5. Survival analysis for recurrence free survival with different pathologic tumor stage
Log rank test for recurrence free survival illustrated, significant difference between pathologic tumor stage (P = .001)

Table 3. Post-chemoradiotherapy pathologic staging compared with initial MRI staging

Initial MRI staging	Post-chemoradiotherapy (yp) pathologic staging													
	Yp T0N0	Yp T1N0	yp T1N1	Yp T1N2	yp T2N0	yp T2N1	yp T2N2	yp T3N0	yp T3N1	yp T3N2	yp T4N0	yp T4N1	yp T4N2	Total (%)
T3N0	8	1	0	0	0	0	0	0	0	0	0	0	0	9(12.3)
T3N+ve	3	8	5	2	0	1	0	0	5	1	0	0	0	25(34.2)
T4N0	0	0	0	0	9	4	1	0	0	0	7	0	0	21(28.8)
T4N+ve	0	0	0	0	0	0	0	6	4	5	0	3	0	18(24.7)
Total	11 (15.1)	9 (12.3)	5 (6.8)	2 (2.7)	9 (12.3)	5 (6.8)	1 (1.4)	6 (8.2)	9 (12.3)	6 (8.2)	7 (9.6)	3 (4.1)	0	73 (100)

Abbreviation: MRI, magnetic resonance imaging. +ve, means positive

Table 4. Post-chemoradiotherapy pathologic staging compared with TRG

TRG	Post-chemoradiotherapy pathologic (yp) tumor staging					
	ypT0	ypT1	ypT2	ypT3	ypT4	Total (%)
1	0	2	0	1	6	9 (12.3)
2	0	1	3	7	4	15 (20.5)
3	4	13	12	12	0	41 (56.2)
4	7	0	0	1	0	8 (11)
Total	11	16	15	21	10	73 (100)

Abbreviation: TRG, Tumor regression grade

We reported that lower T stage was significantly associated with better OS and recurrence free survival, although T stage had no effect on metastasis-free survival. Nodal stage and TRG, had no effect on OS, recurrence free survival and metastasis-free survival. In patients with T3 or T4 rectal tumors, Schou et al., reported that TRG grade was not associated with overall survival or disease-free survival after induction chemotherapy (capecitabine + oxaliplatin) followed by CRT and TME [40]. Yu et al. studied the effect of local excision after neoadjuvant CRT in patients with T3N0M0 or T2N0M0 rectal cancer. They reported no effect of T stage on disease-free survival and a marginally significant effect on the response to CRT on survival [43]. Xu et al., studied the effect of neoadjuvant CRT followed by additional cycle of chemotherapy (capecitabine + oxaliplatin); they reported lower nodal stage was significantly associated with better recurrence free survival but no effect on overall survival or distant metastasis free survival [38]. Tumor stage and TRG had no effect on overall survival, recurrence free survival or metastasis-free survival. Schou et al., reported that patients with positive lymph nodes have worse prognosis than patients without malignant lymph node involvement [42]. Klos et al. fount that, the presence of malignant lymph nodes has been associated with shorter OS and time to local recurrence in patients receiving neoadjuvant CRT [44].

Our study reported lower toxicity rates in contrast to other studies using induction chemotherapy prior to CRT [12,42]. For example, Chau et al., reported clinically significant occurrence of cardiac/thromboembolic toxicity during neoadjuvant oxaliplatin/capecitabine, which led to three mortalities and four deaths occurred during neoadjuvant chemotherapy [12]. Schou et al., reported higher grade 3 and 4 toxic effects during induction chemotherapy (18%) and chemoradiation (11%) [42]. Caravatta et al., reported higher rate of Grade 1 – 2 diarrhea and proctitis (n _ 18; 72%) and grade 3 gastrointestinal toxicity in two patients (8%) were recorded. Overall, grade 3 and 4 toxicity were observed in 28% of patients [35]. This is most probably due to chemotherapy combination (raltitrexed + oxaliplatin) used in the study and high radiation dose (55 Gy/5 weeks).

5. CONCLUSION

Neoadjuvant CRT and one cycle of chemotherapy followed by TME is effective with pCR of 15.1% and overall downstaging rate of 78.1%. In addition to favorable toxicity profile (as we used a weekly schedule of oxaliplatin) which has been reported by our study in contrast to several studies using induction chemotherapy prior to CRT. Furthermore, our preliminary survival data were encouraging, although further follow-up would be required. Therefore, preoperative CRT followed by one cycle of chemotherapy (capecitabine plus oxaliplatin) may be applied to patients with locally advanced rectal cancer for downstaging and facilitate sphincter preservative surgery. In view of these promising results, randomized phase III trials will be necessary to prove these promising results and its impact on long-term survival.

CONSENT

Written informed consent was obtained from all patients included in this study.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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