DOI: 10.14744/ejmi.2022.87902
EJMI 2022;6(4):401–408

Research Article

# Investigation of the Clinicopathological Characteristics and Survival Outcomes of Patients Refusing Surgery Post-Neoadjuvant Therapy in Rectal Cancer

**Senar Ebinc,[1] Zeynep Oruc,[1] Ziya Kalkan,[1] Zuhat Urakci,[1] Savas Topuk,[2] Ulas Aday,[3] Bekir Tasdemir,[4] Muhammet Ali Kaplan,[1] Mehmet Kucukoner,[1] Abdurrahman Isikdogan[1]**

[1]Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[2]Department of Radiation Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[3]Department of Gastrointestinal Surgery, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[4]Department of Nuclear Medicine, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

## Abstract

**Objectives:** In locally advanced rectal cancer, the standard treatment approach consists of post-neoadjuvant surgery and adjuvant chemotherapy. In this study, we aimed to evaluate the clinicopathological characteristics of patients receiving neoadjuvant therapy for a diagnosis of rectal cancer and to compare the survival outcomes of patients who underwent surgery and patients who refused the surgical approach after neoadjuvant therapy, regardless of response status.

**Methods:** Our study included patients who presented to our clinic and underwent neoadjuvant therapy for locally advanced or oligometastatic rectal carcinoma between 2011 and 2021. Patients who did not complete neoadjuvant therapy or progressed on treatment were excluded. Patient data were retrospectively reviewed using the hospital records system.

**Results:** Our study analyzed data from a total of 123 patients, consisting of 98 (79.7%) patients in the surgery arm and 25 (20.3%) patients in the refusal arm. In our study, 65 (52.8%) patients were female and 58 (47.2%) patients were male. Median age at diagnosis was 53 years (20-86). Most of the patients (75.6%) had stage-III disease. Regarding response to neoadjuvant therapy; complete response was obtained in 16.3% (n=20), partial response was obtained in 71.5% (n=88), stable disease was obtained in 12.2% (n=15) of the patients. After neoadjuvant therapy, 20.3% of the patients had refused surgery and started follow-up. Of the 98 (79.7%) operated patients, 77 (26.6%) had been treated with a low anterior resection and 21 (17.1%) with an abdominoperineal resection. During follow-up, 29.3% (n=36) of the patients showed recurrence or progression. While progression-free survival could not be reached for operated patients, patients refusing surgery had a median recurrence free survival of 32 months (6.3-57.6) (Log-rank p=0.003). Median overall survival was 144 months (46.3-241.6) in operated patients as opposed to 41 (23.0-58.9) months in those refusing surgery (Log-rank p<0.001). Operated patients and patients refusing surgery had three-year survival rates of 64.9% vs 40% (p=0.023) and five-year survival rates of 45.4% vs 16% (p=0.007), respectively.

**Conclusion:** We determined that, in rectal cancer, both the overall survival and progression/recurrence-free survival outcomes of patients refusing surgery were poorer than those in the surgery arm, regardless of response status.

**Keywords:** Neoadjuvant therapy, prognosis, rectal cancer, refusal of surgery

***Cite This Article:*** *Ebinc S, Oruc Z, Kalkan Z, Urakci Z, Topuk S, Aday U, et al. Investigation of the Clinicopathological Characteristics and Survival Outcomes of Patients Refusing Surgery Post-Neoadjuvant Therapy in Rectal Cancer. EJMI 2022;6(4):401–408.*

The lifetime incidence of colorectal cancer is approximately 4%. At diagnosis, almost one thirds of the patients are in the local or locally advanced stage.[1] Although the incidence of colorectal cancer has shown a decreasing tendency in developed countries in the recent years; in terms of public health, this form of cancer maintains its sta-

**Address for correspondence:** Senar Ebinc, MD. Dicle Universitesi Tip Fakultesi, Tibbi Onkoloji Anabilim Dali, Diyarbakir, Türkiye
**Phone:** +90 412 258 00 60 (26-12) **E-mail:** senarebinc@gmail.com

**Submitted Date:** July 31, 2022 **Accepted Date:** September 03, 2022 **Available Online Date:** September 30, 2022

tus as an important cause of morbidity and mortality.[2] The predominant treatment approach in locally advanced rectal cancer consists of a procedure of surgery post-neoadjuvant chemoradiotherapy (CRT) and adjuvant chemotherapy.[3] Following the primary treatment, recurrence is observed at a rate of approximately 40% in stage II-III disease. The great majority of these recurrences occur within the first three years, with 90% occurring within the first five-years.[4,5] The fact that surgery is included among the current multimodal approaches and that unwanted surgery-related complications are common in the postoperative period has prompted research into different areas.[6] Since the likelihood of encountering rectal cancer at younger ages is high, the chronicity of these complications becomes a matter of concern and this situation has a significant impact on life quality.[2,7] Following from the hypothesis that, from among the CRT and neoadjuvant therapy approaches, total neoadjuvant therapy could offer a more favorable prognosis in patients achieving clinical complete response (cCR), the Watch-and-Wait (W&W) strategy has become a topic of discussion.[8,9] Previous studies have suggested that patients showing pathological complete response (pCR) postoperatively could have survival outcomes comparable to those showing cCR after neoadjuvant therapy who are followed-up with W&W, that the majority of the patients would be suitable for rescue surgery in the case of the detection of recurrence with close follow-up.[10] However, to date, no data has been produced to serve as evidence for the suggestions regarding the W&W strategy. Therefore, a wide area of application has not yet formed. Nonetheless, total neoadjuvant therapy approaches have been introduced to the guidelines for certain patient groups.[3] In our center, the W&W strategy is not a routinely implemented procedure. However, we have patients who refuse surgery after undergoing neoadjuvant therapy, regardless of response status. In this study, we aimed to compare the overall survival times and recurrence-free or progression-free survival times of patients who refused the surgical approach after neoadjuvant surgery and patients who underwent post-neoadjuvant surgery, and to evaluate their clinicopathological characteristics.

## Methods

### Patients

Our study included patients aged 18 or older who presented to Dicle University Medical Oncology Clinic and underwent neoadjuvant therapy for locally advanced or oligometastatic rectal carcinoma between 2011 and 2021. Clinical (age, gender, smoking status, comorbidities, received treatments, treatment response status, surgery status and surgery type, recurrence and progression status) and laboratory parameters (initial T, N, M stages and pathological subtypes) of the patients were retrospectively examined.

An ethical approval was granted by the Dicle University Medical Faculty Ethics Committee (date/reference number: 12.05.2022/129).

### Diagnostic and inclusion criteria

Patients were diagnosed with endoscopic biopsy. Local staging was done with magnetic resonance imaging (MRI) and pelvic computed tomography (CT), and distant staging was done with thoracic-abdominal CT or fluorodeoxyglucose positron emission computed tomography (FDG-PET CT). The definition of rectal carcinoma included carcinomas localized within the region extending up to 15 cm from the anal verge. Patients who underwent palliative treatment due to widespread metastasis, patients who did not receive neoadjuvant therapy, patients who did not complete the planned medical treatment or progressed on treatment were excluded from the study. Patients with known complete response (CR), partial response (PR) and stable disease (SD) rates who completed the planned medical treatment were included in the study.

### Terminology

The delivery of the entire treatment prior to surgery was defined as total neoadjuvant therapy (TNT). Chemotherapy received before CRT was defined as induction therapy, chemotherapy given during the period between CRT and surgery was defined as consolidation therapy. Chemotherapy delivered later in the postoperative period was termed as adjuvant therapy. Failure free survival (FFS) was defined as the time from the initiation of neoadjuvant therapy to recurrence in operated patients and to progression in non-operated patients. Overall survival (OS) was accepted as the time from the diagnosis to death.

### Treatment and Response Evaluation

As the standard CRT regimen, 50 to 50.4 Gy radiotherapy in 25 to 28 fractions was applied over a 5 to 6 week period with concurrent capecitabine or fluorouracil. As the chemotherapy regimen, during the course of treatment (induction - consolidation -adjuvant), mFOLFOX (fluorouracil, leucovorin, oxaliplatin; 8 cycles) or CapeOx (capecitabine, oxaliplatin; 5 cycles) was administered. Oxaliplatin was not added to the treatment of patients at advanced ages or patients with poor performance status. Response to neoadjuvant therapy was evaluated 4 to 8 weeks after CRT, with digital rectal examination, pelvic MRI and thoracic-abdom-

inal CT. Response evaluation was conducted according to RECIST v1.1.

## Statistical Analysis

The PASW Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, USA) software was used for the statistical analysis of the data. Descriptive statistics were used to evaluate patient characteristics and the frequency of parameters. Normally distributed numeric variables were analyzed using Student's t-test and categorical variables using the chi-square or Fisher's exact tests. For the evaluation of survival analyses, Kaplan-Meier survival analysis was used and the Log rank P value was taken as the basis. In survival analyses, Cox regression analysis was used for univariate and multivariate analyses. The enter method was used for univariate analysis and the backward stepwise likelihood ratio method for the multivariate analysis. The confidence interval was taken as 95% and the two-tailed significance level was taken as $p<0.05$.

## Results

Of the 310 patients whose data were screened in our study, 152 were determined to have received neoadjuvant chemotherapy. Following the exclusion of the patients who did not meet the inclusion criteria, data from a total of 123 patients, consisting of 98 (79.7%) patients in the surgery arm and 25 (20.3%) in the refusal of surgery arm were analyzed (Fig. 1). In our study, 65 of the patients (52.8%) were female and 58 (47.2%) were male. Median age at diagnosis was 53 years (20-86). Thirty-three percent (n=41) of the patients had a history of smoking and 22.8% (n=28) had a comorbidity of any type. The most frequent histopathological subtype was adenocarcinoma with a rate of 87% (n=107). At diagnosis, 65% (n=80) of the patients had T3, 73.2% (n=90) of the patients had N1 and only 4.1% (n=5) of the patients had M1 disease. The majority of the patients

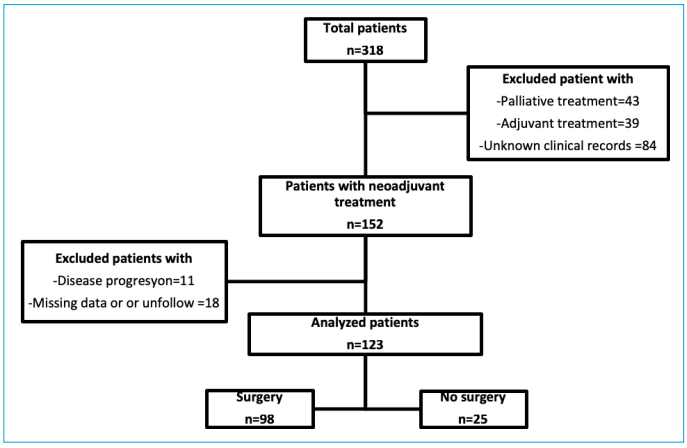


**Figure 1.** Case screening and patient inclusion algorithm.

(75.6%) had stage-III disease at diagnosis. Regarding the treatments received in the neoadjuvant and adjuvant periods, in the arm refusing surgery, 1 (4%) patient had received induction + CRT + consolidation therapy, while 24 (96%) patients had received CRT + consolidation therapy. In the operation arm, 16 (16.3) patients had received TNT. Of these, eight had received induction + CRT + consolidation therapy and eight had received CRT + consolidation therapy. Meanwhile, 82 (83.7%) patients had not received TNT, undergoing a part of or all of chemotherapy as adjuvant therapy. There were 32 (32.6%) patients who received CRT + consolidation + adjuvant therapy and 50 (51.1%) patients who received CRT + adjuvant therapy. Concerning the rates of response to neoadjuvant therapy, CR was obtained in 16.3% (n=20) of the patients, PR was obtained in 71.5% (n=88) of the patients, and SD was obtained in 12.2% (n=15) of the patients. After neoadjuvant therapy, 20.3% (n=25) of the patients had refused surgery and were introduced to follow-up. Of the 98 operated patients, 77 (26.6%) had been treated with a low anterior resection (LAR) and 21 (17.1%) with an abdominoperineal resection (APR). During follow-up, recurrence or progression had occurred in 29.3% (n=36) of the patients (Table 1).

Concerning the distribution of the patients between the surgery and refusal arms; the ages of patients refusing surgery were observed to be more advanced with statistical significance (64 yr vs 52 yr, $p<0.001$). On the other hand, the rate of T3-T4 tumors was significantly higher in the surgical arm compared with the other arm (86.7% vs 56%, $p=0.001$). Gender, smoking, presence of comorbidities, histological subtype, received treatments and response statuses showed a similar distribution across the two arms (Table 2). When the factors influencing FFS were investigated; pathological subtype, T stage and operation status were found to be associated with FFS in multivariate analysis. A poorer FFS was determined in mucinous adenocarcinoma and signet ring cell carcinoma compared with adenocarcinoma [HR:2.48; 95% CI 1.04-5.92; $p=0.04$], in T3-T4 tumors compared with T2 tumors [HR:5.45; 95% CI 1.73-17.14; $p=0.004$] and in non-operated patients compared with operated patients [HR:5.98; 95% CI 2.68-13.33; $p<0.001$]. With regard to OS; the outcome was poorer in mucinous adenocarcinoma and signet ring cell carcinoma compared with adenocarcinoma [HR:3.08; 95% CI 1.26-7.55; $p=0.014$] and in non-operated patients compared with operated patients [HR:5.53; 95% CI 2.50-12.21; $p<0.001$] (Table 3). While progression-free survival was not reached for operated patients, patients refusing surgery had a median FFS of 32 months (6.3-57.6) (Log-rank $p=0.003$) (Fig. 2). Median OS was 144 months (46.3-241.6) in operated patients as opposed to 41 (23.0-58.9) months in those refusing surgery

**Table 1.** Baseline characteristics of patients

| | All patients, n=123 (%) |
|---|---|
| Age (median, range) yr | 53 (20-86) |
| Geder | |
| Female | 65 (52.8) |
| Male | 58 (47.2) |
| Smoking | |
| No | 82 (66.7) |
| Yes | 41 (33.3) |
| Comorbidity | |
| No | 95 (77.2) |
| Yes | 28 (22.8) |
| Pathological subtypes | |
| Adenocarcinoma | 107 (87) |
| Mucinous adenocarcinoma | 10 (8.1) |
| Signet ring cell carcinoma | 6 (4.9) |
| T stage | |
| T2 | 24 (19.5) |
| T3 | 80 (65) |
| T4 | 19 (15.4) |
| N stage | |
| N0 | 25 (20.3) |
| N1 | 90 (73.2) |
| N2 | 8 (6.5) |
| M stage | |
| M0 | 118 (95.9) |
| M1 | 5 (4.1) |
| TNM stage | |
| II | 25 (20.3) |
| III | 93 (75.6) |
| IV | 5 (4.1) |
| First treatment options | |
| CT | 9 (7.3) |
| CRT | 114 (92.7) |
| Radiological response | |
| CR | 20 (16.3) |
| PR | 88 (71.5) |
| SD | 15 (12.2) |
| Type of surgery | |
| LAR | 77 (62.6) |
| APR | 21 (17.1) |
| No | 25 (20.3) |
| Relaps or progression | |
| No | 87 (70.7) |
| Yes | 36 (29.3) |

Yr; years, cm; centimeter, CT; chemotherapy, CRT; chemoradiotherapy, CR; complete response, PR; partial response, SD; stable disease, LAR; low anterior resection, APR; abdominoperineal resection.

(Log-rank p<0.001) (Fig. 3). Operated patients and patients refusing surgery had three-year survival rates of 64.9% vs 40% (p=0.023) and five-year survival rates of 45.4% vs 16% (p=0.007), respectively (Table 4). Both three-year and five-year survival rates were higher in operated patients compared with non-operated patients.

## Discussion

As is the case for all cancer patients, the expectations of rectal cancer patients involve the curative treatment of the disease with an unimpaired quality of life and an organ with preserved functionality at the end of the process. Treatment approaches that do not fulfill these expectations lead some patients to withdraw or refuse treatment. It is important to have knowledge about the situation that awaits the patient after the refusal of surgical treatment and the associated prognosis, as well as to inform the patients correctly at this stage. In this context, our study aims to shed light on the prognosis of rectal cancer patients who refuse treatment or cannot be operated due to medical reasons after neoadjuvant therapy, regardless of response status.

Although there have been advances in the techniques and treatment methods, the treatment of locally advanced rectal cancer is composed of the modalities of neoadjuvant CRT, total mesorectal excision (TME) and adjuvant chemotherapy.[11] Despite this radical approach, a significant portion of the patients would later lose their lives due to recurrence.[12] With the multimodal treatment approach, long-term complications (defecation problems, urinary dysfunction, sexual dysfunction and permanent stoma) may be encountered and the quality of life may be impaired. Therefore, the W&W strategy, which has not yet become a standard approach as an alternative to multimodal treatment, has become a topic of discussion.[9] After neoadjuvant therapy, TME can be refused by a portion of patients who think they would not be able to tolerate the complications that might arise due to surgical treatment.[13] As the patient approach in our study, the initial treatment plan for all patients was the multimodal treatment approach. The treatment plan consisted of TNT for one section of patients and the standard neoadjuvant approach (CRT + TME + adjuvant chemotherapy) for another section of patients. TME was recommended to operable patients who did not develop progression after neoadjuvant therapy. The surgical approach was refused by 20.3% (n=25) of our patients, regardless of cause. Of the patients refusing surgery, 12% (n=3) had shown cCR after neoadjuvant therapy. The remaining 88% (n=22) had shown cPR and cSD. Regarding the rates of response to neoadjuvant therapy, the surgery arm and the refusal of surgery arm had comparable rates (p=0.76). Complete response after neoadjuvant therapy in locally advanced rectal cancer is associated with good survival outcomes.[14] The question of whether avoiding the surgical approach could be

**Table 2.** Comparison of patients with and without surgery in terms of general characteristics

| | All patients, n=123 (%) | No surgery, n(%) | Surgery, n (%) | p |
|---|---|---|---|---|
| Age yr (median, range) | 53 (20-86) | 64 (35-84) | 52 (20-86) | <0.001* |
| Tumor localization cm (mean±std. dev.) | 6.88 (3.04) | 6.68 (3.41) | 6.93 (2.95) | 0.74* |
| Geder | | | | 0.72** |
| Female | 65 (52.8) | 14 (56) | 51 (52) | |
| Male | 58 (47.2) | 11 (44) | 47 (48) | |
| Smoking | | | | 0.52** |
| No | 82 (66.7) | 18 (72) | 64 (65.3) | |
| Yes | 41 (33.3) | 7 (28) | 34 (34.7) | |
| Comorbidity | | | | 0.71** |
| No | 95 (77.2) | 20 (80) | 75 (76.5) | |
| Yes | 28 (22.8) | 5 (20) | 23 (23.5) | |
| Pathological subtypes | | | | 0.18*** |
| Adenocarcinoma | 107 (87) | 24 (96) | 83 (84.7) | |
| Others | 16 (13) | 1 (4) | 15 (15.3) | |
| T stage | | | | 0.001*** |
| T2 | 24 (19.5) | 11 (44) | 13 (13.3) | |
| T3-4 | 99 (80.5) | 14 (56) | 85 (86.7) | |
| N stage | | | | 0.08** |
| N0 | 25 (20.3) | 2 (8) | 23 (23.5) | |
| N+ | 98 (79.7) | 23 (92) | 75 (76.5) | |
| M stage | | | | 0.58*** |
| M0 | 118 (95.9) | 25 (100) | 93 (94.9) | |
| M1 | 5 (4.1) | 0 (0) | 5 (5.1) | |
| First treatment options | | | | 0.68*** |
| CT | 9 (7.3) | 1 (4) | 8 (8.2) | |
| CRT | 114 (92.7) | 24 (96) | 90 (91.8) | |
| Radiological response | | | | 0.76*** |
| CR | 20 (16.3) | 3 (12) | 17 (17.3) | |
| PR-SD | 103 (83.7) | 22 (88) | 81 (82.7) | |
| Neo-adjuvant regimens | | | | 1.00*** |
| FUFA or Capesitabine | 14 (11.4) | 3 (12) | 11 (11.2) | |
| FOLFOX or XELOX | 109 (88.6) | 22 (88) | 87 (88.8) | |

* Student T test, ** Chi-Square test, *** Fisher's Exact test, Yr; years, cm; centimeter, CT; chemotherapy, CRT; chemoradiotherapy, CR; complete response, PR; partial response, SD; stable disease, FUFA; Fluorouracil + Leucoverine, FOLFOX; Fluorouracil + Leucoverine + Oxaliplatin, XELOX; Capesitabine + Oxaliplatin.

an option for patients achieving complete response after neoadjuvant therapy in rectal cancer is currently a frequently discussed question. Patients who show complete response and are followed-up without surgery require a close follow-up as the response status is confirmed with a comprehensive approach (MRI, rectoscopy, digital rectal examination etc.), as well as due to the risk of recurrence.[15] Although there are no randomized controlled phase-III studies on whether close follow-up or surgery offers better outcomes in patients achieving complete response after neoadjuvant therapy in rectal cancer, the results of the phase-II studies investigating follow-up as an option in T2N0 patients are due.[16] Currently, the data pertaining to the non-surgical approach in locally advanced rectal cancer are interpreted based on the accumulating reports. In a meta-analysis of 23 studies investigating the subject of W&W in rectal cancer that mainly consisted of retrospective or non-randomized studies, the rate of local recurrence was reported as 17.5%.[17] When the survival times of the patients in our study are evaluated, the median FFS was 32 months in the arm refusing surgery, while it was not reached in the surgery arm (log rank p=0.003). In non-metastatic rectal cancer, the T stage, particularly >T2, is included among the known poor prognostic factors.[18] Mucinous adenocarcinoma histology, which is predominantly encountered in young patients, is associated with more lymph node metastases, more frequent peritoneal dissemination, lower curative resection rates

**Table 3.** Univariate and multivariate outcomes of survivals

| | | Progression Free survival | | | | | | Overall Survival | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Univariate analysis | | | Multivariate analysis | | | Multivariate analysis | | |
| **Parameters** | **Reference/risk** | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** |
| Age, yr | Linear | 0.99 | 0.96-1.01 | 0.47 | | | | | | |
| Gender | Female/Male | 0.99 | 0.51-1.92 | 0.98 | | | | | | |
| Comorbidity | No/Yes | 0.54 | 0.21-1.41 | 0.21 | 0.40 | 0.15-1.04 | 0.06 | | | |
| Tumor localization, cm | Linear | 0.96 | 0.85-1.08 | 0.53 | | | | | | |
| Pathological subtypes | Adenocarcinoma/others | 2.05 | 0.89-4.69 | 0.08 | 2.48 | 1.04-5.92 | 0.04 | 3.08 | 1.26-7.55 | 0.014 |
| T stage | T2/>T2 | 2.26 | 0.80-6.42 | 0.12 | 5.45 | 1.73-17.14 | 0.004 | 2.16 | 0.82-5.66 | 0.11 |
| N stage | N0/N+ | 1.36 | 0.59-3.12 | 0.46 | | | | | | |
| M stage | M0/M1 | 1.84 | 0.56-6.03 | 0.31 | | | | | | |
| First treatment options | CRT/CT | 1.43 | 0.34-6.05 | 0.62 | | | | | | |
| Response | CR/PR-SD | 1.50 | 0.53-4.25 | 0.44 | | | | | | |
| Surgery status | Yes/No | 2.70 | 1.34-5.42 | 0.005 | 5.98 | 2.68-13.33 | <0.001 | 5.53 | 2.50-12.21 | <0.001 |

HR; hazard ratio, CI; confidence interval, Yr; years, cm; centimeter, CT; chemotherapy, CRT; chemoradiotherapy, CR; complete response, PR; partial response, SD; stable disease.

**Table 4.** Survival times, three-year and five-year survival rates in patients with and without surgery

| | Surgery | | No surgery | | | |
|---|---|---|---|---|---|---|
| | **Median (mo)** | **95% CI** | **Median (mo)** | **95% CI** | **p** | **HR (95% CI)** |
| Failure free survival | NR | NR | 32 | 6.3-57.6 | 0.003* | 0.37 (0.18-0.74) |
| Overall survival | 144 | 46.3-241.6 | 41 | 23.0-58.9 | <0.001* | 0.30 (0.15-0.61) |
| | **n** | **%** | **n** | **%** | | |
| Three-year survival rate | 63 | 64.9 | 10 | 40 | | 0.023** |
| Five-year survival rate | 44 | 45.4 | 4 | 16 | | 0.007** |

* Log rank p, ** Chi-Square test, NR; not reached, mo; months, HR; hazard ratio, CI; confidence interval.

and poorer survival outcomes compared with non-mucinous adenocarcinoma histology.[19] It is known that mucinous histology does not respond well to neoadjuvant and adjuvant therapy.[20,21] Signet ring cell carcinomas are also tumors that are rarely encountered in colorectal anatomical locations and present a poor prognosis.[22] Regarding the factors influencing the FFS in out study, the multivariate analysis determined signet ring cell carcinoma - mucinous adenocarcinoma tumor histology [HR: 2.48; 95% CI: 1.04-5.92; p=0.04], advanced T stage (T3-T4) [HR: 5.45; 95% CI: 1.73-17.14; p=0.004], and the status of surgery refusal [HR: 5.98; 95% CI: 2.68-13.33; p<0.001] as poor prognostic factors for FFS. These results were consistent with the literature. The population involved in our study included patients who refused surgical treatment regardless of response status, which are real life cases we encounter in daily practice. It is apparent that the prognosis would present a poorer course in patients who did not achieve complete response with neoadjuvant therapy and refused surgical treatment. However, having evidence-based knowledge about the fate awaiting these patients would influence the processes of the informing of the patient by the physician and patient decision making. The evaluation of the overall survival outcomes in our study revealed that signet ring cell carcinoma - mucinous adenocarcinoma histology [HR: 3.08; 95% CI: 1.26-7.55; p=0.014] and refusal of surgery [HR: 5.53; 95% CI: 2.50-12.21; p<0.001] were factors associated with a poor prognosis. The median OS was 41 months in the refusal of surgery arm as opposed to 144 months in the surgery arm (Log rank p<0.001). The mean age of the patients refusing surgery in our study was higher compared to that of operated patients (p<0.001). However, the presence of T3-4 tumors and the presence of M1 disease were more common in the surgery arm. Advanced age might be a factor in the refusal of the treatment. Accordingly, other studies con-

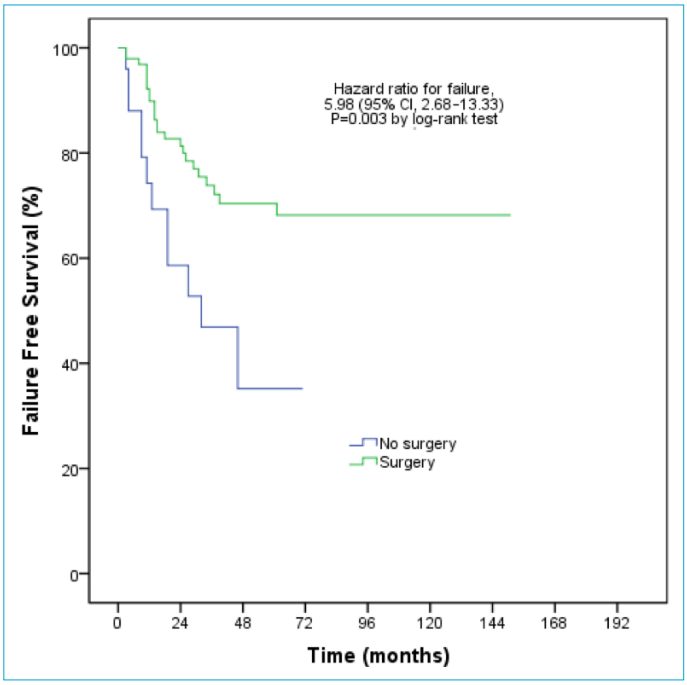


**Figure 2.** Progression-free and recurrence-free survival results in patients with and without surgery, Kaplan Meier survival chart.

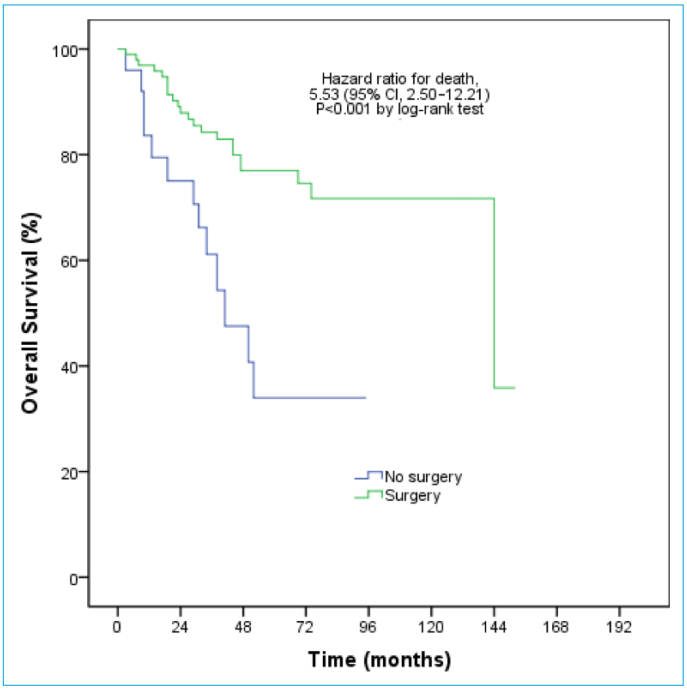


**Figure 3.** Overall survival outcomes in patients with and without surgery, Kaplan Meier survival chart.

ducted on this subject have reported age ≥ 70 as a possible factor for treatment refusal.[23] In addition, advanced age could have contributed to the poorer overall survival. Meanwhile, age, gender, comorbidity, tumor localization, status of receiving induction treatment, N stage, M stage and response after neoadjuvant therapy were not observed to have a statistically significant effect on FFS and OS. Along with these results, the number of patients achieving cCR had comparable percentage rates between the two groups (12% vs 17.3%), however, the low number of total patients in our study hinders a more thorough evaluation of patients showing cCR. When the overall survival rates in rectal adenocarcinoma are reviewed, stage II-III disease is associated with three year survival rates of around 48% to 76% and five year survival rates ranging between 33% and 64%.[24] When the survival rates in our study are evaluated, the surgery arm had a three-year survival rate of 64.9% and a five-year survival rate of 40%. The overall survival rates in the surgery arm were consistent with the literature. Patients refusing surgery had a three-year survival rate of 45.4% (p=0.023) and a five-year survival rate of 16% (p=0.007). The five-year survival rate was reported as 35.7% in patients refusing surgery in previous studies. In comparison to this data, the five-year survival rate in our study was lower.[23] In our study, both the three-year and five-year survival rates were lower in patients refusing surgery compared with the surgery arm, with statistical significance.

The limitations of our study include its retrospective design, its single-center nature and the relatively low number of patients, and the heterogeneity of the patient population.

## Conclusion

This study showed that OS, FFS, three- and five-year survival rates were poorer in patients refusing surgery after neoadjuvant therapy compared with the surgery arm in rectal cancer. This study also determined signet ring cell carcinoma, mucinous carcinoma and the presence of >T2 tumors as poor prognostic factors for FFS.

### Disclosures

**Ethics Committee Approval:** Dicle University Medical Faculty Ethics Committee (date/reference number: 12.05.2022/129).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.E., Z.O., Z.K., Z.U., S.T., U.A., B.T., M.A.K., M.K., A.I.; Design – S.E., Z.O., Z.K., Z.U., S.T., U.A., B.T., M.A.K., M.K., A.I.; Supervision – S.E., Z.O., Z.K., Z.U., S.T., U.A., B.T., M.A.K., M.K., A.I.; Materials – S.E., Z.O., Z.K., Z.U.; Data collection &/or processing – S.E., Z.O., Z.K., Z.U.; Analysis and/or interpretation – S.E., Z.O., Z.K., Z.U.; Literature search – S.E., Z.O., Z.K., Z.U., S.T., U.A., B.T., M.A.K., M.K., A.I.; Writing – S.E., Z.O., Z.K., Z.U., S.T., U.A., B.T., M.A.K., M.K., A.I.; Critical review – S.E., Z.O., Z.K., Z.U., S.T., U.A., B.T., M.A.K., M.K., A.I.

## References


1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33. [CrossRef]
2. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer Epidemiol Biomarkers Prev 2009;18:1695–8.
3. NCCN. NCCN clinical practice guidelines in oncology. Rectal cancer, version 2.2021- September 20, 2021.
4. Kjeldsen BJ, Kronborg O, Fenger C, Jørgensen OD. The pattern of recurrent colorectal cancer in a prospective randomised study and the characteristics of diagnostic tests. Int J Colorectal Dis 1997;12:329–34. [CrossRef]
5. Renouf DJ, Woods R, Speers C, Hay J, Phang PT, Fitzgerald C, et al. Improvements in 5-year outcomes of stage II/III rectal cancer relative to colon cancer. Am J Clin Oncol 2013;36:558–64.
6. Juul T, Ahlberg M, Biondo S, Espin E, Jimenez LM, Matzel KE, et al. Low anterior resection syndrome and quality of life: an international multicenter study. Dis Colon Rectum 2014;57:585–91. [CrossRef]
7. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg 2015;150:17–22. [CrossRef]
8. Smith JJ, Garcia-Aguilar J. Advances and challenges in treatment of locally advanced rectal cancer. J Clin Oncol 2015;33:1797–808. [CrossRef]
9. Smith JJ, Strombom P, Chow OS, Roxburgh CS, Lynn P, Eaton A, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol 2019;5:e185896. [CrossRef]
10. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al; IWWD Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391:2537–45. [CrossRef]
11. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40. [CrossRef]
12. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, et al. Colorectal cancer. Lancet 2010;375:1030–47.
13. Chen TY, Wiltink LM, Nout RA, Meershoek-Klein Kranenbarg E, Laurberg S, Marijnen CA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. Clin Colorectal Cancer 2015;14:106–14. [CrossRef]
14. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835–44.
15. Sao Juliao GP, Habr-Gama A, Vailati BB, Araujo SE, Fernandez LM, Perez RO. New strategies in rectal cancer. Surgical Clin North Am 2017;97:587–604. [CrossRef]
16. Smith JJ, Chow OS, Gollub MJ, Nash GM, Temple LK, Weiser MR, et al; Rectal Cancer Consortium. Organ preservation in rectal adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer 2015;15:767.
17. Garcia-Aguilar J, Patil S, Kim JK, Yuval JB, Thompson H, Verheij F, et al. Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial. J Clin Oncol 2020;38:4008.
18. Micu BV, Vesa ŞC, Pop TR, Micu CM. Evaluation of prognostic factors for 5 year-survival after surgery for colorectal cancer. Ann Ital Chir 2020;91:41–8.
19. Kanemitsu Y, Kato T, Hirai T, Yasui K, Morimoto T, Shimizu Y, et al. Survival after curative resection for mucinous adenocarcinoma of the colorectum. Dis Colon Rectum 2003;46:160–7.
20. Shin US, Yu CS, Kim JH, Kim TW, Lim SB, Yoon SN, et al. Mucinous rectal cancer: effectiveness of preoperative chemoradiotherapy and prognosis. Ann Surg Oncol 2011;18:2232–9.
21. Lee DW, Han SW, Lee HJ, Rhee YY, Bae JM, Cho NY, et al. Prognostic implication of mucinous histology in colorectal cancer patients treated with adjuvant FOLFOX chemotherapy. Br J Cancer 2013;108:1978–84. [CrossRef]
22. Belli S, Aytac HO, Karagulle E, Yabanoglu H, Kayaselcuk F, Yildirim S. Outcomes of surgical treatment of primary signet ring cell carcinoma of the colon and rectum: 22 cases reviewed with literature. Int Surg 2014;99:691–8. [CrossRef]
23. Coffman AR, Tao R, Cohan JN, Huang LC, Pickron TB, Torgeson AM, et al. Factors associated with the refusal of surgery and the associated impact on survival in patients with rectal cancer using the National Cancer Database. J Gastrointest Oncol 2021;12:1482–97. [CrossRef]
24. Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010. p. 143.