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The outcomes of induction chemotherapy, followed by neoadjuvant chemoradiotherapy and surgery, in locally advanced rectal cancer, single institute experience

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Abstract

Background & objectives: Total Neoadjuvant Therapy represents the gold standard for treating locally advanced rectal cancer. We conducted this study to investigate the therapeutic implications of induction chemotherapy followed by neoadjuvant chemoradiotherapy & surgery in locally advanced rectal cancer, in terms of response & toxicity.

Methods: Our retrospective study analyzed data from 40 rectal cancer cases who received treatment between 2018 & 2023 at Rizgary Medical Oncology Center in Hawler, Kurdistan Regional Governorate, Iraq. Patients received induction chemotherapy, and after 3-4 weeks, re-staging was done to exclude metastases. Subsequently, neoadjuvant chemo-radiotherapy was administered, followed by another evaluation 3-4 weeks later to exclude metastases and assess treatment response. Finally, a Total Mesorectal Excision was performed. The study looked at outcomes like downstaging, pathological Complete Response, surgical resection margins, Disease-Free Survival, and Overall Survival, as well as side effects related to the treatment.

Results: Patients' ages ranged from 28 to 81 years old, with an average age of 50.5. After receiving the treatment, there was a 50% reduction in tumor size, and 12.5% of our patients achieved pathological Complete Response. While 75% of the cases showed free surgical margins, which was significantly associated with tumor relapse (p-value = 0.009). The 3-year Disease Free Survival was 50% and the 3-year Overall Survival was 90%, with a median follow-up of 23.5 months. Treatment-related toxicities varied from 2% to 12%, mostly in grades 2 and 3, and were appropriately managed.

Conclusions: Induction chemotherapy followed by neoadjuvant chemoradiotherapy, and surgery might be a good & safe way to treat locally advanced rectal cancer.

Keywords: Neoadjuvant, Outcomes, Rectal cancer

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Introduction

With more than 1.9 million new cases recorded in 2022, colorectal cancer ranks third in the world in terms of cancer incidence, accounting for 9.6% of all cancers. Males outnumber females (10.4% versus 8.9%). Still, it comes in second for cancer-related deaths, with almost 904,000 fatalities globally in the same year, making up 9.3% of all cancer deaths. Men have a slightly lower mortality rate than women (9.2% versus 9.4%).[1] Age, gender, and genetics are non-modifiable risk factors. Among the modifiable risk factors are inactivity, obesity, an unhealthy diet, tobacco use, and excessive alcohol intake.[2] Historically, in the early 1990s, surgery was the only available method, with Total Mesorectal Excision (TME) in 1986 as an established standard procedure for managing all rectal cancers.[3] The advancements in radiotherapy made the introduction of short-course radiation before surgery, improving local control in a Swedish rectal cancer trial in 1997.[4] Adjuvant chemoradiotherapy was utilized for many years until 2004 when a German study on rectal cancer revealed its benefit in reducing local toxicity when administered before surgery.[5] Lately, clinical research has shifted its focus to total neoadjuvant therapy (TNT). In 2020, the findings of a phase 3 randomized clinical trial (RAPIDO and PRODIGE 23) were presented, and this approach was adopted as the standard of care for treating locally advanced rectal cancer by the National Comprehensive Cancer Network (NCCN).[6,7] Although this treatment approach is quite efficient in controlling the tumor locally; nonetheless, distant metastases are the most frequent reason for treatment failure and mortality, affecting more than a quarter of patients who undergo chemoradiotherapy and TME.[8,9] Implementing systemic chemotherapy as the first treatment option is a useful way to deal with micro-metastases at an early stage.[10] There have been many studies that show the benefits of induction chemotherapy. For example, it has been demonstrated to raise the pathological complete response (pCR) rate in patients with locally spread rectal cancer, while still causing manageable side effects.[11] Furthermore, if downstaging before oncologic resection is necessary, induction chemotherapy is perhaps better than consolidation chemotherapy.[12] Therefore, we carried out this study to examine the potential therapeutic effects of induction chemotherapy, neoadjuvant chemotherapy-radiotherapy, and surgery, including toxicity and response. Our specific objectives for this study include the establishment of an accurate data registry for rectal cancer patients in the oncology center, the initial goal of tumor downstaging, the assessment of response concerning pCR, R0, DFS, and OS, and the assessment of chemotherapy, radiotherapy, and surgery-related toxicity.

Patients and methods

In our retrospective study, data from 40 patients with rectal cancer who had treatment between 2018 and 2023 were allocated non-randomly and conveniently, from Rizgary Medical Oncology Center (Hawler/ Kurdistan Regional Governorate/ Iraq) along with permission taken from the center administration. Patient´s eligible criteria included, rectal cancer patients with adenocarcinoma proved histopathology, with a maximum 15cm distance from the anal verge, and staged locally advanced rectal cancer either stage II (cT3-4, cN0) or stage III (any cT, cN1 or cN2) as defined by Tumor Node Metastases classification system (TNM 8th edition), moreover all age group and all racial ethnical group included, and all patients must be with performance status 2 or less according to ECOG (Eastern Cooperative Oncology Group). Exclusion standards comprised non-adenocarcinoma histopathology, stage I and stage IV patients, as well as patients with synchronous cancer

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and unsatisfactory records. The study protocol was accepted & approved by the ethical committee of the Kurdistan Board of Higher Council of Medical Specialties on July 20, 2023. According to National Comprehensive Cancer Network guidelines for the treatment of rectal cancer cases, initially all the patients received induction chemotherapy either mFOLFOX6 (oxaliplatin 85 mg/m^2 IV over 2 hours plus leucovorin 400 mg/m^2 IV over 2 hours plus 5-FU 400 mg/m^2 IV bolus then 2400 mg/m^2 IV continuous infusion 5FU over 46-48 hours) cycled every 2 weeks, or CAPEOX (oxaliplatin 130 mg/m^2 IV over 2 hours plus oral capecitabine 1000mg/m^2 twice daily for 14 days), cycled every 3 weeks, with median of 3 cycles, then after 3-4 weeks of last cycle re-staging done (by CT Scan chest, abdomen & pelvis with contrast) to exclude metastases, After that, neoadjuvant chemo-radiation treatment was administered using a regimen (oral capecitabine 825 mg/m2 given twice a day for the duration of the concurrent radiotherapy days) 50.4 Gray / 28 fraction), subsequently after 3-4 weeks from neoadjuvant chemoradiotherapy, evaluation done (by CT Scan chest, abdomen & pelvis with contrast and MRI pelvis) to exclude any metastases and to assess treatment response, and lastly after excluding metastases, 6–8 weeks following the conclusion of neo-adjuvant therapy, total mesorectal excision (TME) was carried out, included patients were assessed for pathological responses (pCR), & surgery resection margins (R0). Data collection & arrangement of the cases was done by Microsoft Excel 2021 for Windows, the method used to analyze the data was IBM SPSS 2023 version 29th for Windows, Fisher's exact and the Pearson Chi-square test were used (depending on which statistical method was most applicable) to analyze the connection between categorical variables. The Mann-Whitney U test was used for relations between binary & discrete variables; a statistically significant P value was defined as to be ≤ 0.05. Kaplan Meier survival analysis is used to determine overall survival (OS) {calculated from the time of diagnosis to the time of relapse and/or death or the last follow-up} & disease-free survival (DFS), {calculated from the time of surgery to the time of relapse and/or death or the last follow-up}.

Results

The study involved 40 cases of locally advanced rectal cancer between 2018 and 2023. The patients ranged in age from 28 to 81 years old, with an average age of 50.5 years. The number of male and female patients was similar, as shown in Table (1). 75% of the patients were fully active (ECOG 0). Regarding pre-treatment clinical cancer staging, 87.5% of the cases had a T3 stage tumor, while N1b and N2a comprised 80% of the clinical nodal staging for all patients. The majority of cases (65%) occurred in the lower rectum, 4-7 cm from the anal verge. On a histological level, 85% of the patients showed moderate differentiation.

Table (1): Clinicopathological characteristics of patients

Characteristic	Number (n=40)	Percentage (100%)
Age (years)	mean±sd.50.5 ± 12.038	(range) (28-81)
Gender		
Male Female	20 20	50 50
ECOG performance status*		
0 1	30 10	75 25
Clinical T stage (pretreatment)		
T2 T3 T4a T4b	1 35 0 4	2.5 87.5 0 10
Clinical N stage (pretreatment)		
N0 N1a N1b N1c N2a	3 0 18 0 14	7.5 0 45 0 35

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N2b	5	12.5
Distance from anal verge (cm)		
4-7 8-11 12-15	26 11 3	65 27.5 7.5
Tumor grade		
Well differentiation Moderate differentiation Poor differentiation	3 34 3	7.5 85 7.5

*ECOG (Eastern Cooperative Oncology Group)

Regarding changes in TNM staging from pre-treatment to post-treatment, as shown in Table (2), the rate of T3 tumors decreased from 87% to 35% after treatment. Conversely, the percentage of T2 tumors (smaller in size than T3) increased from 2.5% to 40% in the post-treatment setting. Additionally, there was a decrease in nodal involvement for N1b and N2a (before applying treatment) from 45% and 35% to 17.5% and 7.5% respectively (after finishing treatment). Furthermore, cases with no nodal involvement (T0) increased from 3% before treatment to 55% after treatment. These changes demonstrate tumor shrinkage and downstaging following the use of induction chemotherapy with neoadjuvant chemo-radiotherapy.

Table (2): TNM staging pre & post-treatment

TNM* Stage	Pre-treatment (Clinical stage) No. (%)	Post-treatment (Pathological stage) No. (%)
T0 T1 T2 T3 T4a T4b	0 (0) 0 (0) 1 (2.5) 35 (87.5) 0 (0) 4 (10)	5 (12.5) 3 (7.5) 16 (40) 14 (35) 0 (0) 2 (5)
N0 N1a N1b N1c N2a N2b	3 (7.5) 0 (0) 18 (45) 0 (0) 14 (35) 5 (12.5)	22 (55) 8 (20) 7 (17.5) 0 (0) 3 (7.5) 0 (0)

*(Tumor, Node & Metastasis) cancer staging system, 8th edition

Our study evaluated treatment responses using pathological responses, specifically focusing on pathological complete responses (pCR) as the primary endpoint. In Figure (1), 12.5% of patients achieved pathological complete responses (pCR), 75% showed partial responses, 7.5% had stable disease, and 5% experienced disease progression after treatment completion.

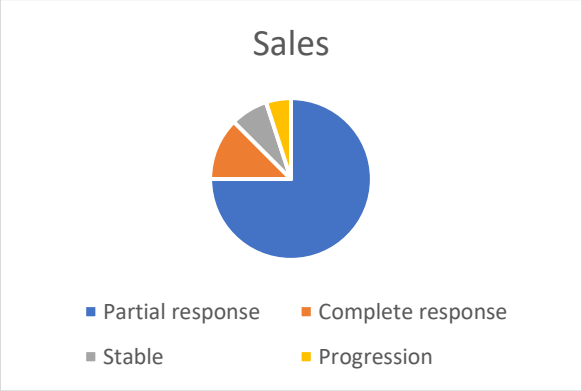

Figure (1): Pathological responses post-treatment

In the other study's endpoint, as in Figure (2), 75% of cases achieved free surgical resection margins (R0).

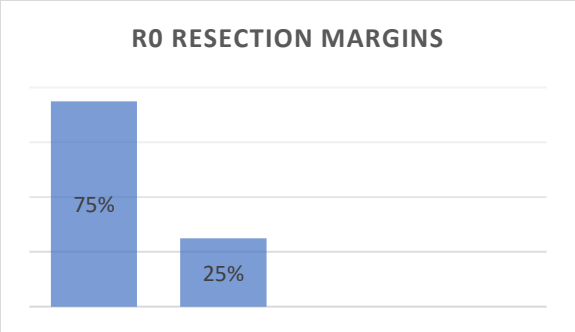

Figure (2): Surgical resection margins post-treatment

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Overall survival (OS) and disease-free survival (DFS) were regarded as secondary goals in our study. In Kaplan-Meier Figure (3) below, with a follow-up interval of 23.5 months on average, 17 out of 40 patients (42.5%) experienced a relapse of their disease following surgery. The mean DFS was 37 months (95% Confidence Interval: 29-46 months), with a 3-year DFS reaching 50%, and 33 months was the median DFS (95% Confidence Interval: 22–43 months).

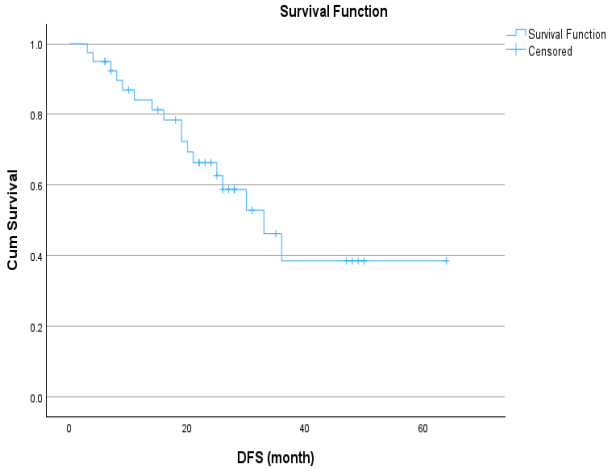

Figure (3): Kaplan-Meier analysis of disease-free survival (DFS)

In our comprehensive analysis, 4 out of 40 patients (10%) had passed away by the end of the study. With a median follow-up of 23.5 months, the average overall survival (OS) was 69 months with a 95% confidence interval of 63-76 months, 3-year OS was 90%, & the median OS was not reached, Figure (4). Table (3) shows the relationship between patient variables and tumor relapse. Patients with moderate and well-differentiated tumors had a lower rate of relapse than those with poorly differentiated types, but with a p-value of 0.812, this difference was not statistically significant. Additionally, patients with an ECOG performance score of 0 had better remission rates than those with a score of 1, but again this was not statistically significant (p-value = 0.717). Surprisingly, patients with pCR had higher relapse rates than no pCR patients, but this was also not statistically significant (p-value = 1.00). As expected, the R0 patients had significantly better remission rates than cases with involved resection margins (p-value = 0.009). Furthermore, both the age of patients and the distance from the anal verge did not show a significant relationship with the relapse state of the disease (with p-values of 0.816 and 0.783, respectively).

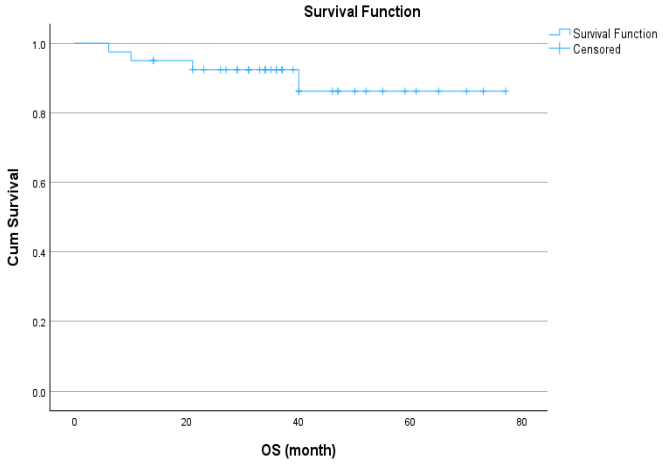

Figure (4): Kaplan-Meier analysis of overall survival (OS)

Table (3): Relationship between patient variables & tumor relapse

Main Category	Subcategories	Tumor relapse status		p-value
		Yes (n=17)	No (n=23)	
Tumor differentiation	Well-differentiation Moderate differentiation Poor differentiation	1 (2.5%) 14 (35%) 2 (5%)	2 (5%) 20 (50%) 1 (2.5%)	0.812*
ECOG performance status	Fully active (1) Restricted	12 (30%) 5 (12.5%)	18 (45%) 5 (12.5 %)	0.717*

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	in difficult activity			
Pathological complete response (pCR)	Yes No	2 (5%) 15 (37.5%)	3 (7.5%) 20 (50%)	1.00 *
Resection margins (R0)	Yes No	9 (22.5%) 8 (20%)	21 (52.5 %) 2 (5%)	0.009*
Age of patient				0.816**
Distance from the anal verge (cm)				0.783 **

*Fischer's Exact test, ** Mann-Whitney U test.

The adverse effects of treatment Table (4) can be categorized into two main aspects: pre-surgery and post-surgery. Pre-surgery treatment includes induction chemotherapy and neoadjuvant chemo-radiotherapy. There was no grade 5 toxicities, and most patients tolerated chemotherapy and radiotherapy well. The only interruptions in treatment occurred when 2 patients had their chemotherapy cycles delayed due to neutropenia. In the post-surgery interval, patients were presented with infections, hydronephrosis, and fistulas, all of which were managed accordingly.

Table (4): Complications encountered during treatment & after operation

Pre-operation complications	Induction chemotherapy No. (%)	Neoadjuvant chemo-radiotherapy No. (%)
Hematologic Diarrhea Neuropathy Infection	2 (5) 4 (10) 1 (2.5) 1 (2.5)	3 (7.5) 5 (12.5) 2 (5) 3 (7.5)
Post-operation complications		
Hydronephrosis Infection Fistula	3 (7.5) 4 (10) 2 (5)	

Discussion

In Asia and Eastern Europe, the prevalence of colorectal cancer is increasing.[13] Our local studies support this trend. Ibrahem S and his colleagues have highlighted this growing health issue in Iraq, primarily due to lifestyle changes influenced by Western habits.[14] While the latest research has indicated a decrease in the incidence of colorectal cancer in the US, largely due to early detection and endoscopic excision of precancerous tumors.[15] Appropriate treatment of rectal cancer is crucial for patient prognosis and survival.[16] The purpose of this analytical study was to look at the potential toxicity and responsiveness in rectal cancer patients who had undergone induction chemotherapy, neoadjuvant chemotherapy with radiation, & surgery. As far as we know, this is the first paper discussing the outcomes using this specific treatment method in this particular group of patients in our local region & Iraq. The earliest outcome of our study was disease downstaging & tumor regression & consequently, easier operation with better survival at the end, Tumor volume (T) & lymph node involvement (N) as TNM staging demonstrated almost 50% reduction in size after applying the treatment method, these findings align with the published outcomes of a phase III randomized clinical trial from China.[17,18] Secondly, the study's initial endpoint was pCR, which was observed in 12.5% of our patients, which is equivalent to studies conducted in Europe that reported rates of 11–16%.[19, 20] The other primary target of our study was non-involvement of surgical resection margins by the tumor (R0), which was achieved in 75% of the studied cases, this result is comparable to the conclusions of STELLAR, a long-term multiple-center study conducted in China.[21] In addition, we found that R0 is significantly associated with the relapse of the tumor (p-value = 0.009), which, in rectal cases having surgery, is the most significant anticipator for

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relapse, this crucial relationship is discussed by Fernandez et al, in the extended outcomes of the Spanish randomized study.[22] Regarding our secondary endpoints, with a follow-up of 23.5 months on average, 3-year DFS reached 50% & 3-year OS was almost 90%, these survival achievements agree with the POLISH II study, which K Bujko conducted with the same median follow-up.[23] Given these results, it can be said that using the (induction chemotherapy with neoadjuvant chemoradiotherapy) method may improve patients' outcomes in terms of DFS and OS in locally advanced rectal cancer, The first-ever evaluation of this technique was by the NSABP R-03 phase III study, which demonstrated a substantial enhancement in DFS.[24] One important benefit of this treatment plan is that an earlier administration of systemic treatment may enable the delivery of a complete dosage of chemotherapy and tumor reduction, it is believed that in more than one-third of rectal cancer patients, adjuvant chemotherapy is discontinued or dosed down, leading to a greater chance of systemic failure.[25] Our patients experienced toxicities varying between 2-12%, mostly of grades 2 & 3, Overall, the induction chemotherapy period was less toxic than neoadjuvant chemo-radiotherapy and had fewer complications, while complications following surgery were appropriately handled. It is crucial to note many limitations in this research. Firstly, the retrospective design imposes limitations. Secondly, more study with bigger samples is required due to the sample size's inherent bias. Third, the generalizability of the findings is lowered since samples were chosen from a referral medical facility. Fourthly, more accurate results can be achieved if the evaluation is based on high-risk variables, including lower rectal tumors, T4 or N2, & involvement of the mesorectal fascia (MRF). Finally, a short follow-up may have led to unsatisfactory disease-free survival (DFS) or overall survival (OS) results. As a result, more work is necessary to conduct a prospective randomized controlled trial and longer-term follow-up.

Conclusion

The study's results show that starting with induction chemotherapy, then neoadjuvant chemoradiotherapy and surgery is a good way to treat locally advanced rectal cancer with acceptable side effects, despite the limitations listed above. As a result, this treatment is recommended for these patients.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

None

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