Evaluation of the role of neoadjuvant chemotherapy in the management of rectal cancer

Original Article

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ABSTRACT

Background: The current standard of care for locally advanced rectal cancer is neoadjuvant chemoradiotherapy followed by surgery. Recent research has highlighted the possible advantages of induction chemotherapy before concurrent Chemoradiotherapy (CRT) for individuals with locally advanced rectal cancer (LARC). Our research assesses the efficacy and viability of induction chemotherapy before concomitant chemoradiotherapy for locally advanced rectal cancer.

Patients and Methods: Forty patients with locally advanced cancer rectum were enrolled in our study in 2019–2021. Initially, they underwent an induction chemotherapy regimen consisting of 3 cycles of FOLFOX (oxaliplatin, leucovorin, 5 fluorouracil) over 3 months. Response assessment of the patients was done by pelvic MRI. Concurrent chemoradiotherapy was given 2 weeks after completion of induction chemotherapy. Four weeks later, the patients were reassessed by pelvic MRI, computed tomography chest, and abdomen. Total mesorectal excision was performed at 6–8 weeks after the end of radiotherapy. Included patients were evaluated for pCR, Circumferential resection margins (CRM), RO resection, sphincter preservation, treatment toxicity, and postoperative morbidity and mortality.

Results: In this study, sphincter preservation was achieved in eight out of 21 (38%) patients with low rectal tumors less than or equal to 5 cm who were candidates for Abdominoperineal resection (APR) and shifted to Anterior resection (AR); complete pathological response was achieved in seven (20.5%) patient; R0 resection was achieved in 34 (92%) patients; CRM was positive in three patients; two of them developed local recurrence and one of them developed distant metastasis.

Conclusion: For locally advanced rectal cancer, induction chemotherapy followed by neoadjuvant chemotherapy, radiation, and surgery would be a safe and effective treatment option.

Key Words: Cancer rectum, neoadjuvant chemotherapy, pathological complete response (pCR), total mesorectal excision (TME).

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INTRODUCTION

Colorectal cancer (CRC) is among the leading causes of mortality and morbidity throughout the world, thus representing a major public health problem. It is the third most common cancer worldwide following tumors of the lung and breast and the fourth most common cause of oncological deaths[1].

The current standard management for Stage II (T3/T4N0) and Stage III (T any, N1/N2) rectal cancer is neoadjuvant chemoradiotherapy, followed by surgery and 4 months of adjuvant systemic chemotherapy is given at the end[2].

The conventional treatment for locally advanced rectal cancer is neoadjuvant 5 fluorouracil (FU)-based chemoradiotherapy, which is followed by total mesorectal resection and adjuvant systemic chemotherapy. This combination of treatments has been found to produce good control of local disease. However because distant recurrence is the most prevalent cause of mortality, prognosis is still generally dismal[3].

Before neoadjuvant chemoradiotherapy, induction chemotherapy might be used as a tactic to mitigate the negative effects of the prior plan. Patients who get induction chemotherapy tend to tolerate it better, and a full dosage of chemotherapy can be prescribed using this technique. The technique also has the advantage of shrinking locally progressed tumors, which makes surgery easier and enables early treatment of micrometastases[4].

PATIENTS AND METHODS:

This study was performed as a prospective nonrandomized case series study in which 40 new patients with locally advanced rectal cancer were enrolled, and were referred to Alexandria Armed Forces Medical Complex and Menoufia University Hospitals from 2019 to 2021.

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The patients were between 35 and 65 years old with presence of rectal adenocarcinoma up to a maximum of 15 cm from the anal verge, presence of T3 or T4 and/or involvement of lymph nodes according to the eighth edition of the American Joint Committee on Cancer (AJCC), performance status of less than 2 (ECOG) from the Eastern Cooperative Oncology Group, normal hematological, hepatic, and renal functions, no evidence of distant metastases, no history of prior chemotherapy, radiation to the pelvis, or history of another malignancy were all included.

Patients excluded if they had a contraindication to radiation, nonadenocarcinoma tumors, T1 N0 or T2 N0 tumors, pregnancy and lactation, comorbidity such as CHF or MI over the last 6 months, or any other malignancy.

A thorough medical history, a clinical examination that included a digital rectal examination, and an evaluation of performance status were all part of the pretreatment workup.

Comprehensive blood count, serum chemistry, liver and renal function panel, electrolytes, and carcinoembryonic antigen (CEA) are among the laboratory examination parameters.

Radiological examination, MRI pelvis with rectal protocol for tumor staging, computed tomography scan (CT) of the thorax, abdomen, and pelvis with or without (IV)/oral contrast. Endoscopic examination of the entire colon was performed. All patients' information were recorded.

The standard protocol was initiated after a plan was formulated by (MDT) meetings. All patients received an induction chemotherapy regimen consisting of 3 cycles of FOLFOX (oxaliplatin, leucovorin, 5 fluorouracil) over 3 months.

Each cycle consists of two sessions over days 1 and 15 with each session lasting 2 days (1 and 2) and (15 and 16), and then the cycle repeats.

The regimen was as follows: Oxaliplatin 85 mg/m2 I.V in 250 ml D5w over 2 hours, Leucovorin 400 mg/m² I.V in 250 ml D5w over 2 h, 5 fluorouracil 400 mg/m2 I.V bolus and then 5 fluorouracil 1200 mg/m2/ day I.V over 23 h in D5w to a total volume of 1000 ml by continuous infusion for 2 days. Premedication by antiemetics and H2 blockers was administered.

Response assessment of the patients was done by pelvic MRI. Nonresponders underwent surgery.

Responders who achieve a complete clinical response are given another 3 cycles of FOLFOX and are then followed-up (watch-and-wait startegy).

However, partial response patients were given concurrent chemoradiotherapy 2 weeks after completion of induction chemotherapy.

Capecitabine is administered at a dose of 825 mg/m²/bid on radiotherapy days throughout the treatment period. Radiotherapy is given at a dose of 50.4 Gray for 28 fractions with 1.8 Gray per fraction 5 days a week over 5 and a half weeks.

At 4 weeks later, the patients were reassessed by pelvic MRI and CT chest and abdomen, and total mesorectal excision was performed 6–8 weeks after the end of radiotherapy.

Patients receiving chemotherapy should be monitored for signs and symptoms of drug toxicity either hematological or nonhematological following each round.

Chemotherapy dosage adjustments may be taken into consideration in circumstances when toxicity is intolerable.

Patients receiving radiation therapy were evaluated at least once a week for any acute radiation toxicities and early side effects. This assessment included a physical examination, complete blood count, and serum chemical measurements taken both during treatment and 4 weeks thereafter.

The common toxicity criteria (CTC) were used to rate and report the toxicity of chemoradiation.

Complete clinical response was defined as no visible tumor on pelvic MRI. The pathologic specimens after TME were evaluated using standard pathological guidelines. Pathological complete response (pCR) was defined as the complete disappearance of all tumor cells in postoperative specimens including regional lymph nodes.

Postoperatively, patients were evaluated for pCR, CRM, RO resection, sphincter preservation, postoperative morbidity, and mortality.

Patients were followed-up 3 monthly for 1 year, every 6 months for 2 years with CEA plus clinical examination, CT chest of the abdomen, pelvis, and colonoscopy were performed yearly.

A more intensive follow-up protocol was used in the watch-and-wait approach than in the routine surveillance. Patients were followed-up by digital rectal examination, rigid proctoscopy, and CEA level every 3 months. Pelvic MRI with rectal protocol was performed every 6 months.

The study was performed following the Declaration of Helsinki and the hospital ethics committee.

RESULTS:

Patients' demographic and clinicopathological variables were reevaluated. Specifically, we included age group of 35–65 years, both sexes, tumor stage T, lymph nodal stage N, pathological tumor stage ypT, pathological nodal stage ypN, circumferential resection margin CRM status of less than or equal to 1 mm, which is considered positive while more than 1 mm is considered negative, pathological complete response pCR, and surgical procedure (Table 1).

Table 1: Patients' demographic and clinicopathological variables

Characteristic	Number (%)
(1) Age	
Range	(35–65year)
Median (IQR)	55.0 (50.0–60.0)
Mean±SD	53.75±9.46
(2) Sex	
Male	27 patients (67.5)
Female	13 patients (32.5)
(3) Performance status	
0	22 patients (55)
1	18 patients (45)
(4) Family history	
Positive	10 patients (25)
Negative	30 patients (75)
(5) Tumor distance from anal verge	
≤5cm→	21 patients (52.5)
>5cm–≤10cm→	8 patients (20)
>10cm–≤15cm	11 patients (27.5)
(6) Tumor differentiation:	
Well differentiated→	12 patients (30)
Moderately differentiated→	20 patients (50)
Poorly differentiated→	8 patients (20%)
(7) Preoperative radiological tumor assessment	
T2→	1 patient (2.5)
T3→	25 patients (62.5)
T4a→	9 patients (22.5)
T4b→	5 patients (12.5)
(8) Preoperative radiological nodal assessment :	
N0→	4 patients (10)
N1a→	3 patients (7.5
N1b→	6 patients (15)
N2a→	8 patients (20)
N2b→	11 patients (27.5)
N2c→	8 patients (20)
(9) Postoperative pathological T:	
ypT0→	7 patients (20)
ypT1→	2 patients (5)
ypT2→	11 patients (32)
ypT3→	9 patients (26)
ypT4a→	6 patients (17)
ypT4b→	2 patients (5)
(10) Postoperative pathological N	
ypN0→	10 patients (27)
ypN1a→	12 patients (32.4)
ypN1b→	10 patients (27)
ypN2a→	4 patients (10.8)
ypN2b→	1 patient (2.7)
(11) Pathological TNM stage	
Stage 0→	7 patients (18.9)
Stage I →	2 patients (5.4)
Stage II→	1 patient (2, 7)
Stage III→	27 patients (72.9)
(12) Type of surgery	
APR→	10 patients (27)
AR→	19 patients (51)
ULAR→	5 patients (13.7)
(13) MRF involvement	
Positive→	24 patients (60)
Negative→	16 patients (40)
(14) Pretreatment CEA level	
High→	17 patients (42.5)
Normal→	23 patients (57.5)

Twenty-seven patients were males (67.5%); the median age at diagnosis was 55 years; low-sited tumors were the most presenting site (52.5) less than or equal to 5 cm from the anal verge. The most presenting tumor stage was T3 in about 25 (62.5%) patients and radiologically positive lymph nodes were presented in 90% of cases. Tumor differentiation is mostly moderate differentiation in 20 (50%) patients, lymphovascular invasion is positive in 24 (60%) patients, and the level of pretreatment CEA is high in 27 (42.5%) patients.

The planned induction chemotherapy was completed in all patients and assessment for response by pelvic MRI with rectal protocol was done.

Five (12.5%) patients achieved complete clinical response; they were counseled in MDT meetings about the strategy of watch and wait with organ preservation and avoiding surgical morbidity.

Three patients accepted this strategy and were given another three cycles of FOLFOX and were followed-up for tumor recurrence, while the other two patients refused

and prepared for anterior resection of the rectum with total mesorectal excision.

Three patients did not give any response and classified as nonresponders (poor response) and underwent surgery (abdominoperineal resection with total mesorectal excision) with adjuvant chemotherapy.

Thirty-two patients achieved tumor regression and were classified as partial response patients, who were given concurrent chemoradiotherapy and reassessed by pelvic MRI for tumor response. Five patients achieved complete clinical response and underwent anterior resection with total mesorectal excision.

Twenty-seven patients achieved tumor downstaging and were prepared for surgery as follows:

Five patients underwent ultralow anterior resection, 12 patients underwent anterior resection, and 10 patients underwent abdominoperineal resection.

Complete clinical response cT0N0 was achieved in 10 (25%) patients.

Complete pathological response ypT0N0 was achieved in seven (20%) patients.

Near complete pathological downstaging (ypT1N0) achieved in two (5.3%) patients.

Tumor downstaging was achieved in 32 (80%) patients and nodal downstaging was achieved in 22 (55%) patients.

Eight out of 21 patients with low-sited tumors less than or equal to 5 cm who were candidates for APR were shifted to AR with sphincter preservation (38%).

R0 resection was achieved in 34 patients, while CRM was positive in three patients; two developed local recurrence and one patient developed distant metastasis.

The 30 day postoperative mortality rate was 2.5%; one patient died due to pulmonary embolism.

Postoperative complications (32.5%):

12 patients developed complications and were divided as follows:

Two patients developed wound infection who were managed conservatively.

One patient developed a pelvic abscess and required ultrasound guided drainage.

Three patients developed ileus, which was managed conservatively.

One patient developed perineal wound dehiscence managed by secondary suturing.

One patient developed intraabdominal bleeding and required blood and plasma transfusion.

Three patients suffered from skin burn and inflammation from ileostomy and required extensive skin care.

One patient developed urological dysfunction with frequency and incomplete evacuation and improved with medical treatment

Induction chemotherapy-related toxicity (22.5%):

Nine patients suffered from side effects of chemotherapy and were divided into three groups:

(a) Hematological: two patients developed neutropenia and one patient developed thrombocytopenia.

(b) Gastrointestinal: two patients complained of diarrhea and two patients from vomiting.

(c) Neuropathy occurred in two patients.

Concurrent chemoradiotherapy-related toxicity (40%):

Thirteen patients complained of side effects of chemotherapy and radiotherapy as follows:

(a) GIT symptoms in the form of diarrhea in three patients.

(b) Skin manifestations as dermatitis in four patients.

(c) Hematological such as anemia occurred in three patients.

(d) Urological such as cystitis occurred in three patients.

None of the patients had treatment interruption due to side effects of chemotherapy or radiotherapy.

Pattern of relapse

After a median of a 20-month follow-up period (12–26), two patients experienced local recurrences at 15 and 18 months. After a year, one patient experienced distant metastases to the liver.

During follow-up period cases of watch-and-wait strategy no incidence of tumor recurrences developed.

DISCUSSION

The aim was to gain a better understanding of the potential therapeutic effects of induction chemotherapy followed by concomitant chemoradiotherapy and surgery for patients with locally advanced rectal cancer. Our research included 40 patients, of whom seven (20.5%) achieved pCR. This is in line with the findings of Chau and colleagues' study, which showed that among patients who had surgery, the pCR rate was 23%[5].

Cercek *et al*. studied 49 patients with rectal cancer to determine the impact of FOLFOX chemotherapy before chemoradiotherapy and surgery. Of these patients, 27% had pCR and 47% had a tumor response of greater than 90%. Furthermore, there were no significant adverse effects that call for delaying chemoradiotherapy[6].

In our study, 34 (92%) patients had R0 resection, which is comparable to the results reported by Schou *et al*. (94%)[7]. Also, 32 (80%) patients had tumor downstaging, which is comparable to the results published by Schou *et al*.[7], who found that 84 (69%) patients achieved T downstaging following induction treatment with capecitabine and oxaliplatin (CAPOX) and RT concurrent with capecitabine.

In contrast, T-stage downstaging in the Calvo *et al* series was 75% after two rounds of induction with Tegafur and FOLFoX 4 in conjunction with RT [8]. A greater tumor downstaging rate of 81% was reported by Marsh *et al*.[9]

In all, 22 (55%) patients with clinically positive nodes experienced nodal downstaging. These results align with those of Koeberle *et al*., who reported 48% nodal downstaging, while Doi *et al*. reported 70% nodal downstaging in their series[10].

Vomiting and diarrhea were noted in four (10%) individuals after induction chemotherapy, making gastrointestinal toxicities the most frequently reported toxicity. In our research, leukopenia and thrombocytopenia were the most frequent hematological toxicity cases (7.5%). All cases were of grade 1 and 2, which were accepted and tolerable and agrees with that recorded from the previous series.[11].

The research by Sauer R *et al*. found 36% of postoperative problems, which is comparable to our findings of 32.4%. The most frequent postoperative surgical problems, occurring in six (16%) patients, were delayed wound healing and wound infection, followed by ileostomy difficulties and ileus[2].

One case of liver metastasis developed 12 months postoperatively representing a 2.5% relapse pattern which is compared with other studies. Cercek *et al*. reported that one patient developed liver metastases during treatment despite a significant regression of the primary tumor[6].

Engy M *et al*. reported that three patients developed distant metastasis in the liver, both liver and lung, and paraortic lymph node after 12, 15, and 16 months postoperatively, respectively, following the treatment approach[12].

Overall survival was 95% and the 2-year DFS was 87.5% as per our results, which were somewhat better than those of Engy M *et al*. OS was 87.5% and DFS was 70.2%[12].

Our findings suggest that it is possible to achieve induction FOLFOX in LARC, followed by conventional RT and concomitant 5-FU. This study's short-term results are encouraging, with pCR increasing. However, further observation is needed to evaluate OS and late toxicity. In summary, pCR in LARC was improved by short-intense induction of FOLFOX and concomitant chemoradiotherapy; this combination was achievable with excellent tolerance and tolerable toxicity.

CONCLUSION

For locally advanced rectal cancer, induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery would be a safe and effective treatment option.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. 2012. CA Cancer J Clin 2015; 65:87–108.

2. Sauer R, Becker H, Hohenberger W, *et al*. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351:1731–40.

3. Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L., *et al*. Adjuvant chemotherapy after preoperative (chemo) radiotherapy and surgery for patients with rectal cancer: a systematic review and metaanalysis of individual patient data. Lancet Oncol 2015; 16:200–7.

4. Glynne-Jones R, Grainger J, Harrison J, Markis A. Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: Should we be more cautious?. ■ 2006; 94:363–71.

5. Chua YJ, Barbachano Y, Cunningham D, *et al*. Neoadjuvantcapecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010; 11:241–8

6. Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, *et al*. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J NatlComprCancNetw 2014; 12:513–9.].

7. Schou JV, Larsen FO, Rasch L, *et al*. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol 2012; 23:2627–33.

8. Calvo FA, Serrano FJ, Diaz-Gonza´lez JA, *et al*. Improved incidenrectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol 2006; 17:1103–10.

9. Marsh RW, George TJ, Siddiqui T, *et al*. A phase II trial of neoadjuvantcapecitabine combined with hyperfractionated accelerated radiation therapy in locally advanced rectal cancer. Am J ClinOncol 2010; 33:251–6.

10. Doi H, Beppu N, Odawara S, *et al*. Neoadjuvant short-course hyperfractionated accelerated radiotherapy (SC-HART) combined with S-1 for locally advanced rectal cancer. J Radiat Res 2013; 54:1118–24.

11. Marechal R, Vos B, Polu M, *et al*. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Ann Oncol 2012; 23:1525–30.

12. Engy M, Mohamed A, Entesar I, *et al*. Induction FOLFOX followed by preoperative hyperfractionated radiotherapy plus bolus 5-fluorouracil in locally advanced rectal carcinoma: single arm phase I–II study. Med Oncol 2015; 32:108.