



The comparison of FOLFOX regimens with different doses of 5-FU for the adjuvant treatment of colorectal cancer: a multicenter study

Nadiye Akdeniz¹ · Muhammet Ali Kaplan² · Doğan Uncu³ · Mevlüde İnanç⁴ · Serap Kaya⁵ · Faysal Dane⁵ · Mehmet Küçüköner² · Ayşe Demirci⁶ · Mehmet Bilici⁷ · Ayşe Gök Durnali⁸ · Lokman Koral⁹ · Mehmet Ali Nahit Şendur³ · Cihan Erol³ · Esmâ Türkmen¹⁰ · Ömer Fatih Ölmez¹¹ · Özgür Açıkgöz¹¹ · Şahin Laçın¹² · Hayriye Şahinli¹³ · Zuhat Uraççı² · Abdurrahman Işıkdöğün²

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Abstract

Purpose We aim to compare the efficiency and toxicity of three different 5-fluorouracil (5-FU) administration types in 5-FU, leucovorin, and oxaliplatin (FOLFOX) combination treatment for adjuvant therapy in colorectal cancer (CRC).

Methods Five hundred and seventy patients with stage III colorectal carcinoma who received different FOLFOX regimens after curative resection were included. Patients were divided into three groups as FOLFOX-4, modified FOLFOX-6 (mFOLFOX-6), and mFOLFOX-4 for comparison of toxicity and disease-free survival (DFS) and overall survival (OS) times.

Results Three-year DFS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 65%, 72%, and 72%, respectively. Five-year OS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 69%, 75%, and 67%, respectively. There was no statistically significant difference between the three treatment groups in terms of DFS and OS ($p = 0.079$, and $p = 0.147$, respectively). Among grade 1–2 adverse events (AE), thrombocytopenia, neuropathy, and stomatitis were more common in the mFOLFOX-6-treated group. The frequency of grade 1–2 nausea and vomiting were similar in mFOLFOX-6 (36.3% and 24%, respectively) and mFOLFOX-4 (32.4% and 24.7%, respectively) groups but were higher than that in the FOLFOX-4 (19.5% and 11.3%, respectively) group. Among the most common grade 3–4 AE, neutropenia (53.4%, 9%, and 13.5%, respectively) and diarrhea (10.5%, 2.2%, and 2.4, respectively) were more common in FOLFOX-4. The rate of anemia and febrile neutropenia was similar in treatment groups ($p = 0.063$, and $p = 0.210$, respectively).

Conclusion In the adjuvant treatment of stage III CRC patients, three different 5-FU administration types in FOLFOX combination treatment can be used with similar efficiency and manageable toxicity.

Keywords Adjuvant chemotherapy · Colorectal cancer; FOLFOX regimens · Stage III

✉ Nadiye Akdeniz
nadiyeakdeniz21@gmail.com

¹ Department of Medical Oncology, Adiyaman Training and Research Hospital, 02100 Adiyaman, Turkey

² Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Turkey

³ Department of Medical Oncology, Ankara City Hospital, Ankara, Turkey

⁴ Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Turkey

⁵ Department of Medical Oncology, Marmara University Faculty of Medicine, Istanbul, Turkey

⁶ Department of Medical Oncology, Sakarya University Faculty of Medicine, Sakarya, Turkey

⁷ Department of Medical Oncology, Atatürk University Faculty of Medicine, Erzurum, Turkey

⁸ Department of Medical Oncology, Ankara Oncology Training and Research Hospital, Ankara, Turkey

⁹ Department of Medical Oncology, Çanakkale Onsekiz Mart University Faculty of Medicine, Çanakkale, Turkey

¹⁰ Department of Medical Oncology, Derince Training and Research Hospital, Izmit, Turkey

¹¹ Department of Medical Oncology, Medipol University Faculty of Medicine, İstanbul, Turkey

¹² Department of Medical Oncology, Yeditepe University Faculty of Medicine, İstanbul, Turkey

¹³ Department of Medical Oncology, Diskapi Training and Research Hospital, Ankara, Turkey

Introduction

Colorectal cancer (CRC) is commonly encountered worldwide and is the third leading cause of cancer-related deaths [1]. Almost one-third of patients have locoregional lymph node metastasis at the time of diagnosis and are diagnosed at stage III [2]. When treated with surgery alone, 40–50% of patients with locoregional disease develop relapse or distant metastases due to micrometastases [3]. Adjuvant chemotherapy aims to eliminate these micrometastases and achieve cure. For the first time in the literature, Moertel et al. showed that a 12-month use of 5-fluorouracil (5-FU) and levamisole combination for stage III lymph node-positive colon cancer resulted in 33% decrease in mortality rates [4]. After the 6-month use of 5-FU and leucovorin (LV) combination was proven to have survival advantage, 5-FU/LV-based adjuvant chemotherapy for 6 months has become the standard treatment in stage III colon cancer [5]. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study found that by adding oxaliplatin to 5-FU/LV a 7.5% increase in 5-year disease-free survival (DFS) and a 4.2% increase in 6-year overall survival (OS) was achieved, and oxaliplatin-based chemotherapy was recommended as standard postoperative treatment for these patients [6, 7].

FOLFOX-4 regimen, including the combination of oxaliplatin with LV and bolus or infusion 5-FU, is well-proven in the adjuvant therapy [7]. However, this regimen has evolved to modified FOLFOX-6 (mFOLFOX-6) and modified FOLFOX-4 (mFOLFOX-4) regimens, which are as effective with the advantage of avoiding hospital admissions by being administered through a portacath. In this study, we aim to compare these three FOLFOX regimens with the same oxaliplatin but different 5-FU administrations, which are used as adjuvant therapy in CRC, in terms of efficiency and toxicity.

Materials and methods

Study population and data collection

Five hundred and seventy patients who underwent curative surgery and received postoperative adjuvant oxaliplatin and 5-FU/LV combination therapy in 12 different oncology centers in Turkey between May 2004 and March 2019 were recruited to the study. Patients who were histopathologically diagnosed with colorectal adenocarcinoma and have stage III disease at diagnosis were included. Patients who were treated with neoadjuvant therapy for rectal cancer were excluded. The study was approved by the local Ethics Committee and conducted in accordance with the Helsinki Declaration and ethical principles (Approval no: 147/2019). Data about the

sex, age at diagnosis, performance status, tumor location, stage, treatment regimen, survival, and toxicity were retrieved from patient files.

The performance status of the patients was determined according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS) criteria. Staging was performed according to American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging Systems version 7. Toxicity was evaluated according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment schedules

FOLFOX-4 regimen is administered every 14 days with 85 mg/m² oxaliplatin plus 200 mg/m² LV on day 1 and 5-FU 400 mg bolus plus 600 mg/m² as a 22-h infusion on days 1 and 2. Modified FOLFOX-4 regimen is administered every 14 days with 85 mg/m² oxaliplatin plus 200 mg/m² LV and 5-FU 400 mg/m² bolus on day 1 followed by 1600 mg/m² 5-FU as a 46-h infusion. Modified FOLFOX-6 regimen is administered every 14 days with 85 mg/m² oxaliplatin plus 400 mg/m² LV and 5-FU 400 mg/m² bolus on day 1 followed by 2400 mg/m² 5-FU as a 46-h infusion. All patients with rectal primaries received adjuvant radiotherapy of 46 Gy to the pelvic area and a 4 Gy boost, for a total dose of 50 Gy, concomitantly with capecitabine 825 mg/m² twice daily on the days of radiotherapy, or 225 mg/m² 5-FU infusion. Two cycles of chemotherapy were administered before, and the remaining 10 cycles were administered after the completion of chemoradiotherapy. Patients were followed up at 3-month intervals for the first 2 years, then at 6-month intervals until 5 years completed, with clinical visits.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21 software (IBM Corp., Armonk, NY, USA). Descriptive analyses were presented as median, mean, and percentages. Categorical variables are given as percentages and were compared using the Chi-square or Fisher's exact test, when appropriate. Kruskal–Wallis test was conducted to compare numerical variables among the treatment groups. A *p*-value of less than 0.05 was considered to show a statistically significant result. The OS and DFS rates were estimated with the Kaplan–Meier method. DFS was defined as the time from initiation of the first cycle of chemotherapy to the date of recurrence or death. OS was defined as the time from the first cycle of chemotherapy until death or last follow-up. The differences between treatment groups were assessed with the log-rank test. Parameters for which *p* < 0.200 in the univariate Cox models were further

assessed in the multivariate Cox models. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Results

Five hundred and seventy patients were evaluated in the study. Among them, 133 patients were in the FOLFOX-4 group, 267 patients were in the mFOLFOX-6 group and 170 patients were in the mFOLFOX-4 group. Three hundred and thirty-nine patients (59.5%) were male. Median age at diagnosis was 57 years (18–84) for the entire population. Median ages at diagnosis for FOLFOX-4, mFOLFOX-6 and mFOLFOX-4 groups were 56, 59, and 54.5 years, respectively ($p = 0.020$). There was no statistically significant difference between the groups in terms of ECOG PS, tumor location, nodal stage, and TNM stage ($p = 0.109$, $p = 0.080$, $p = 0.256$, and $p = 0.237$, respectively). On the other hand, T stage, grade, and lymphovascular invasion showed significant difference ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In rectal cancer patients, surgical margin positivity was detected in 4 (8.9%) patients, 1 (1.3%), and 1 (1.5%) patient in FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups, respectively. The number of patients who received adjuvant radiation therapy was 63 (37%) in the mFOLFOX-4 group, 33 (25%) in the FOLFOX-4 group, and 46 (17%) in the mFOLFOX-6 group ($p < 0.001$). Patient characteristics are summarized in Table 1.

Survival

Median follow-up period was 62 months (4–161). Sixty-one (45.9%) patients in the FOLFOX-4 group, 76 (28.5%) patients in the mFOLFOX-6 group, and 59 (34.7%) patients in the mFOLFOX-4 group developed relapse. In patients with rectal cancer, local recurrence was detected in 5 (14.7%), 3 (3.7%), and 8 (11.7%) patients, in FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups, respectively. Fifty-seven (42.9%) patients in the FOLFOX-4 group, 59 (22.1%) patients in the mFOLFOX-6 group, and 79 (46.5%) patients in the mFOLFOX-4 group were deceased. Median value for DFS could not be reached in all patients and 3-year and 5-year DFS rates were 71% and 64.6%, respectively. Median OS of all patients was 157.5 months (95% CI, 113.8–201.2), and 3-year and 5-year OS rates were 85% and 71%, respectively.

In univariate analyses, median value could not be reached for DFS according to treatment groups. Three-year DFS rates for FOLFOX-4, mFOLFOX-6 and mFOLFOX-4 groups were 65%, 72%, and 72%, respectively. No statistically significant difference was observed between the three groups in terms of DFS ($p = 0.129$) (Fig. 1). DFS also showed no significant difference according to age ($p = 0.165$), sex ($p = 0.936$), tumor location ($p = 0.825$), grade ($p = 0.276$), lymphovascular

invasion ($p = 0.383$), and nodal and TNM stage ($p = 0.123$, and $p = 0.101$, respectively). ECOG PS resulted in a significant difference in DFS ($p = 0.019$). Patients with ECOG PS 2 had significantly lower DFS than patients with PS 0 and PS 1 ($p = 0.006$, and $p = 0.024$, respectively). T stage also resulted in a significant difference in DFS ($p = 0.006$). Patients with T4 disease had significantly lower DFS than patients with T2 ($p = 0.013$) and T3 ($p = 0.007$) disease. Factors associated with DFS are presented in Table 2.

When OS was evaluated according to treatment groups in univariate analyses, median value could not be reached in FOLFOX-4 and mFOLFOX-6 groups, while median OS was 139.8 months (95% CI, 122.9–156.8) in the mFOLFOX-4 group. Three-year OS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 84%, 88%, and 83%, respectively. Five-year OS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 69%, 75%, and 67%, respectively. There was no statistically significant difference between treatment groups in terms of OS ($p = 0.152$) (Fig. 2). OS also showed no significant difference according to age ($p = 0.162$), sex ($p = 0.817$), tumor location ($p = 0.343$), grade ($p = 0.257$), lymphovascular invasion ($p = 0.897$), and nodal and TNM stage ($p = 0.329$, and $p = 0.099$, respectively). ECOG PS resulted in a significant difference in OS ($p < 0.001$). Patients with ECOG PS 2 had significantly lower OS than patients with PS 0 and PS 1 ($p < 0.001$, and $p = 0.004$, respectively). T stage also resulted in a significant difference in OS ($p = 0.038$). Patients with T4 disease had significantly lower OS than patients with T2 disease ($p = 0.015$). Factors associated with OS are presented in Table 2.

In subgroup analysis, DFS and OS were evaluated separately in patients with rectal cancer. In the univariate analysis, median DFS value could not be reached in mFOLFOX-6 and mFOLFOX-4 groups, while median DFS was 55.8 months in the FOLFOX-4 group. Three-year DFS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 60%, 72%, and 80%, respectively. There was a statistically significant difference between the three groups in terms of DFS ($p = 0.003$). The median OS value was 87.7 months in FOLFOX-4, 120 months in mFOLFOX-6, and 143 months in the mFOLFOX-4 groups. Three-year OS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 80%, 90%, and 91%, respectively. Five-year OS rates for FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups were 60%, 75%, and 73%, respectively. There was no statistically significant difference between treatment groups in terms of OS ($p = 0.123$) (Fig. 3).

Multivariate analyses revealed that ECOG PS ($p = 0.023$, and $p = 0.016$, respectively) and T stage ($p = 0.012$, and $p = 0.015$, respectively) were independent prognostic factors for DFS and OS. There was no statistically significant difference between the three treatment groups in terms of DFS and OS ($p = 0.079$, and $p = 0.147$, respectively) (Table 3).

Table 1 Patient and disease characteristics of treatment groups

Characteristics	FOLFOX-4 (n=133) N(%)	mFOLFOX-6 (n=267) N(%)	mFOLFOX-4 (n=170) N(%)	p-value
Age median (min - max)	56 (25–79)	59 (26–84)	54.5 (17–76)	0.020
Gender				0.497
Male	83 (62)	152 (57)	104 (61)	
Female	50 (38)	115 (43)	66 (39)	
ECOG PS				0.109
0	76 (57)	156 (58)	78 (46)	
1	54 (41)	102 (38)	85 (50)	
2	3 (2)	9 (3)	7 (4)	
Tumor localization				0.080
Rectum	45 (34)	79 (30)	68 (40)	
Colon	88 (66)	188 (70)	102 (60)	
T stage				< 0.001
T2	8 (6)	26 (10)	8 (5)	
T3	99 (74)	156 (58)	150 (88)	
T4	26 (20)	85 (32)	12 (7)	
N stage				0.256
N1	86 (65)	150 (56)	98 (58)	
N2	47 (35)	117 (44)	72 (42)	
TNM Stage				0.237
IIIA	10 (8)	27 (10)	7 (4)	
IIIB	79 (59)	152 (57)	100 (59)	
IIIC	44 (33)	88 (33)	63 (37)	
Grade				< 0.001
Well	27 (20)	34 (13)	62 (37)	
Moderately	79 (59)	167 (63)	70 (41)	
Poor	26 (20)	53 (20)	15 (9)	
Unknown	1 (1)	13 (4)	23 (13)	
Lymphovascular invasion				< 0.001
Yes	52 (39)	156 (58)	40 (24)	
No	78 (59)	110 (41)	70 (41)	
Unkown	3 (2)	1 (1)	60 (35)	
Adjuvant Radiotherapy				< 0.001
Yes	33 (25)	46 (17)	63 (37)	
No	100 (75)	221 (83)	107 (63)	

Data in bold indicates statistical significant results

FOLFOX 5-fluorouracil, leucovorin, and oxaliplatin; *mFOLFOX* modified 5-fluorouracil, leucovorin, and oxaliplatin; *ECOG PS*: Eastern Cooperative Oncology Group performance status; *min* minimum;

max maximum

Toxicity

Median number of chemotherapy cycles was 12 (6–12) for the entire population and all three treatment groups. Dose reduction was performed in 65 (48.9%), 59 (22.5%), and 11 (6.5%) patients in FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups, respectively. Dose delay was performed in 92 (69.2%), 70 (26.2%), and 30 (17.6%) patients in FOLFOX-4, mFOLFOX-6, and mFOLFOX-4 groups, respectively. In patients with rectal cancer, dose reduction was performed in 23 (52.3%), 16 (20.3%), and 3 (5.9%) patients in FOLFOX-4,

mFOLFOX-6, and mFOLFOX-4 groups respectively, and similarly dose delay had been needed in 32 (72.7%), 25 (50%), and 10 (20%) patients, respectively. Anemia and febrile neutropenia were not different between treatment groups ($p = 0.063$, and $p = 0.210$, respectively). Among the most common grade 3–4 adverse events, neutropenia (53.4%, 9%, and 13.5%, respectively) and diarrhea (10.5%, 2.2%, and 2.4%, respectively) were more common in the FOLFOX-4 group than in the mFOLFOX-6 and mFOLFOX-4 groups. Among grade 1–2 adverse events, thrombocytopenia (24.7%, 17.3%, and 13.5%, respectively), neuropathy (37.5%, 20.3%, and

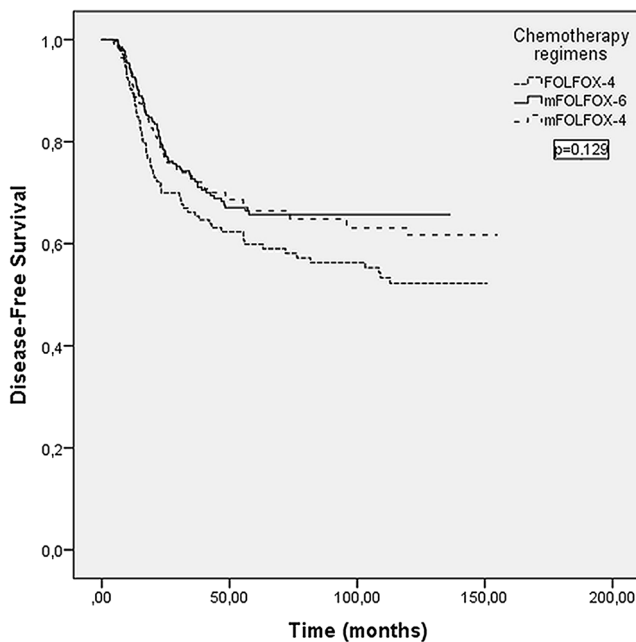


Fig. 1 Kaplan-Meier curve of disease-free survival according to treatment groups for all patients

18.8%, respectively), and stomatitis (18%, 11.3%, and 10.6%, respectively) were more common in the mFOLFOX-6 group than in the FOLFOX-4 and mFOLFOX-4 groups. The frequency of grade 1–2 nausea and vomiting were similar in mFOLFOX-6 (36.3% and 24%, respectively) and mFOLFOX-4 (32.4% and 24.7%, respectively) groups and higher than FOLFOX-4 (19.5% and 11.3%, respectively) group (Table 4).

Discussion

In this study, we compared three different 5-FU administration types in FOLFOX combination treatment used after surgery in stage III colon cancer in terms of efficiency and toxicity. We demonstrated that DFS and OS did not exhibit a significant difference between the three treatment groups. The frequency of neutropenia and diarrhea, grade 3–4 adverse events important for treatment continuity, was higher in the FOLFOX-4 group than in others. However, the rates of thrombocytopenia, neuropathy, and stomatitis, which were grade 1–2 adverse events, were higher in the mFOLFOX-6 group than in the other treatment groups. The frequency of grade 1–2 nausea and vomiting was similar in the mFOLFOX-6 and mFOLFOX-4 groups, which was higher than that in the FOLFOX-4 group. To our best knowledge, because there is not enough information in the literature regarding these regime comparisons, prospective study of the mFOLFOX-4 regimen, our findings become much more valuable and attractive.

With the introduction of postoperative adjuvant chemotherapy in stage 3 colon cancer patients, significant reductions in local relapse and distant metastasis rates have been achieved. Because relapse is usually encountered in the first three years in colon cancer, studies usually report 3-year DFS rates [8]. Also, Sargent et al. reported that 3-year DFS rates were associated with 5-year OS [9].

MOSAIC and The National Surgical Adjuvant Breast and Bowel Project 07 (NSABP C07) studies are the two main randomized controlled adjuvant colon cancer studies that investigate the oxaliplatin and 5-FU/LV combination. NSABP C07 study showed that with the FLOX regimen, adding oxaliplatin to 5-FU/LV therapy yielded a 6.6% additional increase in 3-year DFS rates [6, 10]. Also, the 5-year OS rate of stage 3 patients receiving FLOX is reported to be 76.5% [10]. However, the FLOX regimen is not preferred in daily practice due to significant toxicity. MOSAIC study reported the 3-year DFS rate and 6-year OS rate to be 72.2% and 73%, respectively, in the FOLFOX-4 arm in stage 3 colon cancer. In our study, the 3-year DFS rate was 65% and the 5-year OS rate was 69% in the FOLFOX-4 group. The survival differences with the literature were due to our subjects having more poor prognostic factors than in previous studies. In our study, the ratio of patients with N2 disease (35% vs 15.1%) and poorly differentiated tumor (20% vs 12.6%) were higher than the MOSAIC study. Also, the MOSAIC study excluded patients with rectal cancer, while our study had 45 patients with rectal cancer in the FOLFOX-4 arm.

When compared with FOLFOX-4 regimen, the mFOLFOX-6 regimen is easier to administer because it only requires 1 day in the hospital, has lower costs, and is shown to have similar DFS in two phase 3 studies [11, 12]. NSABPC-08 study reported that the 3-year DFS rate was 71.7% and the 5-year OS rate was 77.6% in the mFOLFOX-6 arm of stage 3 patients [13]. In our study, consistent with the literature, the 3-year DFS rate was 72% and the 5-year OS rate was 88% in the group receiving mFOLFOX-6 therapy.

The results obtained with metastatic patients and the convenience of only one day of hospital visit made the mFOLFOX-4 regimen preferred in daily clinical practice. In a retrospective study with stage III colorectal cancer, 3-year DFS and OS rates were reported to be 65.6% and 84.3% in the mFOLFOX-4 group. In our study, we achieved a better 3-year DFS rate (72%) and a similar 3-year OS rate (83%) with the mFOLFOX-4 regimen. We were also able to achieve the 3-year DFS rate obtained with the standard FOLFOX-4 arm in the MOSAIC study (72% vs 72.2%), showing that the mFOLFOX-4 regimen is non-inferior to standard FOLFOX-4 [14].

In the subgroup analysis of patients with rectal cancer, the 3-year DFS rate for the FOLFOX-4 group was 60% and found to be lower than the other two treatment groups ($p = 0.003$). The local recurrence rate was also detected higher in 14.7% of

Table 2 Univariate analysis of the factors affecting disease-free survival and overall survival

Factors	3-year DFS (%)	5-year DFS (%)	<i>p</i> -value	3-year OS (%)	5-year OS (%)	<i>p</i> -value
Chemotherapy regimens			0.129			0.152
FOLFOX-4	65	59		84	69	
mFOLFOX-6	72	65		88	75	
mFOLFOX-4	72	66		83	67	
Age			0.165			0.162
< 70 years	70	65		85	72	
≥ 70 years	72	54		86	63	
Gender			0.936			0.817
Male	70	64		77	70	
Female	71	64		78	72	
ECOG-PS			0.019			<0.001
0	73	66		87	73	
1	70	63		84	69	
2	42	42		66	53	
Tumor localization			0.825			0.343
Rectum	71	65		76	69	
Colon	70	64		78	71	
T stage			0.006			0.038
T2	84	76		92	85	
T3	73	66		87	71	
T4	59	54		78	64	
N stage			0.123			0.329
N1	72	66		87	73	
N2	68	62		82	67	
TNM stage			0.101			0.099
IIIA	86	73		95	80	
IIIB	70	65		86	72	
IIIC	68	61		82	66	
Grade			0.276			0.257
Well	79	70		94	80	
Moderately	68	63		85	68	
Poor	64	60		74	64	
Lymphovascular invasion			0.383			0.897
Yes	68	62		84	68	
No	71	63		86	72	
Adjuvant Radiotherapy			0.362			0.826
Yes	74	68		88	73	
No	69	63		84	70	

Data in bold indicates statistical significant results

DFS disease-free survival; OS overall survival; FOLFOX 5-fluorouracil, leucovorin, and oxaliplatin; mFOLFOX modified 5-fluorouracil, leucovorin, and oxaliplatin; ECOG PS: Eastern Cooperative Oncology Group performance status

patients in the FOLFOX-4 group. The shorter DFS may be due to factors that include the high positivity rate of surgical margins, 2-day bolus therapy applications that may cause a reduction in the treatment compliance with radiotherapy.

In the MOSAIC study, the most common grade 3–4 adverse events in the FOLFOX-4 arm were neutropenia with 41.1%, neuropathy with 12.4%, and diarrhea with 10.8%

[6]. In our study, neutropenia was higher than the MOSAIC study with 53.4%, diarrhea was similar with 10.5%, and neuropathy was less with 3%.

In the NSABPC-08 study that evaluates adjuvant mFOLFOX-6 regimen, among grade 3–4 toxicities, neutropenia was reported to be 32.6%, thrombocytopenia 3.4%, and neuropathy 14.4% [15]. Another phase 3 study that assessed

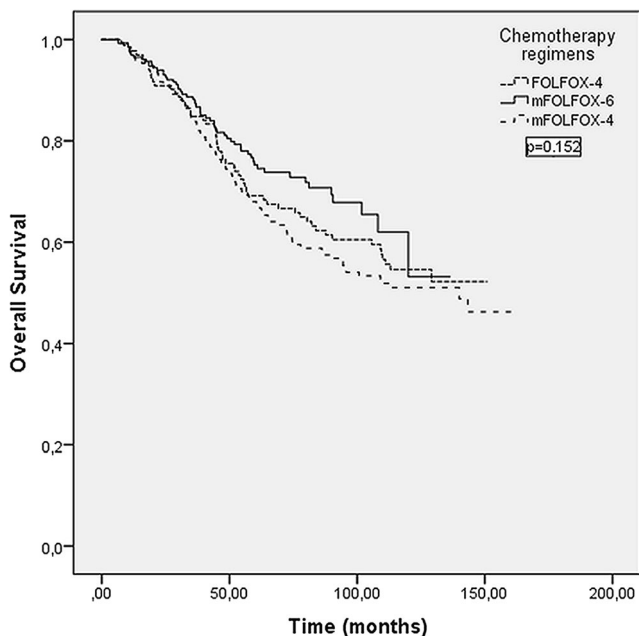


Fig. 2 Kaplan-Meier curve of overall survival according to treatment groups for all patients

adjuvant mFOLFOX-6 regimen reported the most common grade 3-4 adverse events to be neutropenia with 26.9%, thrombocytopenia with 2.5%, neuropathy with 7.1%, and diarrhea with 4% [16]. In our study, we observed 9% grade 3-4 neutropenia, 2.6% thrombocytopenia, 2.6% neuropathy, and 2.2% diarrhea in the mFOLFOX-6 group. Grade 1-2 adverse events neuropathy (37.5%), thrombocytopenia (24.7%), and stomatitis (18%) were encountered more in the mFOLFOX-6 group than the other two treatment groups. Toxicity rates

showed variations due to the retrospective nature of our study and data retrieval from patient records.

In a retrospective study that investigated the mFOLFOX-4 regimen in rectal cancer, grade 3-4 leukopenia and neuropathy were reported 9.1% and thrombocytopenia was not reported [17]. In our study, we observed more grade 3-4 neutropenia with 1.5% and less neuropathy with 4.7% in the mFOLFOX-4 arm. Thrombocytopenia was reported to be 1.2%. The number of patients receiving chemoradiotherapy was higher in the current study and the rate of neuropathy was higher due to common use of oxaliplatin.

In the adjuvant setting, the completion of all preplanned treatments after surgery is challenging due to patient tolerance and drug toxicity, and dose reduction is common oncological practice for patient management [18]. Almost all chemotherapy treatments are dosed based on body surface area (BSA) and recommended treatment doses (mg) per BSA (meters squared, m²) are derived from trials testing for dose-limiting toxicities. Body composition is one factor influencing the pharmacokinetics and metabolism of many chemotherapy agents [19]. Therefore, patients' treatment tolerance is different, for overcoming treatment toxicity and to increase tolerance dose reduction and delays are commonly used by oncologists in their daily practice. Thereby, the maximum tolerable dose of patients can be determined. The cut-off values for dose reduction, and intensity, which will not adversely affect treatment success, are determined by adjuvant colorectal cancer studies [18, 20]. Therefore, we think, in our study, dose reductions and delays have not negatively affected the results.

The major strength of our study is including heterogeneous patients from different centers and the major

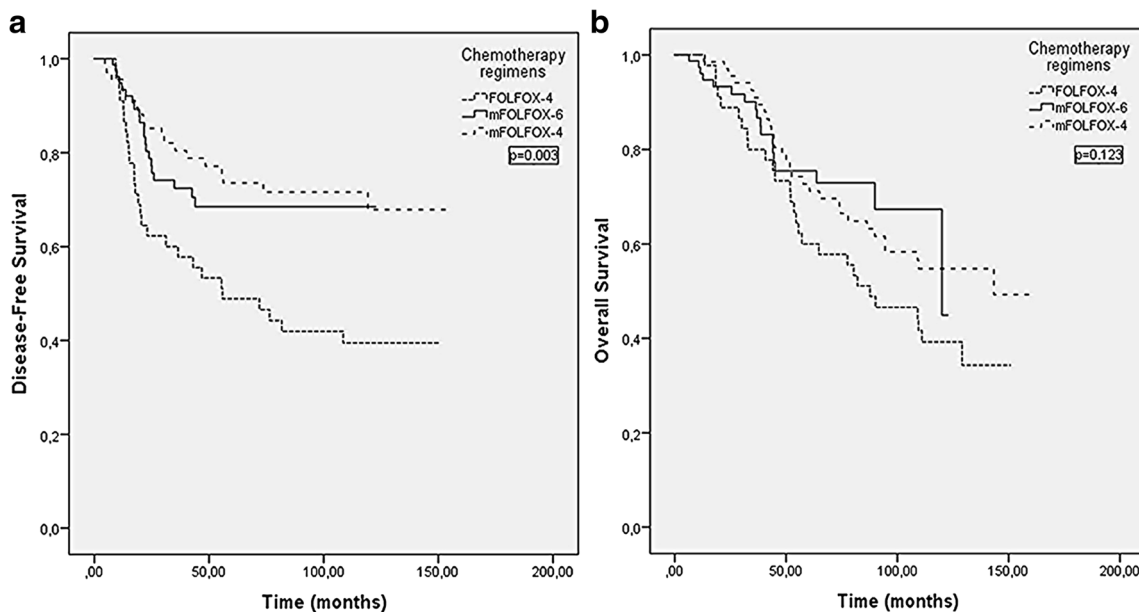


Fig. 3 Kaplan-Meier curve of disease-free survival (a) and overall survival (b) according to treatment groups for rectal cancer

Table 3 Multivariate analysis of the factors affecting disease-free survival and overall survival

Factors	Disease-free survival		Overall survival	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age	0.997 (0.985–1.010)	0.699	1.004 (0.991–1.018)	0.517
ECOG PS		0.023		0.016
ECOG 1 vs ECOG 0	0.383 (0.193–0.761)	0.006	0.375 (0.193–0.730)	0.004
ECOG 2 vs ECOG 0	0.438 (0.224–0.857)	0.016	0.430 (0.225–0.822)	0.011
T		0.005		0.021
T3 vs T2	0.418 (0.212–0.825)	0.012	0.398 (0.187–0.847)	0.017
T4 vs T2	0.616 (0.440–0.863)	0.005	0.684 (0.481–0.971)	0.034
N N1 vs N2	0.794 (0.598–1.055)	0.112		
Treatment		0.079		0.147
mFOLFOX-6 vs FOLFOX-4	1.344 (0.931–1.942)	0.115	0.776 (0.533–1.130)	0.186
mFOLFOX-4 vs FOLFOX-4	0.917 (0.632–1.331)	0.648	1.124 (0.791–1.596)	0.516

Data in bold indicates statistical significant results

FOLFOX 5-fluorouracil, leucovorin, and oxaliplatin; *mFOLFOX* modified 5-fluorouracil, leucovorin, and oxaliplatin; *ECOG PS* Eastern Cooperative Oncology Group performance status; *HR* hazard ratio; *CI* confidence interval

limitation is its retrospective nature. Also, even though certain prognostic factors were not evenly distributed, they are shown to not affect DFS and OS. Despite our limitations, our study is a large scale study that enough to separately evaluate these three different treatment arms in terms of efficiency and toxicity profile. In addition, due

to the administration challenges of standard FOLFOX-4 regimen, mFOLFOX-6, and mFOLFOX-4 regimens being easy to implement into daily practice, and both regimens proving non-inferior to the standard regimen with manageable toxicity profiles in this study, our research may provide a significant contribution to the literature.

Table 4 Toxicity profile of the treatment regimens

Toxicity	FOLFOX-4 (N = 133)		mFOLFOX-6 (N = 267)		mFOLFOX-4 (N = 170)		<i>p</i> -value
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	
Neutropenia							< 0.001
<i>N</i> (%)	30 (22.6)	71(53.4)	86 (32.2)	24 (9)	59 (34.7)	23(13.5)	
Anemia							0.063
<i>N</i> (%)	28 (21.1)	0	68(25.5)	1 (0.5)	57(33.5)	2 (1.2)	
Thrombocytopenia							0.030
<i>N</i> (%)	23 (17.3)	2 (1.5)	66(24.7)	7 (2.6)	23(13.5)	2 (1.2)	
Diarrhea							< 0.001
<i>N</i> (%)	18 (13.5)	14(10.5)	62(23.2)	6 (2.2)	18(10.6)	4 (2.4)	
Neuropathy							< 0.001
<i>N</i> (%)	27 (20.3)	4 (3)	100(37.5)	7 (2.6)	32(18.8)	8 (4.7)	
Nausea							0.011
<i>N</i> (%)	26 (19.5)	1 (0.8)	97 (36.3)	4 (1.5)	55(32.4)	1 (0.6)	
Vomiting							0.035
<i>N</i> (%)	15 (11.3)	1 (0.8)	64 (24)	2 (0.7)	42(24.7)	1 (0.6)	
Stomatitis							0.005
<i>N</i> (%)	15 (11.3)	4 (3)	48 (18)	1 (0.4)	18(10.6)	0	
Febrile neutropenia							0.210
<i>N</i> (%)	0	5 (3.8)	0	4 (1.5)	0	2 (1.2)	

Data in bold indicates statistical significant results

FOLFOX 5-fluorouracil, leucovorin, and oxaliplatin; *mFOLFOX* modified 5-fluorouracil, leucovorin, and oxaliplatin

In conclusion, three chemotherapy regimens with the same doses of oxaliplatin but different 5-FU administrations can be used in daily practice for the adjuvant treatment of stage III colon cancer with similar efficiency and manageable toxicity.

Declarations

Ethical approval The study was approved by the local Ethics Committee of Dicle University (Approval no: 147/2019) and conducted in accordance with the Helsinki Declaration and ethical principles.

Consent for publication All authors have approved the manuscript and consent for publication.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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