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Survival Patterns in Early-onset Colorectal Cancer Receiving Adjuvant Capecitabine Based Therapy

Oğuzcan ÖZKAN[1], Aslı GEÇGEL[1], Zeynep Sıla GÖKDERE[1], Barış EMEKDAŞ[2], Hasan Çağrı YILDIRIM[1]

[1]Ege University Faculty of Medicine, Department of Medical Oncology, İzmir, Türkiye
[2]Ege University Faculty of Medicine, Department of Gastroenterology, İzmir, Türkiye

ABSTRACT

Objective: The incidence of early-onset colorectal cancer (EOCRC) is increasing worldwide, yet optimal adjuvant treatment strategies remain unclear. This study evaluated survival outcomes and prognostic factors in EOCRC patients treated with adjuvant capecitabine-based chemotherapy.

Material and Methods: This retrospective study included 51 patients aged younger than 50 years with high-risk stage II or stage III colorectal cancer who underwent curative surgery followed by capecitabine-based adjuvant therapy between 2017 and 2021. Overall survival (OS) and recurrence-free survival (RFS) were analyzed using Kaplan-Meier curves and Cox regression models.

Results: The median follow-up was 32 months. Stage III patients had significantly poorer OS and RFS than those of Stage II patients ($p<0.05$). In multivariate analysis, recurrence was the only independent predictor of OS [hazard ratio (HR)=12.45, p=0.002]. For RFS, nodal status remained an independent prognostic factor (HR=0.032, p=0.006). Among stage II patients, the XELOX regimen was associated with a significantly different recurrence risk compared to capecitabine monotherapy (HR=14.87, p=0.038).

Conclusion: In EOCRC, stage and nodal status are key prognostic determinants. Adjuvant therapy should be tailored to pathological risk rather than age alone, as XELOX may offer a recurrence benefit in selected stage II patients, whereas routine treatment intensification risks avoidable toxicity.

Keywords: Carly-onset colorectal cancer; adjuvant chemotherapy; capecitabine; survival analysis; prognostic factors; recurrence-free survival

INTRODUCTION

Colorectal cancer (CRC) is still a serious worldwide health issue, and in recent years a noticeable rise has been observed particularly among individuals younger than 50, a group classified as early-onset colorectal cancer (EOCRC).[1-4] Unlike late-onset CRC, EOCRC often presents with more advanced disease, distinct molecular profiles, and delays in diagnosis, as routine screening is not recommended for average-risk individuals younger than 50 years.[5-7]

While inherited conditions, such as Lynch syndrome and familial adenomatous polyposis, account for a subset of cases, most EOCRCs occur sporadically and are associated with lifestyle and metabolic factors, including obesity, diet, physical inactivity, and alterations in the gut microbiome.[8-11]

For individuals with high-risk stage II or stage III CRC, the recommended standard treatment involves adjuvant chemotherapy (ACT) based on fluoropyrimidines.[12,13] Younger patients are more frequently treated with multi-agent regimens such as capecitabine plus oxaliplatin (XELOX) and often receive higher cumulative doses and more intensive therapy than older patients.[13,14] However, evidence regarding the survival benefit of aggressive adjuvant therapy in EOCRC remains inconsistent. Several studies suggest that younger age is associated with higher recurrence rates, which may reflect more aggressive tumor biology, yet the benefit of intensified adjuvant therapy in low-risk stage II disease is unclear, and intensified adjuvant therapy may increase the risk of long-term treatment-related toxicity.[15-17]

Correspondence: Oğuzcan ÖZKAN MD,
Ege University Faculty of Medicine, Department of Medical Oncology, İzmir, Türkiye
E-mail: droguzcanozkan@yahoo.com
ORCID ID: orcid.org/0000-0002-4075-7775

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Given the rising incidence of EOCRC and ongoing uncertainty regarding optimal adjuvant treatment strategies, evaluating real-world treatment patterns and survival outcomes in this population is of clinical importance. This study aimed to investigate overall survival (OS), recurrence-free survival (RFS) and prognostic factors among patients with EOCRC who received capecitabine-based ACT following curative resection.

MATERIAL AND METHODS

Study Design and Patient Selection

Patients with high-risk stage II or stage III CRC who underwent curative surgical resection and received adjuvant capecitabine-based chemotherapy at our institution between January 2017 and December 2021 were included in this retrospective cohort analysis. Of the 190 eligible patients, 51 (26.8%) were younger than 50 years and were categorized as EOCRC. Patients were excluded if they (i) received adjuvant 5-fluorouracil-based regimens instead of capecitabine, (ii) had insufficient clinical or pathological data, or (iii) had evidence of metastatic disease at diagnosis. Clinical, pathological, and treatment-related data were obtained from electronic medical records.

Follow-up and Outcome Measures

The follow-up period was measured starting from the date of surgery. RFS was defined as the interval from surgery to the first documented radiologic or clinical recurrence, whereas OS was defined as the interval from surgery to death from any cause. Patients who did not experience an event were censored at their most recent follow-up, which extended through September 2025.

The authors state that they have obtained Ege University Medical Research Ethics Committee approval (date: 06.11.2025, approval number: 25-11T/76).

Statistical Analysis

Patient characteristics were summarized using descriptive statistics. Kaplan-Meier (KM) curves and log-rank tests were used for survival analysis, while Cox regression (CRA) was used to identify prognostic markers. Analyses were performed using SPSS v22; $p<0.05$ was considered statistically significant.

RESULTS

A total of 190 patients were screened, of whom 51 (26.8%) were identified as having EOCRC, defined as a diagnosis before the age of 50. The mean age at diagnosis in this cohort was 40.3±7.8 years, and the median age was 44 years [interquartile range (IQR) 35.5-46.0]. Of the included patients, 34 (66.7%) were male and 17 (33.3%) were female.

Regarding disease stage, 26 patients (51.0%) had stage II disease and 25 (49.0%) had stage III disease. Most tumors were classified as pT3-T4 at diagnosis, and nodal status was predominantly N0-N1. The median follow-up duration was 32 months (IQR, 24-45 months). Detailed clinicopathological characteristics of the study population are presented in Table 1.

A significant difference in gender distribution was observed between stage II and stage III patients ($p=0.022$); males were more common in stage III. The XELOX regimen was also used more frequently in stage III patients ($p=0.006$). No significant differences were found between the groups regarding pT stage, nodal status, histological grade, lymphovascular invasion (LVI), perineural invasion (PNI), microsatellite instability (MSI), mucinous component, or tumor localization ($p>0.05$ for all). Comparative clinicopathological data of patients with stage II and stage III disease are presented in Supplementary Table 1.

No significant association was observed between age at diagnosis and disease stage ($p=0.492$). In contrast, multiple clinicopathological variables, including sex, primary tumor (pT) stage, nodal status, tumor budding, tumor-infiltrating lymphocytes (TIL), histological grade, LVI, PNI, MSI status, mucinous histology, and human epidermal growth factor receptor 2 expression, showed significant associations with disease stage. In addition, recurrence status, number of metastatic sites, peritoneal involvement, baseline carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 levels, and adjuvant treatment regimen and duration were significantly associated with stage at diagnosis. These associations, evaluated using the chi-square test, are summarized in Table 2.

In the KM analysis, median OS was not reached for stage II patients, whereas it was 80.6 months for stage III patients. The difference in OS between the two groups was statistically significant (log-rank $p<0.05$). The estimated 2- and 5-year OS rates were 95% and 88%, respectively, in the stage II group, compared with 82% and 65% in the stage III group. KM OS curves by stage at diagnosis in patients with EOCRC receiving adjuvant capecitabine-based therapy are shown in Figure 1.

The median RFS was 95.2 months [95% confidence interval (CI): 85.8-104.5] in stage II patients and 70.4 months (95% CI: 51.2-89.7) in those with stage III disease. This difference was statistically significant (log-rank $p=0.005$), indicating that stage at diagnosis is an important prognostic factor for RFS. Based on KM estimates, the 2- and 5-year RFS rates were 92.0% and 82.5% for stage II patients and 83.8% and 63.4% for stage III patients, respectively. These findings demonstrate significantly better short- and long-term recurrence outcomes among patients with stage II disease. KM RFS curves stratified by stage at diagnosis in patients with

TABLE 1: Demographic and clinicopathological characteristics of patients at diagnosis.			
Variable	**Category**	**n**	**%**
Sex	Male	34	64.2%
	Female	17	32.1%
Stage at diagnosis	Stage II	26	49.1%
	Stage III	25	47.2%
pT	1	1	3.6%
	2	1	3.6%
	3	33	60.0%
	4	15	27.3%
pN	0	26	49.1%
	1	18	34.0%
	2	7	13.2%
Tumor budding	No	38	74.5%
	Yes	13	24.5%
TIL	No	41	80.3%
	Yes	3	19.7%
Positive surgical margin	No	50	98.1%
	Yes	1	1.9%
Grade	2	31	60.8%
	3	13	25.5%
	1	4	7.8%
LVI	0	31	63.3%
	1	16	32.7%
PNI	0	32	65.3%
	1	15	30.6%
MSI	Low	18	54.5%
	High	13	39.4%
Mucinous component	No	44	83.0%
	Yes	7	13.2%
Localization	Left	20	36.4%
	Rectum	14	25.5%
	Right	12	21.8%
	Multifocal	5	9.1%
Local therapies	No	42	79.2%
	Yes	9	17.0%
Recurrence	No	39	76.5%
	Yes	12	23.5%
Peritoneal carcinomatosis	No	48	90.6%
	Yes	3	5.7%
Baseline CEA	<5	41	77.4%
	>5	10	18.9%
Baseline CA19-9	<27	45	84.9%
	>27	6	11.3%

LVI: Lymphovascular invasion; PNI: Perineural invasion; MSI: Microsatellite instability; TIL: Tumor-infiltrating lymphocytes; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

TABLE 2: Association between stage at diagnosis and clinicopathological variables.

Variable	P-value
Age	0.492
Sex	<0.001
pT	<0.001
N0	<0.001
Budding	<0.001
TIL	<0.001
Surgical margin	<0.001
Grade	<0.001
LVI	<0.001
PNI	<0.001
MSI	<0.001
Mucinous component	<0.001
HER2	<0.001
Localization	<0.001
Adjuvant therapy regimen	<0.001
Adjuvant therapy duration	<0.001
Recurrence (Yes/No)	0.007
Metastatic site number	0.028
Peritoneal carcinomatosis	<0.001
Baseline CEA	<0.001
Baseline CA19-9	<0.001
Local therapies	<0.001

Comparisons were performed using the chi-square test. LVI: Lymphovascular invasion; PNI: Perineural invasion; MSI: Microsatellite instability; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9. P<0.05 was considered statistically significant.

EOCRC receiving adjuvant capecitabine-based therapy are presented in Figure 2.

In the univariate (UV) CRA for RFS, nodal status and baseline CEA levels emerged as significant prognostic factors. Patients with node-negative disease (N0) had a significantly lower recurrence risk [hazard ratio (HR)=0.076, 95% CI: 0.015-0.393; p=0.002], whereas elevated baseline CEA was associated with an increased recurrence risk (HR=5.192, 95% CI: 1.727-15.606; p=0.003). Higher pT stage (p=0.073) and node-positive disease (N+, p=0.087) showed borderline associations. Other clinicopathological variables, including age, sex, tumor grade, tumor budding, TIL, LVI, PNI, MSI status, mucinous histology, adjuvant regimen, and use of local therapies, were not significantly associated with RFS.

Variables with p<0.10 in the UV analysis (pT stage, nodal status, and baseline CEA), along with clinically relevant factors from the literature (MSI and LVI), were included in the multivariate (MV) model. In MV analysis, nodal status remained the only independent prognostic factor for RFS, with N0 status retaining its protective effect (HR=0.032; 95% CI, 0.003-0.371; p=0.006). Elevated baseline CEA (HR=4.418, 95% CI: 0.824-23.684, p=0.083) and MSI-high status (HR=0.193, 95% CI: 0.036-1.036, p=0.055) were of borderline statistical significance. pT stage, disease stage, and adjuvant regimen were not significant predictors in the adjusted model. The UV and MV CRA for RFS are shown in Table 3.

In the UV CRA for OS, the following were identified as significant prognostic factors: stage at diagnosis (HR=5.68, 95% CI: 1.24-26.1, p=0.025), nodal involvement (HR=2.45, 95%

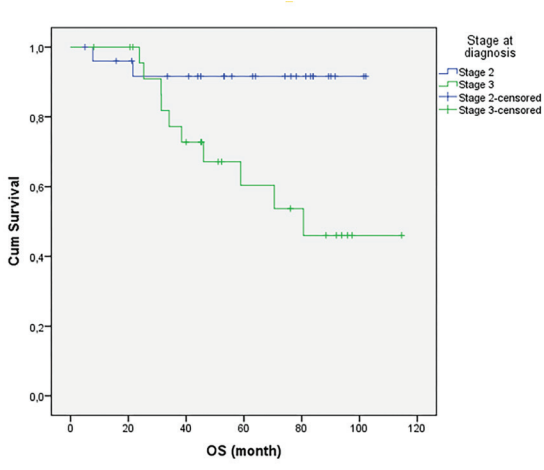

FIGURE 1: Kaplan-Meier OS curves according to stage at diagnosis in patients with EOCRC receiving adjuvant capecitabine-based therapy. Median OS was not reached in stage II patients, whereas it was 80.6 months in stage III patients. The difference between the groups was statistically significant (log-rank test, p<0.05).

EOCRC: Early-onset colorectal cancer; OS: Overall survival

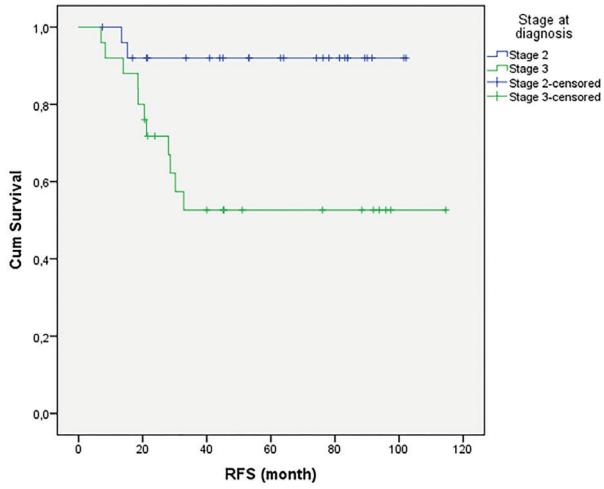

FIGURE 2: Kaplan-Meier RFS curves according to stage at diagnosis in patients with EOCRC receiving adjuvant capecitabine-based therapy. Stage II patients had a significantly longer RFS than stage III patients (median RFS: 95.2 vs. 70.4 months; log-rank p=0.005).

EOCRC: Early-onset colorectal cancer; RFS: Recurrence-free survival

CI: 1.17-5.15, p=0.018), presence of recurrence (HR=14.56, 95% CI: 3.72-57.0, p<0.001), and elevated baseline CEA at the time of metastasis (HR=3.19, 95% CI: 1.01-10.1, p=0.048). Other clinicopathological variables, including pT stage, tumor grade, LVI, PNI, MSI, mucinous histology, tumor localization, duration of adjuvant therapy, and TIL were not significantly associated with OS.

In the MV CRA, only the presence of recurrence remained an independent predictor of poorer OS (HR=12.45; 95% CI: 2.51-61.7; p=0.002). Stage at diagnosis, nodal involvement, and baseline CEA did not retain statistical significance after adjustment. These findings suggest that the limited number of survival events and potential intercorrelations between variables may have reduced the statistical power of the MV model. Table 4 shows the results of UV and MV CRA for the OS prognostic variables in EOCRC patients undergoing adjuvant capecitabine-based treatment.

When RFS was evaluated according to the adjuvant treatment regimen among stage II patients, the median RFS was 65.1 months (95% CI: 49.9-80.3) in the XELOX group and 69.0 months (95% CI: 46.0-91.9) in the capecitabine group, with no statistically significant difference (log-rank p=0.562). KM RFS curves by adjuvant treatment regimen (XELOX vs. capecitabine monotherapy) among patients with stage II EOCRC are shown in Figure 3.

In UV CRA, the type of adjuvant therapy did not show a significant association with RFS. Similarly, pT stage, lymphovascular invasion, tumor budding, mucinous histology, and nodal status were not significant predictors. However, MSI-high status (HR=0.24, 95% CI: 0.05-1.19, p=0.080) and N1 status (HR=0.17, 95% CI: 0.03-1.05, p=0.056) demonstrated borderline associations, suggesting potential prognostic relevance.

In the MV CRA, which included adjuvant therapy type, nodal status, and MSI due to clinical relevance and near-significant UV effects, the model was statistically significant overall (χ^2=11.221, p=0.024). Adjuvant therapy type emerged as an independent prognostic factor for RFS, with patients receiving capecitabine monotherapy having a significantly higher risk of recurrence compared to those receiving XELOX (HR=14.87, 95% CI: 1.16-191.39, p=0.038). Nodal status also retained independent prognostic significance, with N0 disease associated with a reduced recurrence risk (HR=0.065, 95% CI: 0.005-0.782, p=0.031). MSI-high status did not reach statistical significance in the adjusted model. UV and MV CRA of prognostic factors for RFS in stage II EOCRC patients are provided in Table 5.

TABLE 3: Univariate and multivariate Cox regression analyses for RFS.

Variable	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age at diagnosis	1.007 (0.937-1.083)	0.843	-	-
Gender	1.116 (0.344-3.628)	0.855	-	-
Stage at diagnosis	0.439 (0.135-1.424)	0.170	1.561 (0.320-7.609)	0.581
pT	2.586 (0.914-7.314)	0.073	0.851 (0.267-2.707)	0.784
Nodal status (overall)	-	0.008	-	0.022
N0	0.076 (0.015-0.393)	0.002	0.032 (0.003-0.371)	0.006
N+	0.353 (0.107-1.162)	0.087	0.363 (0.078-1.691)	0.197
Tumor budding	1.395 (0.604-3.221)	0.435	-	-
TIL	1.259 (0.111-14.251)	0.853	-	-
Grade	0.666 (0.268-1.655)	0.381	-	-
LVI	1.073 (0.351-3.281)	0.902	-	-
PNI	1.266 (0.414-3.871)	0.679	-	-
MSI	0.393 (0.103-1.497)	0.171	0.193 (0.036-1.036)	0.055
Mucinous component	2.450 (0.673-8.916)	0.174	-	-
Localization	- (unstable model)	0.842	-	-
Adjuvant therapy	1.455 (0.476-4.449)	0.511	3.548 (0.704-17.877)	0.125
Local therapies	0.356 (0.050-2.940)	0.356	-	-
Baseline CEA	5.192 (1.727-15.606)	0.003	4.418 (0.824-23.684)	0.083

Variables with p<0.10 in univariate analysis and those considered clinically relevant were included in the multivariate model. HR: Hazard ratio; CI: Confidence interval; LVI: Lymphovascular invasion; PNI: Perineural invasion; MSI: Microsatellite instability; TIL: Tumor-infiltrating lymphocytes; CEA: Carcinoembryonic antigen; RFS: Recurrence-free survival. P<0.05 was considered statistically significant.

TABLE 4: Univariate and multivariate Cox regression analysis of prognostic factors for OS in patients with EOCRC receiving adjuvant capecitabine-based therapy.

Variable	P-value (univariate)	OS HR (univariate)	95% CI (min-max)	P-value (multivariate)	OS HR (multivariate)	95% CI (min-max)
Stage at diagnosis	0.025	5.684	1.242-26.022	0.560	2.123	0.182-24.77
pT	0.813	1.122	0.434-2.903	-	-	-
N0	0.018	2.453	1.164-5.164	0.884	0.898	0.217-3.70
TIL	0.950	1.080	0.096-12.177	-	-	-
Grade	0.672	0.818	0.322-2.075	-	-	-
LVI	0.860	1.109	0.351-3.503	-	-	-
PNI	0.564	1.402	0.445-4.422	-	-	-
MSI	0.123	0.289	0.060-1.396	0.476	0.554	0.121-2.54
Mucinous component	0.282	2.051	0.554-7.593	-	-	-
Localization	0.286	0.555	0.188-1.637	-	-	-
Duration of adjuvant therapy	0.242	2.184	0.591-8.071	-	-	-
Recurrence	<0.001	14.558	3.802-55.735	0.002	12.451	2.51-61.7
Baseline CEA1 at metastasis	0.048	3.190	1.012-10.060	0.683	0.762	0.205-2.83

Variables with p<0.10 in univariate analysis and those considered clinically relevant were included in the multivariate model. OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; LVI: Lymphovascular invasion; PNI: Perineural invasion; MSI: Microsatellite instability; TIL: Tumor-infiltrating lymphocytes; CEA: Carcinoembryonic antigen; min-max: Minimum-maximum; EOCRC: Early-onset colorectal cancer. P<0.05 was considered statistically significant.

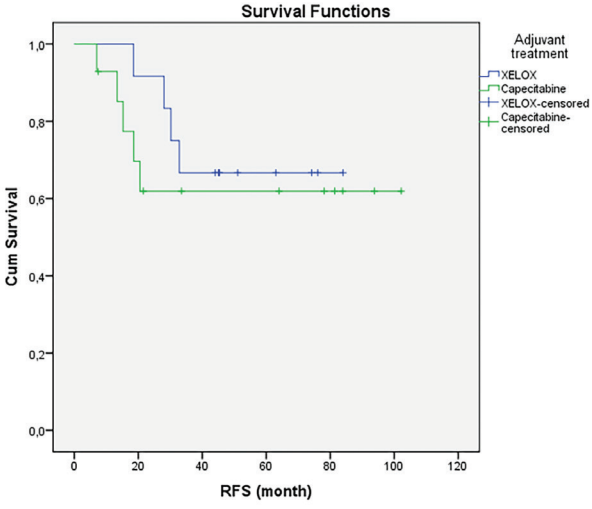

FIGURE 3: Kaplan-Meier RFS curves according to adjuvant treatment regimen (XELOX vs. capecitabine monotherapy) in stage II EOCRC patients. The XELOX regimen was associated with a significantly higher risk of recurrence compared to capecitabine alone (multivariate HR=14.87, p=0.038).

EOCRC: Early-onset colorectal cancer; RFS: Recurrence-free survival; HR: Hazard ratio

DISCUSSION

CRC continues to increase in prevalence among younger adults, and these patients are more likely to receive intensive ACT compared with older individuals. However, relying on age alone when making adjuvant therapy decisions may lead to overtreatment and unnecessary long-term toxicities. In a recent pooled analysis of six randomized trials from the IDEA collaboration, EOCRC patients demonstrated higher adherence to ACT, yet high-risk stage III (T4/N2) EOCRC patients had significantly lower 3-year RFS compared with older patients (54% vs. 64%, p<0.01), and younger age was identified as an independent adverse prognostic factor, supporting the concept of more aggressive tumor biology in EOCRC.[18]

Consistent with these findings, our study showed that patients with stage III EOCRC had significantly lower OS and RFS rates than those with stage II disease; nodal involvement emerged as an independent adverse prognostic factor. Similarly, a large cohort study evaluating the benefit of ACT in stage II EOCRC reported no significant survival advantage in most patients. Data from the XJCRC and SEER cohorts (n>3.500) showed no meaningful improvement in OS with adjuvant therapy

TABLE 5: Univariate and multivariate Cox regression analysis of prognostic factors for RFS in stage II EOCRC patients.

Variable	Univariate HR	Univariate 95% CI	P-value univariate	Multivariate HR	Multivariate 95% CI	P-value multivariate
Adjuvant treatment (XELOX vs. capecitabine)	1.474	0.394-5.517	0.564	14.873	1.156-191.391	0.038
pT	2.100	0.636-6.930	0.223	-	-	-
N0	0.172	0.028-1.046	0.056	0.065	0.005-0.782	0.031
N+	0.622	0.137-2.818	0.538	3.163	0.301-33.257	0.337
MSI	0.236	0.047-1.191	0.080	0.335	0.064-1.756	0.196
Tumor budding	1.144	0.452-2.897	0.777	-	-	-
LVI	0.502	0.104-2.428	0.392	-	-	-
Mucinous component	1.346	0.168-10.805	0.780	-	-	-

Variables with p<0.10 in univariate analysis and those considered clinically relevant were included in the multivariate model. HR: Hazard ratio; CI: Confidence interval; LVI: Lymphovascular invasion; PNI: Perineural invasion; MSI: Microsatellite instability; TIL: Tumor-infiltrating lymphocytes; CEA: Carcinoembryonic antigen; EOCRC: Early-onset colorectal cancer; RFS: Recurrence-free survival. P<0.05 was considered statistically significant.

among the dMMR, pMMR, or T3 subgroups (p=0.48, p=0.07, p=0.83), whereas patients with T4 disease experienced a significant long-term survival benefit, particularly beginning in the third year post-treatment (p=0.007).[19] Together, these results indicate that the survival benefit of ACT in stage II EOCRC is limited for most patients and suggest that treatment decisions should prioritize pathological risk factors such as T4 stage and nodal involvement rather than age alone.

A nationwide, real-world study using the Flatiron Health database reported that patients with stage II EOCRC were substantially more likely than older patients to receive ACT, particularly in the stage IIA subgroup, suggesting a more aggressive age-driven treatment approach.[20] However, no significant differences in OS or time to metastatic progression were observed between younger and older patients, regardless of whether adjuvant therapy was administered. These findings emphasize that extending adjuvant treatment beyond guideline-based indications may expose young, low-risk stage II patients to unnecessary toxicity without a demonstrable survival benefit.

Consistent with this, our results showed no significant difference in median RFS between XELOX and capecitabine monotherapy in stage II EOCRC when evaluated by KM analysis. However, MV CRA demonstrated that XELOX was associated with a significantly lower recurrence risk (HR=14.87, p=0.038), and node-negative (N0) disease independently predicted a favorable prognosis. This suggests that the benefit of oxaliplatin-based therapy in stage II EOCRC is not uniform and may be more relevant in selected patients rather than applied broadly. Although XELOX was associated with a reduced recurrence risk compared to capecitabine monotherapy in stage II patients, the small sample size and wide confidence intervals limit the robustness of this finding, which should be regarded as hypothesis-generating.

Similarly, a large population-based cohort study from Alberta, Canada, evaluating stage II EOCRC found that although ACT was more commonly used in patients with T4 tumors and high-grade histology, treatment was not associated with a statistically significant survival advantage (HR for recurrence=0.79; HR for mortality=0.80).[21] The authors emphasized the need for caution in interpreting these findings due to sample size limitations but highlighted that potential benefit may exist in biologically high-risk subgroups. Taken together, the emerging evidence suggests that adjuvant therapy in stage II EOCRC should not be based on age alone; rather, treatment decisions should incorporate adverse pathological features such as T4 disease and nodal involvement, and consideration should be given to the potential benefit of XELOX in carefully selected node-negative patients. Zhou et al. conducted a retrospective cohort study between 2013 and 2018 examining ACT patterns and survival outcomes in patients with stage II colon cancer.[22] Younger patients (18-49 years) had fewer comorbidities but demonstrated higher rates of poor differentiation (p=0.017) and MSI-H tumors (21.5%). They were significantly more likely to receive ACT [odds ratio (OR)=4.19; 95% CI: 2.25-7.83] and combination regimens (OR=3.18; 95% CI: 1.26-8.06) compared with older patients. However, survival outcomes did not differ between age groups, indicating that more intensive treatment approaches in younger patients do not necessarily confer improved clinical benefits. Consistent with these findings, in our study, adjuvant treatment type was not associated with OS in stage II EOCRC.

Tashkandi et al.[23] reported that treatment intensity declines with advancing age, with older patients receiving less surgery and chemotherapy. Younger patients, on the other hand, typically receive more intense care, especially regimens based on oxaliplatin. But a recent review showed that oxaliplatin-

based adjuvant therapy in stage II - stage III colon cancer was linked to a higher long-term risk of secondary malignancies, emphasising the need to weigh the benefit of early recurrence against the risk of late toxicity.[24]

In a population-based Korean study, the addition of oxaliplatin improved survival in stage III patients younger than 70 years, but no benefit was observed in older individuals or in stage II disease.[25] Similarly, another retrospective analysis found that ACT improved 5-year disease-free survival and OS only in high-risk stage II patients, whereas MSI-high tumors had a favorable prognosis and derived limited benefit from 5-fluorouracil-based regimens.[26] Ambalathandi and Meenakshisundaram[27] reported that EOCRC accounted for 14.5% of diagnosed cases, with a median age of 34 years and an OS rate of 81.5% at 20 months for localized disease. In contrast, a single-center cohort analysis found no independent prognostic effect of age (≤50 vs. >50 years) on tumor stage, location, or OS.[28] Additionally, the combined assessment of KRAS and MSI status in early-stage CRC is essential for more accurate risk stratification and for more effective guidance of adjuvant treatment strategies.[29] Collectively, these findings reinforce that age alone does not dictate prognosis or response to adjuvant therapy and further support a treatment approach focused on pathological and molecular risk factors rather than chronological age.

Study Limitations

There are some limitations to this study. Because of its retrospective design, single-center setting, and modest sample size, the generalizability of the results may be limited. Second, the statistical power of the MV models may have been reduced due to the heterogeneity of adjuvant regimens and the low number of survival events. Accordingly, the wide confidence intervals observed in some Cox regression models likely reflect the limited number of events, which may have reduced statistical power and necessitate cautious interpretation of these findings. Third, because of the small subgroup size and a limited number of deaths, OS comparisons by adjuvant treatment type could not be reliably performed in patients with stage II disease. Fourth, we were unable to stratify stage II patients into high- and low-risk categories, which limits the interpretation of treatment benefit in specific subgroups. This limitation is particularly relevant when interpreting the apparent benefit of oxaliplatin-based adjuvant therapy, as treatment effects may vary substantially across unrecognized risk strata within the heterogeneous stage II population. Although MSI status was included in the analysis, the absence of other relevant molecular markers, such as KRAS and BRAF mutations, may have further limited the ability to risk stratification and influenced the interpretation of prognostic and treatment-related outcomes. Additionally, since all patients in our cohort received ACT, selection bias is likely, reflecting a population with higher-risk disease. Finally, the median follow-up duration of 32 months may not fully capture long-term outcomes. Larger, prospective, multi-institutional studies incorporating molecular stratification are needed to validate these results and refine adjuvant treatment strategies for EOCRC.

In summary, accumulating evidence indicates that treatment decisions in EOCRC should prioritize tumor biology and pathological risk factors—such as MSI status, nodal involvement, T4 disease, and other adverse histological markers—rather than age alone. Our findings support a personalized, risk-adapted approach in which ACT is selectively intensified for high-risk patients while avoiding unnecessary toxicity in low-risk stage II cases. Such a strategy may optimize treatment efficacy and improve long-term outcomes in this increasingly relevant patient population.

CONCLUSION

In this retrospective study of EOCRC patients receiving adjuvant capecitabine-based therapy, stage at diagnosis and nodal status were key prognostic determinants. Recurrence was the strongest independent predictor of poor OS, and patients with stage III disease exhibited significantly lower OS and RFS. Among stage II patients, oxaliplatin-based therapy was associated with a reduced risk of recurrence in MV analysis, suggesting potential benefit in selected cases, while nodal negativity emerged as an independent protective factor. These findings underscore the importance of tailoring adjuvant therapy in EOCRC according to pathological and molecular risk features rather than patient age alone to optimize therapeutic efficacy and minimize unnecessary toxicity in young low-risk individuals.

Ethics

Ethics Committee Approval: The authors state that they have obtained Ege University Medical Research Ethics Committee approval (date: 06.11.2025, approval number: 25-11T/76).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: O.Ö., A.G., Design: O.Ö., A.G., Z.S.G., B.E., H.Ç.Y., Data Collection or Processing: O.Ö., A.G., Z.S.G., B.E., Analysis or Interpretation: O.Ö., A.G., Literature Search: O.Ö., A.G., Z.S.G., B.E., H.Ç.Y., Writing: O.Ö., A.G., H.Ç.Y.

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