Original Article

# Assessing the Efficacy and Safety of Shorter versus Extended Adjuvant Treatment Duration for Stage III Low-Risk Colon Cancer: A Comparative Analysis

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**Abstract**

**Background:** In recent years, reducing adjuvant treatment period from 6 months to 3 months in low-risk stage 3 colon cancer has shown no decline in efficiency and fewer adverse effects, particularly neuropathy. **Aim:** We examined the efficacy and side effects of 3- and 6-month adjuvant chemotherapy regimens in low-risk stage 3 colon cancer patients. **Methods:** Twelve oncology centers retrospectively scanned operated, low-risk, stage 3 (T1-3, N1) colon cancer patients. Capecitabine and oxaliplatin (CAPOX) were given to all 3-month adjuvant chemotherapy patients, while 6-month patients received FOLFOX orCAPOX. Two adjuvant treatment groups compared DFS (disease-free survival) and side effects. **Results:** In total, 204 patients were included in our study and the patients' median age was 56 years. Regarding treatment duration, 40.6% of patients (n:83) were treated for 3 months and 59.4% (n:121) were treated for 6 months. The 24-month DFS was numerically high in the 6-month treatment arm, but the difference was not statistically significant (91% vs 84%, respectively; HR: 0.7 95 CI% 0.3–1.58, p: 0.38). During the treatment time, both in all grades (30% vs 54.5%) and in grade 3 (6% vs 15%), neuropathy was significantly higher in the 6-month treatment arm. After the end of the treatment, the average persistent neuropathy frequency after 12 months of follow-up was significantly higher in the 6-month treatment arm, and all of them were at grade 1–2 (12% vs 31%, respectively). **Conclusion:** In adjuvant treatment of low-risk stage 3 colon cancer, 3-month CAPOX and 6-month FOLFOX/CAPOX had similar 2-year DFS.The neuropathy was significantly lower in the 3-month treatment arm.

**Keywords:** *Adjuvant therapy, colon cancer, low risk, stage III*

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## Introduction

Among types of cancer, colon cancer ranks third in the world in terms of prevalence and second in terms of cancer-associated death.[1] Approximately 1/3 of patients present at stage 3 at the time of diagnosis.[2] Stage 3 colon cancer is divided into two groups by relapse risk in clinical practice, rather than in a single subgroup. Low-risk stage 3 colon cancer is defined as pT1, pT2 or pT3 and pN1 (≤ 3 positive nodes).[3] Fifty percent of patients with stage 3 colon cancer are only cured by surgery and the remaining 30% benefit from adjuvant chemotherapy, which is applied in addition to surgery. In the remaining 20%, adjuvant chemotherapy is not necessary because tumor recurrence will not occur.[4] Studies have shown that adjuvant chemotherapy improves survival and reduces recurrence in patients with stage 3 colon cancer.[5] Patients receiving adjuvant chemotherapy have approximately 7–10% improvement in disease-free survival (DFS) compared to patients not receiving chemotherapy.[6] Initial studies of adjuvant chemotherapy have shown that chemotherapy given as monotherapy (5-fluorouracil, levamisole) is more beneficial than patients who receive surgery alone.[7] The 2004 study MOSAIC found that the addition of oxaliplatin to 5 fluorouracil previously given as monotherapy in the adjuvant treatment of stage 3 colon cancer increased 5-year DFS from 67.5% to 73.2%. After this study, the FOLFOX regimen (folinic acid, fluorouracil, and oxaliplatin) was considered a standard treatment in the adjuvant treatment of stage 3 colon cancer.[8] The adjuvant chemotherapy regimen originally administered as FOLFOX 4 was replaced by the more manageable regimen, FOLFOX 6.[9] The subsequent NO169968 study showed that, with the combination of oxaliplatin with capecitabine, which is a form of oral 5 fluorouracil, the CAPOX regimen used for the treatment of stage 3 colon cancer had a similar effectiveness with the standard FOLFOX regimen. In particular, when using the FOLFOX regimen, a long-term infusion of 5-fluorouracil is required.[10] Infusion pump implantation is undesirable for some patients. However, the cumulative neuropathic effects of oxaliplatin, the indispensable component of these two treatments, on the nervous system represented the most troublesome side effect of adjuvant treatment. Although the recommended duration of adjuvant chemotherapy after surgery is 6 months, it is observed that most patients do not persist through this period due to side effects.[11] Adjuvant chemotherapy for colorectal cancer has been shown in some studies to have similar survival with short-term administration as with long-term administration.[12] In 2018, the pooled data analysis by the collaborative study called the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) changed the standard by showing that 3 months of CAPOX treatment was noninferior to 6 months of FOLFOX treatment, especially in patients with low-risk and stage 3 colon cancer.[13] While it is not desirable to expose patients to potential side effects of chemotherapy through long treatments, shorter treatment applications may be associated with an increased risk of relapse. Therefore, the toxicity must be well balanced with effectiveness. Given the current evidence on adjuvant treatment of low-risk stage 3 colon cancer, we aimed to compare the efficacy and side effects, particularly neuropathy, of 3-month and 6-month treatments in this multicenter retrospective study.

## Material and Method

A retrospective analysis was conducted on data from patients diagnosed with low-risk stage 3 colon cancer who underwent adjuvant chemotherapy between June 2008 and May 2022. These patients were referred to 12 different oncology centers in Turkey. Patients aged at least 18 years with histopathologically proven colon cancer, stage T1-3 and N1 according to TNM 8$^{th}$ Edition, ECOG (Eastern Cooperative Oncology Group) PS (Performance Score) 0-1, normal liver and kidney function tests and hemogram parameters, and treated with 3 months of CAPOX or 6 months of CAPOX/FOLFOX were included in the study. Patients with tumor deposits were classified as N1c. Patients who were not at stage 3, patients with neuropathy before treatment, patients receiving treatment other than FOLFOX or CAPOX, and patients with secondary cancer were excluded. Exclusion criteria of our study were presence of secondary malignancy, presence of multiple colon cancer, and patients receiving neoadjuvant chemotherapy. Adjuvant chemotherapy was started 4–8 weeks after surgery. Patients who were not in stage 3A, patients with neuropathy before treatment, patients who received adjuvant chemotherapy other than FOLFOX or CAPOX, and patients with a second cancer were excluded. Patients were followed up every 3 months for the first 2 years after surgery and every 6 months for the following 2–5 years. After the 5$^{th}$ year, annual follow-up was scheduled. Detailed history was observed, and physical examination and serological examination [blood routine, biochemical, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9)] were performed. Neuropathy side effects of patients were questioned at each control. Imaging studies [e.g. abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)/

CT] and colonoscopy were performed. The presence of recurrence or metastasis was confirmed by CT, MRI, CT, PET/CT, or pathology. Age, sex, comorbidity status, tumor location, pathologic features, type of surgery, adjuvant chemotherapy, duration, toxicity types, and grades were recorded from patient records. Tumor localization is divided into the right colon and left colon. The ascending colon and transverse colon are shown as the right colon, and the sigmoid colon and descending colon are shown as the left colon. The presence of diabetes, hypertension, and ischemic disease in the patients was accepted as the presence of additional disease. The duration of adjuvant chemotherapy administered to patients and the preferred chemotherapy regimen according to physician and patient preference were implemented as 3-month CAPOX or 6-month FOLFOX or CAPOX regimens. The CAPOX regimen was administered as follows: oxaliplatin 130 mg/m2 intravenously (IV), every 21 days, and oral capecitabine at a dose of 1000 mg per m2 of body surface area, every 12 hours, every 21 days, and twice daily from day 1 to day 14. The FOLFOX regimen is as follows: 85 mg/m2 oxaliplatin IV, and concurrent 400 mg/m2 leucovorin (LV) for more than 2 hours, followed by 5 FU 400 mg/m2 IV bolus and 46 hours 2400 mg/m2 IV 5-FU infusion, every 14 days. Peripheral neuropathy and other adverse events associated with chemotherapy were classified based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0). Neuropathy was graded as follows: Grade 0: no symptoms; Grade 1: subjective weakness, no objective findings; Grade 2: mild objective abnormality affecting functions but not daily activities; Grade 3: objective weakness with impairment of function; and Grade 4: paralysis. Ethic number E1-22-2367, Ethic date: 09.02.2022.

### Statistical analysis

The time between the date on which they received the treatments subject to analysis and relapse or death by any reason was calculated as DFS.

The statistical analysis was performed by using the Statistical Package for the Social Sciences Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparison of two groups was performed by the Mann–Whitney U test and Pearson Chi-square or Fisher test for continuous and categorical variables, respectively. DFS was analyzed with the log-rank test using the Kaplan–Meier method. $P < 0.05$ was taken to indicate statistical significance. The factors found significant in the univariate analysis were evaluated by the multivariate analysis. The Cox regression test was used for multivariate analysis.

## Results

A total of 204 patients were enrolled in our study, and the mean age was 56 years (24–81). While 118 (57.8%) of our patients were male, 86 (42.2%) were female. While 115 (56.3%) of our patients had an ECOG PS of 0, 89 (43.7%) had an ECOG PS of 1. Adjuvant CAPOX therapy was used in 83 (40.6%) patients for 3 months, while FOLFOX or CAPOX therapy was used in 121 (59.4%) patients for 6 months. Of the patients treated for 6 months, 62 (51.2%) received FOLFOX and 59 (48.8%) received CAPOX. While the tumor was located in the right colon in 66 (32.3%) of the patients, it was located in the left colon in 138 (67.7%) patients. While 40 (19.6%) of our patients underwent urgent surgery, 164 (81.4%) patients underwent elective surgery. Microsatellite instability (MSI) status was determined in 118 patients by immunohistochemical examination of pathologic surgical material. While 15 (7.3%) patients were MSI-H, 103 (50.4%) patients were CNS. All patients had pathological N1 lymph node involvement. Tumor budding was present in 48 (23.5%) patients. While 186 (91.1%) patients had pathologic T3 invasion, 14 (6.8%) patients had T2 invasion and only 4 (1.9%) patients had T1 invasion. While the tumor was poorly differentiated in 19 (9.3%) patients, it was wellto moderately differentiated in 185 (91.7%) patients. While perineural invasion was present in 83 (40.6%) patients, lymphatic invasion was present in 136 (66.6%) patients. The distribution of patient characteristics between the 3- and 6-month treatment groups was homogeneous, and there was no significant difference. Because 6-month adjuvant chemotherapy was administered to all patients with the mucinous adenocarcinoma subtype, these patients were excluded to avoid bias. Baseline patient characteristics are shown in Table 1.

The median follow-up time in our study was 18.3 months. The 12-month DFS was 96% in the

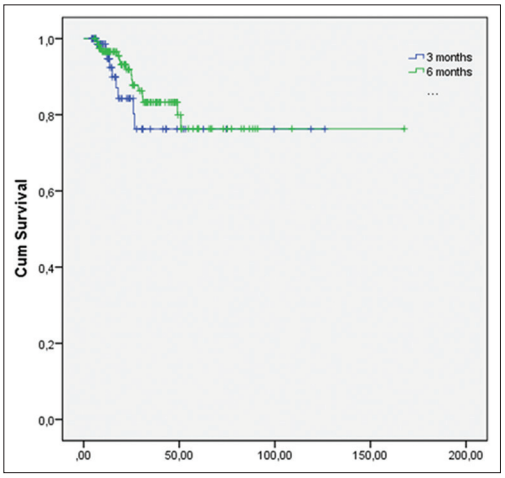


**Figure 1:** Disease free survival

**Table 1: Baseline characteristics of patients receiving adjuvant therapy for stage-3 colon cancer**

| Characteristic | 3 months *n*: 83 (%) | 6 months *n*: 121 (%) | *P* |
|---|---|---|---|
| Sex | | | 0.998 |
| Male | 48 (57.8%) | 70 (57.8%) | |
| Female | 35 (42.2%) | 51 (42.2%) | |
| Age (yr) | | | |
| Median | 54 | 56 | |
| Range | 24-81 | 34-80 | |
| ECOG performance score (%)* | | | 0.276 |
| 0 | 43 (51.8%) | 72 (59.5%) | |
| 1 | 40 (48.2%) | 49 (40.5%) | |
| Lymphovascular invasion | | | 0.614 |
| Present | 57 (68.6%) | 79 (65.2%) | |
| None | 26 (31.4%) | 42 (34.8%) | |
| pTumor stage (%)* | | | 0.222 |
| T1 | 0 (0%) | 4 (3%) | |
| T2 | 5 (6%) | 9 (7%) | |
| T3 | 78 (94%) | 108 (90%) | |
| MSI | | | 0.842 |
| MSI-H | 6 (12%) | 9 (13.2%) | |
| MSS | 44 (88%) | 59 (86.8%) | |
| Tumor Deposits | | | 0.079 |
| Present | 28 (54.9%) | 20 (37.7%) | |
| None | 23 (45.1%) | 33 (62.3%) | |
| Comorbidity | | | 0.422 |
| Present | 29 (34.9%) | 49 (40.4%) | |
| None | 54 (65.1%) | 72 (59.6%) | |
| Perineural Invasion | | | 0.608 |
| Present | 32 (38.5%) | 51 (42.1%) | |
| None | 51 (61.5%) | 70 (57.9%) | |
| Differentiation | | | 0.396 |
| Well-Moderate | 77 (92.7%) | 108 (89.2%) | |
| Poor | 6 (7.3%) | 13 (11.8%) | |
| Tumor Localization | | | 0.240 |
| Right | 23 (27.7%) | 43 (35.6%) | |
| Left | 60 (72.3%) | 78 (64.4%) | |
| Type of Surgery | | | 0.536 |
| Urgent | 18 (21.7%) | 22 (18.2%) | |
| Elective | 65 (78.3%) | 99 (81.8%) | |
| Diabetes Mellitus | | | 0.221 |
| Present | 11 (14.3%) | 24 (19.9%) | |
| None | 72 (86.7%) | 97 (80.1%) | |
| Hypertension | | | 0.268 |
| Present | 17 (20.5%) | 33 (27.3%) | |
| None | 66 (79.5%) | 88 (72.7%) | |
| Ischemic Heart Disease | | | 0.871 |
| Present | 7 (9.5%) | 11 (10%) | |
| None | 76 (91.5%) | 110 (90%) | |

ECOG=Eastern Cooperative Oncology Group, MSI=Microsatellite Instability

6-month treatment group, whereas it was 94% in the 3-month treatment group. The 24-month DFS was numerically higher in the 6-month treatment group, but the difference was not statistically significant. (91% and 84%, respectively; HR: 0.7 95 CI% 0.3–1.58, p: 0.38). The survival curve indicating the 24-month DFS outcomes of patients is shown in Figure 1.

Overall survival could not be calculated due to the short follow-up time of the patien. The most common treatment-related adverse event was anemia (34.9%) in the 3-month treatment group, whereas the anemia rate was 64.9% in the 6-month treatment group. Neutropenic fever or hepatotoxicity did not occur in any patients in the 3-month treatment group. The development of treatment-related neuropathies was compared on the basis of the presence of neuropathies both during treatment and during the 12-month treatment follow-up period. During the treatment period, neuropathies occurred significantly more frequently in both all grades (30% vs 54.5%) and grade 3 (6% vs 15%) in the 6-month treatment arm. After treatment completion, the mean incidence of persistent neuropathy at 12-month follow-up was significantly higher in the 6-month treatment group, and all were grade 1–2 (12% vs 31%). The comparison for toxicities other than neuropathy during treatment showed that vomiting (8.3% vs 20.3%) and hepatotoxicity (0% vs 7.3%) were significantly more frequent in the 6-month treatment group. From the point of view of grade 3–4 severe toxicities, thrombocytopenia was more frequent in the 6-month treatment group (0% vs 3.6%). No death due to treatment-related adverse events was observed during our study. Selected adverse events depending on the treatment regimen and duration are listed in Table 2.

## Discussion

In our retrospective multicenter study, we reported the efficacy and side effect results of the adjuvant 3-month treatment group (CAPOX) and the 6-month treatment group (FOLFOX/CAPOX) in low-risk stage 3 colon cancer patients. Although there was a numerical difference in 2-year DFS results between the 3-month treatment group and the 6-month treatment group of adjuvant treatment, there was no statistical difference, 84% versus 91%, respectively, HR: 0.7, 95% CI 0.3–1.58, p: 0.38).

The most important study on the shortened adjuvant treatment period in colon cancer is the IDEA study, in which 6 randomized studies (TOSCA, IDEA, CALGB, HORG, ACHIEVE, SCOT) were included and tried to determine the duration of adjuvant treatment. In this study, results comparing DFS between 3-month

**Table 2: Selected adverse events, according to treatment and duration of therapy in stage-3 colon cancer**

| Toxicity | All Grades of Events | | *P* | Grade 3 Events (Severe) | | *P* |
|---|---|---|---|---|---|---|
| | 3 months (%) | 6 months (%) | | 3months (%) | 6 months (%) | |
| Diarrhea | 10 (12%) | 20 (%16.5) | 0.37 | 2 (2.4%) | 2 (1.7%) | 0.70 |
| Nausea | 28 (33.7%) | 28 (23.1%) | 0.09 | 0 | 2 (1.2%) | 0.23 |
| Vomiting | 10 (8.3%) | 17 (20.5%) | 0.01 | 0 | 0 | |
| Mucositis | 9 (10.8) | 17 (14.0%) | 0.50 | 0 | 1 (0.8%) | 0.40 |
| Neuropathy | 25 (30%) | 66 (54.5%) | 0.001 | 5 (6%) | 19 (15%) | 0.03 |
| Hand–foot syndrome | 13 (10.7%) | 7 (8.4%) | 0.58 | 0 | 0 | |
| Anemia | 26 (35.1%) | 48 (64.9%) | 0.22 | 0 | 1 (1.2%) | 0.22 |
| Neutropenia | 16 (19.3%) | 30 (24.8%) | 0.35 | 4 (3.3%) | 6 (7.2%) | 0.20 |
| Febrile neutropenia | 0 | 1 (0.8%) | 0.40 | | | |
| Thrombocytopenia | 12 (14.5%) | 29 (24%) | 0.09 | 0 | 3 (3.6%) | 0.03 |
| Rash | 1 (1.2%) | 5 (4.1%) | 0.22 | 0 | 1 (0.8%) | 0.40 |
| Fatigue or asthenia | 29 (34.9%) | 38 (31.4%) | 0.59 | 1 (1.2%) | 4 (3.3%) | 0.34 |
| Hepatotoxicity | 0 | 9 (7.4%) | 0.01 | 0 | 1 (0.8%) | 0.40 |

and 6-month treatments in adjuvant treatment of stage 3 colon cancer have been shown to vary depending on risk groups and chemotherapy regimen given. The primary endpoint of the IDEA study was the DFS rate at 3 years. This study was multicenter and prospectively designed with a large number of patients. In the comparison of the efficacy of 3-month adjuvant therapy with 6-month adjuvant therapy, a noninferior margin was determined to reach a clinically meaningful result. IDEA team members agreed that a noninferior margin of 1.12 was acceptable. This margin had a 95% confidence interval for 3-year DFS. If the two-sided 95% confidence interval for the hazard ratio does not go above 1.12, then 3-month adjuvant therapy is just as effective as 6-month adjuvant therapy. In the IDEA study, "non-inferiority" means that the 3-month adjuvant treatment is not worse or less effective than the 6-month adjuvant treatment. The IDEA study compared the effectiveness of 3-month CAPOX and 6-month CAPOX treatments in patients with stage 3 low-risk colon cancer. The results showed that both treatment durations had similar efficacy, with a 3-year DFS rate of 85% in the 3-month CAPOX group and 83.1% in the 6-month group. However, in the subgroup of stage 3 low-risk colon cancer, 3-year DFS was 81.9% with 3-month adjuvant FOLFOX treatment, compared to 83.5% with 6-month adjuvant FOLFOX treatment. The efficacy of adjuvant 3-month folfox treatment was inferior to that of 6-month folfox treatment.[14] The results indicated that both the duration of chemotherapy and the specific chemotherapy regimen used were significant factors for noninferiority. Since 3-month FOLFOX treatment was found to be inferior in the IDEA study, we included only patients who received CAPOX for 3-months in our study. Patients who received FOLFOX during the 3-month adjuvant treatment phase were excluded from our study. In the IDEA study, the follow-up period was longer than in our study. Consistent with these studies, our study demonstrated statistically comparable rates of DFS.

However, in our study, it was observed that the survival curves were different, especially in the early years, but converged later. Although the difference was not statistically significant, there was a 7% difference in the 2-year DFS in favor of the 6-month group. It is well known that the efficacy of adjuvant chemotherapy is more pronounced in the early years. This situation means that the 6-month treatment duration has a greater impact on delaying recurrences during the initial years. Indeed, in the ACCENT/IDEA study, which evaluated 11 adjuvant trials together, it was observed that early discontinuation of oxaliplatin and completion of treatment with 5fu/capecitabine for 6 months made no difference in survival in high-risk stage 3 patients.[15] As a result of these studies, ınstead of continuing the CAPOX/FOLFOX treatment for the entire 6-month treatment period, an alternative option could be to stop using oxaliplatin after 3 months of combination therapy and complete the remaining 3 months of adjuvant therapy with capecitabine/5-FU as a single agent. Upon analysing our survival curves, we believe that this approach could potentially be considered for patients with a low risk profile. Regarding the development of neuropathy adverse events in the IDEA study, it was higher in the 6-month treatment group than in the 3-month treatment group (46% and 16%, respectively).[14] However, among the neuropathies mentioned in the IDEA study, there were no grade 1 neuropathies. The inclusion of grade 1 neuropathies in our study may be the reason why the adverse event neuropathy was higher than IDEA.

In the MASCOT study, a trial to measure the safety of the FOLFOX regimen as adjuvant therapy particularly in Asian populations, peripheral sensorineural neuropathies grade ≥1 adverse events were 86%, and grade ≥3 adverse events were 5.7%.[10] In the MOSAIC study, peripheral sensorineural neuropathy due to FOLFOX regimen grade ≥1 neuropathies was 92%, and grade ≥3 adverse events were 12%.[16]

Examining these studies in the literature, we find that both the frequency and magnitude of neuropathy side effects vary widely. In our study, neuropathies occurred more frequently in the 6-month treatment group than in the 3-month treatment group (grade ≥1 (54.5% vs 30%), grade 3 (15% vs 6%), respectively). The rates of peripheral neuropathy at follow-up were 31% in the 6-month treatment group and 12% in the 3-month treatment group, which had a lower rate. Oxaliplatin neurotoxicity is cumulative, peaking particularly months after the last oxaliplatin exposure. In some patients, symptoms may persist for 1–3 years or for life after completion of treatment.[17] This makes it difficult to empirically individualize the dose. These toxic effects can sometimes be severe and persistent. This toxicity, beyond adjuvant treatment, affects the daily living activities of patients on this treatment, which they receive for disease that is unlikely to return for the rest of their lives. Consideration is being given to reducing the cumulative neurotoxic side effects of oxaliplatin by using these treatments with similar efficacy over a shorter period of time. The development of side effects other than neuropathy (hepatotoxicity, vomiting) was observed less in patients receiving the 3-month CAPOX regimen, as expected. Our main limitations were the retrospective nature of our study and the relatively small number of patients. Another limitation was the short follow-up period. The progression of the survival curves will be seen with a longer follow-up period.

## Conclusion

In our study of adjuvant treatment for low-risk stage 3 colon cancer, we found no statistically significant difference in 2-year DFS between 3-month CAPOX and 6-month FOLFOX/CAPOX. Persistent neuropathy both during and after treatment was more common in the 6-month treatment group. These data suggest that longer oxaliplatin-based therapy does not provide an advantage in efficacy, especially against the increased risk of toxicity, including persistent neurotoxicity. Considering the limitations of our study (retrospective study design, short median follow-up period), it is difficult to make a complete judgement about the optimal duration of adjuvant chemotherapy.

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### Conflicts of interest

There are no conflicts of interest.

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