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The impact of adjuvant oxaliplatin and tumor sidedness on the overall survival of stage IIB colon cancer patients: a multicentre study

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ABSTRACT

The aim of this multicentre retrospective study was to compare the efficacy of adjuvant chemotherapy regimens both with and without oxaliplatin and tumor sidedness in stage IIB (pT4aN0) colon cancer patients. This study included patients with stage IIB colon cancer who underwent curative surgery and received adjuvant chemotherapy. The patients were divided into two groups (one with and one without oxaliplatin) to compare the overall survival (OS) in right- and left-sided tumors. The study population included 298 patients with stage IIB colon cancer (median age: 57) of whom 69.1% were male. Forty-four per cent of these patients (n = 131) were diagnosed with right-sided colon cancer. The median follow-up duration was 35.9 months. In the entire population, a median OS was not reached, and the five-year OS was 83%. The median disease-free survival (DFS) was 12 months. There was no significant difference in terms of the five-year OS between right- (82%) and left-sided (84%) colon tumors ($p = 0.67$). In addition, the five-year OS of patients treated with and without oxaliplatin were 76% and 89%, respectively, and there was no statistically significant difference ($p = 0.23$). The five-year OS of the patients treated with and without oxaliplatin were 83% and 96.5%, respectively, ($p = 0.8$) in right-sided colon tumors, while it was 75% and 93% ($p = 0.06$), respectively, in left-sided colon tumors. Tumor sidedness and the addition of oxaliplatin to adjuvant chemotherapy were not found to be associated with the OS in stage IIB colon cancer patients in our study. Further large prospective studies that also include MSI, RAS and BRAF status data are warranted in colon cancer patients.

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Overal survival; colon cancer; stage IIB; oxaliplatin

Introduction

Colon cancer is the third most common cancer in both men and women [1]. The cornerstone of treatment for non-metastatic colon cancer has traditionally been surgical resection with adequate lymphadenectomy [2]. Disease recurrence is believed to be caused by clinically occult micro-metastases that are present at the time of surgery in patients who have had a potentially curative resection. The goal of postoperative (adjuvant) therapy is to eradicate these micro-metastases and thereby increase the cure rate. After surgical resection, adjuvant chemotherapy (AC) is the standard of care for stage III colon cancer patients because it provides an approximately 30% relative reduction in the risk of disease recurrence and a 22–32% relative reduction in mortality; as a result, this treatment has become the standard approach in this setting [3]. However, the benefits of AC in stage II (node-negative) disease are less certain, and the use of AC in this group therefore remains controversial [4–9].

The United Kingdom QUASAR (QUick And Simple And Reliable) Study is one of the largest trials

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that has investigated the benefits of AC in patients with stage II colon cancer [9]. The QUASAR reported that AC using 5-fluorouracil (5-FU) was associated with an 18% reduction in the risk of death, which translated into a small but meaningful 3.6% (95% confidence interval [CI]: 1.0–6.0%) increase in the five-year overall survival (OS). The MOSAIC and NSABP C-07 trials established a role for the addition of oxaliplatin in the adjuvant setting in patients with stage II and III colon cancer. However, neither trial presented definitive evidence of a benefit for oxaliplatin in patients with stage II disease [4, 10].

Consideration of the heterogeneity of stage II colon cancer risk stratification is essential to determine which patients will benefit from AC. The histopathological, molecular and clinical characteristics are all used to stratify a patient's risk. The current guidelines recommend AC for patients with high-risk features, including a pathologic stage of pT4, emergency clinical presentation (bowel obstruction or perforation), lympho-vascular invasion (LVI) and perineural invasion, inadequate lymph node (LN) sampling (<12 nodes) and poorly differentiated histology (grade 3) [11, 12].

One of the most significant prognostic factors in colon cancer is the pathologic T stage (the degree of penetration of the tumor into the bowel wall). A stage of pT3 is defined as the invasion of the muscularis propria, while pT4 is characterised by the presence of the serosa, penetration of the visceral peritoneum (T4a) or invasion of adjacent organs (T4b) [13].

Previous studies have demonstrated that the five-year OS rate in stage II patients treated with surgery alone was 85–88% when staged as pT3 and 70–75% when staged as pT4 [8, 14, 15]. Furthermore, a prognostic difference was observed between pT4a and pT4b, with five-year OS rates of 79.6% and 58.4%, respectively [14]. Interestingly, stage IIB tumors graded as pT4N0 have demonstrated worse outcomes compared to stage IIIA pT1–2 N1 colon cancer both with surgery alone and with a combination of surgery and AC [16]. Patients with stage IIB colon cancer have a lower five-year survival rate (72.2%) than node-positive stage IIIA patients (83.4%), which implies that pT4 can be an even worse prognostic feature than limited LN involvement [15].

The predictive relevance of the original tumor's sidedness in colorectal cancer has piqued researchers' curiosity. In patients with unresectable colorectal cancer who were treated with molecular targeted agents, pooled analyses of several randomized trials that assessed the prognostic influence of the primary tumor's location have revealed that right-sided colon (RCC) tumors were significantly associated with a worse OS than left-sided colon (LCC) and rectum tumors [17]. In individuals with stage II–III colon cancer, the tumor position has also been demonstrated to influence the prognosis following recurrence, with RCC being associated with considerably shorter cancer-specific survival after recurrence compared to LCC [18].

In this multicentre retrospective study, we aimed to compare the efficacy of AC regimens based on whether they contained oxaliplatin and also the tumor sidedness in stage IIB (pT4aN0) colon cancer patients.

Materials and methods

Study population and data collection

Colon cancer patients who underwent curative surgery (R0-resected) and received postoperative AC at 11 oncology centres in Turkey between June 2007 and December 2019 were recruited for this multicentre retrospective study. Patients who were histopathologically diagnosed with colon adenocarcinoma and had stage IIB (pT4aN0) disease at diagnosis were included. Patients with rectal cancer alone, those who were younger than 18 years old, people with a secondary tumor, those not treated with AC, and anyone who had missing data were excluded. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki and its ethical principles (Approval number: 48670771-514.10/38).

The following data were obtained from the patients' medical records: demographics (i.e., sex, age), dates of cancer diagnosis and surgery, any presence of obstruction and tumor characteristics, such as the tumor's sidedness (left or right), histological grade, number of examined LNs, presence of LVI, perineural invasion, chemotherapy regimens (folinic acid, 5-FU, oxaliplatin [FOLFOX], capecitabine and oxaliplatin [CAPOX], folinic acid and 5-FU [FUFA], and capecitabine), treatment duration (three, three to six or six months) and dates of recurrence and death. The patients were grouped according to whether the chemotherapy regimen they received included oxaliplatin (FOLFOX, CAPOX) or did not (FUFA, capecitabine). Data that detailed the microsatellite instability (MSI), RAS and BRAF status of our patients were not recorded due to their unavailability.

The primary endpoints of this study were the OS and disease-free survival (DFS) rates. The DFS was defined as the time from the diagnosis until a recurrence or metastasis, while the OS was determined as

Table 1. Patients characteristics according to the adjuvant chemotherapy regimen.

	Oxaliplatin containing chemotherapy		Non-Oxaliplatin containing chemotherapy		*p*
	N	%	N	%	
Age of diagnosis (mean ± std. deviation)	57 ± 9	–	57 ± 11	–	
Gender					
Male	110	64.3	69	54.3	
Female	61	35.7	58	45.7	*0.08*
Bowel obstruction					
Present	125	73.1	94	74	
Absent	46	26.9	33	26	*0.86*
Grade					
1	15	9	22	17	
2	126	76	94	75	
3	23	14	9	7	
Unknown	5	1	4	1	***0.03***
Number of lymph nodes dissected					
<12	18	10.5	16	12.6	
≥12	153	89.5	111	87.4	*0.58*
Tumor location					
Right	73	42.7	58	45.7	
Left	98	57.3	69	54.3	*0.61*
Perineural invasion					
Positive	92	53.8	90	70.9	
Negative	79	46.2	37	29.1	***0.03***
Lymphovascular invasion					
Positive	90	52.6	73	57.5	
Negative	81	47.4	54	42.5	*0.41*
Duration of adjuvant chemotherapy					
3 months	19	11.1	11	8.7	
3-6 months	9	5.3	6	4.7	
6 months	143	83.6	110	86.6	*0.76*
Number of chemotherapy cycles (mean ± std. deviation)	5.2 ± 1.4		5.2 ± 1.4		

the time from the initial diagnosis until death or the last follow-up visit.

Statistical analysis

A descriptive analysis of the population was conducted using percentages for clinical and demographic features. Where appropriate, a Chi-square test or Fisher's exact test was used to compare these variables. Kaplan-Meier survival estimates were also calculated. The effect of adjuvant treatment durations on the DFS and OS rates were investigated using a Log rank test. Any effects on survival variables were demonstrated by separate Log rank tests using tumor sidedness as a stratum. The possible factors identified with univariate analyses that had a p value of <0.20 were further entered into a Cox regression analysis (with enter selection) to determine the independent predictors of survival. Strongly correlated variables were excluded, and only those with clinical significance were included. A p value of <0.05 was used to infer statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences software.

Results

Two hundred and ninety-eight patients with stage IIB colon cancer were included in this study. The demographic features of our patients and the clinical and histopathological features of their tumors in addition to the duration and number of AC cycles are shown in Table 1. The median age at diagnosis was 57 (range: 18–81) years, and 69.1% of the patients were male. Forty-four per cent of patients (n = 131) were diagnosed with RCC. In total, 34 patients (11.4%) had <12 LNs examined. The most commonly used AC regimen was CAPOX (40.3%), followed by capecitabine (22.5%), FUFA (20.1%) and FOLFOX (17.1%). An oxaliplatin-containing AC regimen was applied in 171 (57.4%) patients. The majority of our patients (84.9%) had received six months of AC treatment.

No statistical difference existed between the patient groups with and without oxaliplatin AC in terms of the presence of bowel obstruction, number of LNs removed, the presence of LVI and the duration of AC. Histological grade 3 tumors and tumors that did not show perineural invasion were ranked significantly higher in the oxaliplatin-containing AC group ($p = 0.03$ and $p = 0.03$, respectively, Table 1).

Survival analysis

The median follow-up time in our study was 35.9 months. In our cohort, a median OS was not

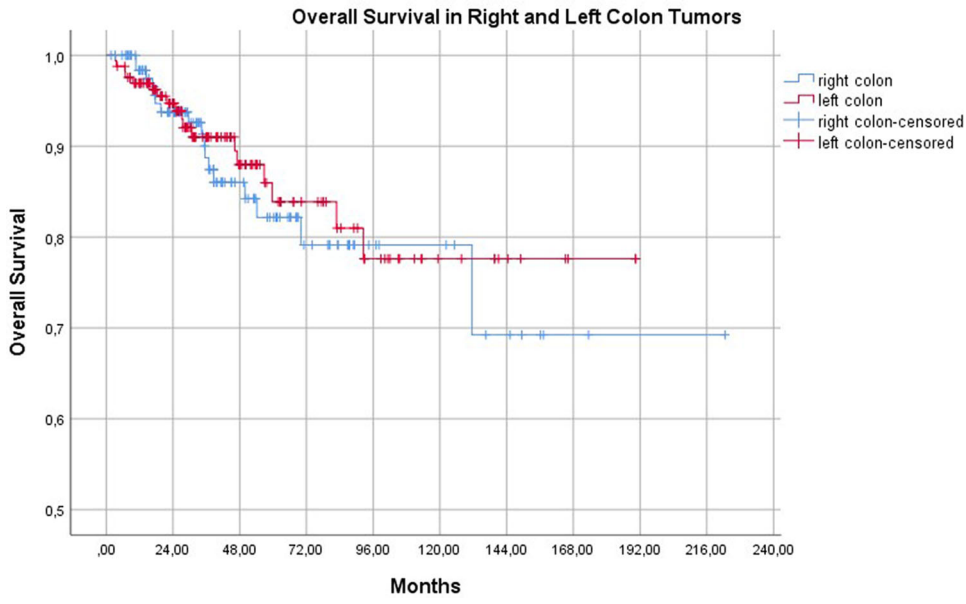

Figure 1. Overall survival in right and left colon tumors.

reached, but the five-year OS was 83%, while the median DFS was 12 months.

There was no significant difference in terms of the OS between RCC and LCC tumors ($p = 0.67$); the five-year OS rates were 82% and 84% for RCC and LCC tumors, respectively (Figure 1). The five-year OS rates of patients who received AC both with and without oxaliplatin were 76% and 89%, respectively, which were not statistically significant ($p = 0.23$) (Figure 2).

In RCC tumors, the five-year OS of patients receiving an oxaliplatin-containing AC regimen was 83%, while patients who did not receive oxaliplatin in their AC regimen had a five-year OS of 96.5%. Neither result was statistically significant ($p = 0.8$) (Figure 3). In LCC tumors, the five-year OS rates of patients were 75% for oxaliplatin-containing regimens and 93% for AC regimens without oxaliplatin ($p = 0.06$), which was not statistically significant (Figure 4).

The median DFS were 9.1 (95% CI: 2.1–16.2) and 12.3 (95% CI: 6.5–18.1) months in LCC and RCC patients, respectively ($p = 0.82$) (Figure 5). The median DFS were 9.1 (95% CI: 1.9–16.4) and 6.9 (95% CI: 0–31.5) months in RCC patients treated both with and without oxaliplatin-containing AC, respectively, which were not statistically significant ($p = 0.081$) (Figure 6). The median DFS were 15.3 (95% CI: 8.2–22.5) and 11 (95% CI: 8.2–13.8) months in LCC patients treated both with and without oxaliplatin-containing AC, respectively, which were not statistically significant ($p = 0.17$) (Figure 7).

Upon univariate Cox regression analysis, it was found that receiving six months of AC treatment and being LVI-negative had a significantly favourable effect on survival (Table 2). After excluding strongly correlated variables, we performed a multivariate Cox regression analysis. The independent prognostic factors were the duration of AC treatment, the presence of LVI and an oxaliplatin-containing AC administration. A six-month duration of AC treatment provided a significantly better OS rate than a three-month treatment (Hazard ratio: 0.16, 95% CI: 0.06–0.843, $p < 0.001$). LVI-positive patients had a higher risk of death than LVI-negative patients (RR: 3.87, 95% CI: 1.71–8.78, $p = 0.001$). The patients who received AC containing oxaliplatin had a higher risk of death than those who did not (RR: 2.3, 95% CI: 1.76–3.1, $p < 0.001$) (Table 3).

Upon univariate and multivariate Cox regression analyses, there was no statistically significant factor for the DFS of our colon cancer patients (Supplementary Table 1, Table 2).

Discussion

The current study was conducted to provide a better assessment of the OS benefit of adjuvant oxaliplatin-containing chemotherapy in stage IIB colon cancer with regard to tumor sideness. However, it was found that both tumor localization and adding oxaliplatin to the AC regimen were not associated with the OS in stage IIB colon cancer.

Surgical resection is the mainstay of treatment for stage II colon cancer and has a wide five-year OS range, highlighting the variability in recurrence rates. Adjuvant chemotherapy has a well-established survival advantage in stage III patients, although there is no

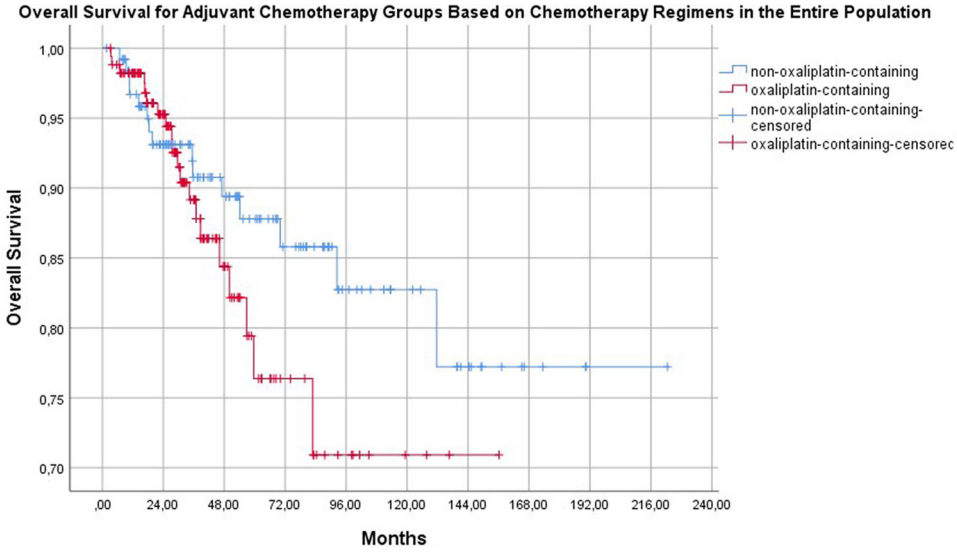

Figure 2. Overall survival for adjuvant chemotherapy groups based on chemotherapy regimens in the entire population.

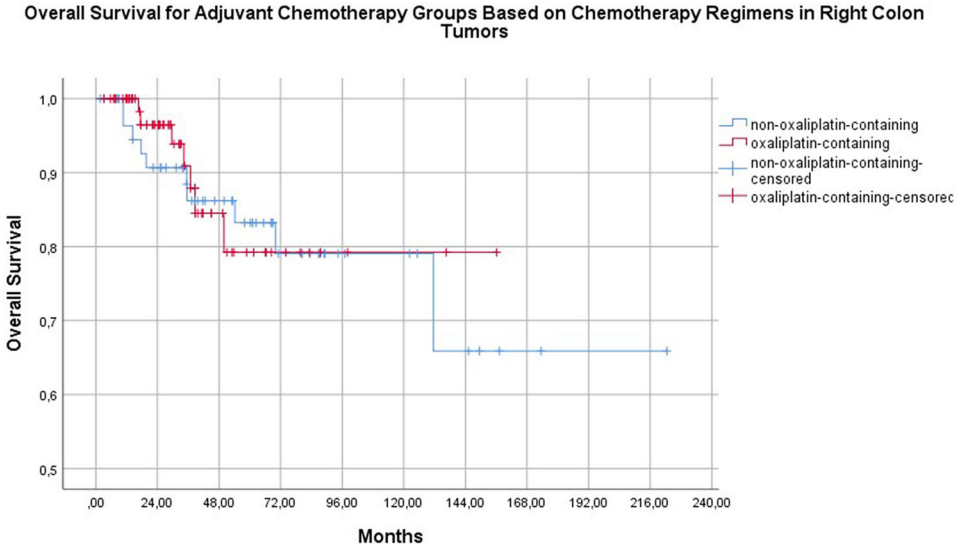

Figure 3. Overall survival for adjuvant chemotherapy groups based on chemotherapy regimens in right colon tumors.

definitive benefit in stage II patients [19]. Tumor perforation, pT4, bowel obstruction, a high tumor grade or poorly differentiated tumors, LVI and <12 examined LNs were historically considered high-risk characteristics in stage II colon cancer patients. According to the current guidelines, clinicians should discuss AC with patients who have any one or a combination of these risk factors [11, 12].

A data analysis from the Netherlands Cancer Registry demonstrated that AC improved the survival outcomes in patients with pT4 stage II colon cancer [20]. A multivariate survival analysis indicated that age was not a prognostic factor for OS in our study. A recent analysis of the National Cancer Database demonstrated that age was a prognostic factor in patients with stage II colon cancer [21].

Our study showed that tumor sidedness was not a prognostic factor for OS in stage IIB colon cancer patients. A recent Chinese study also reported that the tumor location was not an independent prognostic factor in patients with stage I–III colon cancer [22]. Weiss et aldemonstrated that there was no difference in the five-year mortality between RCC and LCC tumors of any stage from I–III. However, stage II RCCs showed a lower mortality than LCCs, while stage III RCCs exhibited a higher mortality [23].

In our cohort, the presence of LVI was a negative prognostic factor for OS upon univariate analysis but was not an independent risk factor in our multivariate analysis. Perineural invasion was also not a prognostic factor in either the univariate or multivariate analysis. An analysis of 32,493 patients with stage II colon

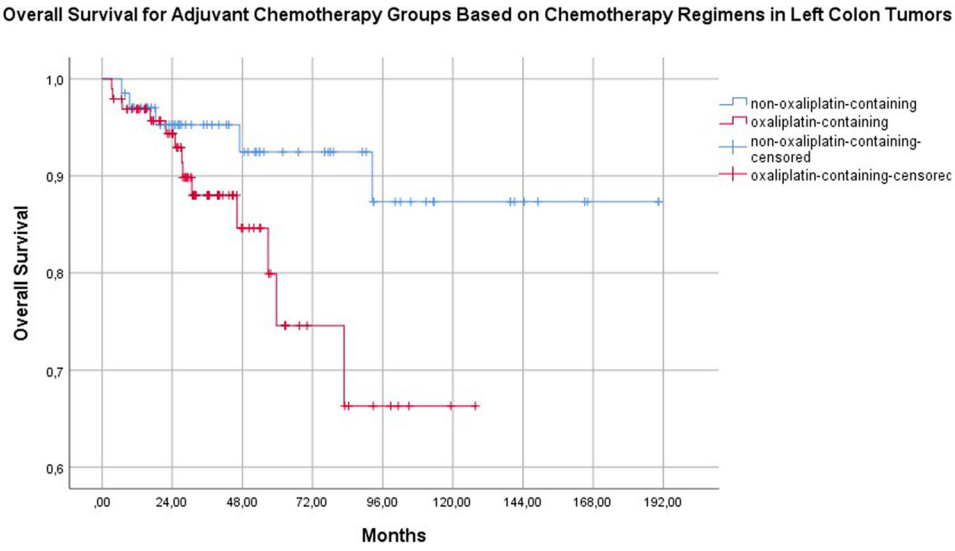

Figure 4. Overall survival for adjuvant chemotherapy groups based on chemotherapy regimens in left colon tumors.

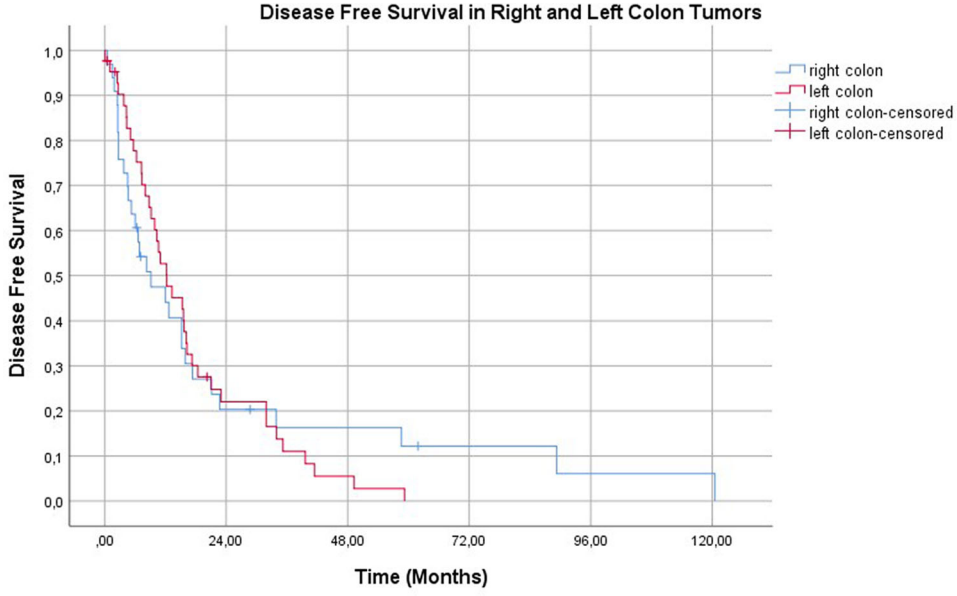

Figure 5. Disease free survival in right and left colon tumors.

cancer showed that the five-year OS decreased in the presence of LVI and also with perineural invasion compared to patients without these features [24]. However, there is still no consensus about the prognostic value of LVI and perineural invasion in stage II colon cancer patients [25].

The analysis by Gill et al. of a population of 3302 stage II and stage III colon cancer patients found a lower five-year OS rate in patients with high-grade disease [8]. In our study, no correlation was found between the tumor grade and the OS, which may be explained by our relatively small sample size.

Inadequate LN sampling has been associated with poor outcomes in colon cancer patients. Swanson et al. found that the five-year survival rates in 35,787 stage II patients varied greatly depending on the number of retrieved LNs; the five-year OS rate was 49.8% for patients with 1–7 retrieved LNs, 56.2% for 8–12 LNs and 63.4% for >13 LNs [26]. The Intergroup 0089 study reported that stage II patients with >20 negative LNs examined had a 14% higher absolute five-year OS rate than those with <10 negative LNs examined [27]. In our study, LN sampling of >12 LNs was not found to be associated with the survival time. The reason for this trend may be that our study population consisted of only stage IIB patients, and all patients received AC treatment and surgical resection at various centres.

Our univariate analysis indicated that a six-month duration of AC was a favourable factor for the OS.

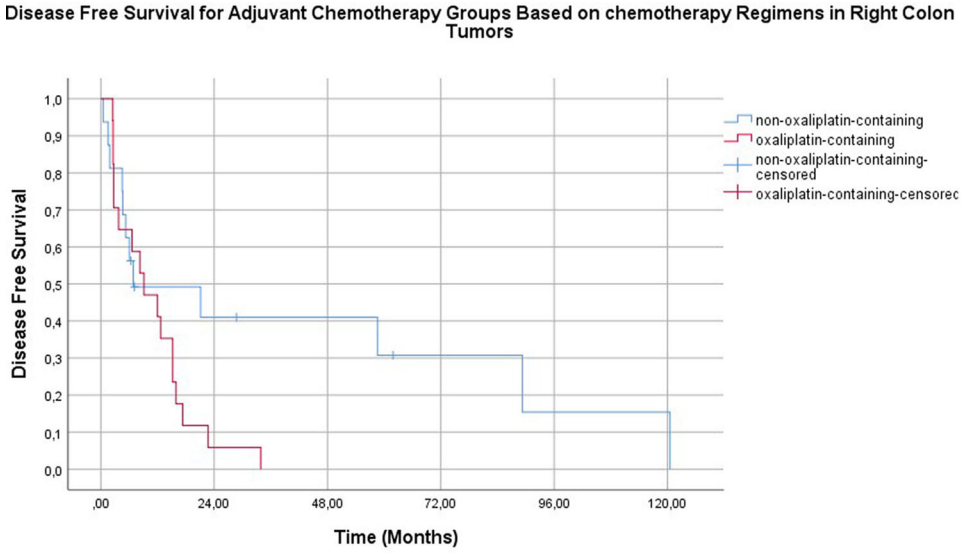

Figure 6. Disease free survival for adjuvant chemotherapy groups based on chemotherapy regimens in right colon tumors.

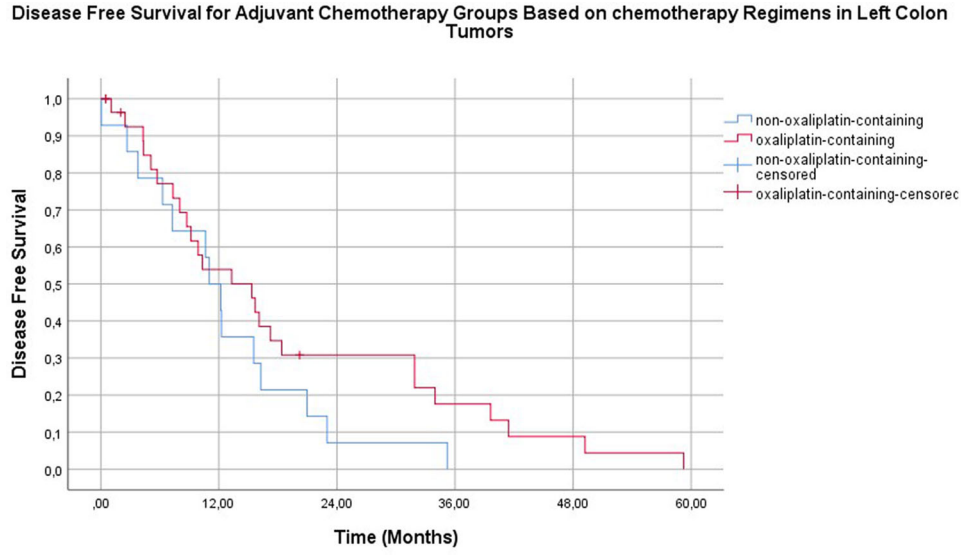

Figure 7. Disease free survival for adjuvant chemotherapy groups based on chemotherapy regimens in left colon tumors.

The findings of a pooled study of the four IDEA trials, which included 3273 stage II patients, revealed that three months of adjuvant CAPOX therapy was as effective as six months and also had significantly less toxicity [28]. However, six months of FOLFOX yielded greater efficacy than three months of the same treatment but produced slightly more side effects [28]. Since our sample size was relatively small, we could not analyse our participants in terms of the treatment duration for each chemotherapy regimen in this study.

Our study demonstrated that the addition of oxaliplatin to fluorouracil/capecitabine did not improve the five-year OS. Previously, two randomized clinical trials investigated the addition of oxaliplatin in stage II colon cancer [5, 10]. In the MOSAIC trial, the addition of oxaliplatin did not improve the five-year OS (89% vs. 90%) or the five-year DFS (83.2% vs. 80.1%), respectively [5]. The NSABP-C07 trial also did not show any benefit in terms of the five-year OS (89.7% vs. 89.6%) and the five-year DFS (82.1% vs. 80.1%), respectively [10]. We also found that the addition of oxaliplatin did not improve the five-year OS in stage IIB RCC and LCC patients.

To the best of our knowledge, this is the first study to assess the effect of oxaliplatin in right- and left-sided stage IIB colon cancer patients. Although the results were not statistically significant, we found that patients who received oxaliplatin exhibited a worse OS (Figure 2), which may be due to the presence of

Table 2. Univariate Cox Regression analysis for overall survival.

	HR	95.0% CI for HR		*p*
Age of diagnosis				
65 years≤ (Ref.)				
65 years>	0.52	0.26	1.04	*0.06*
Tumor location				
Right (Ref.)				
Left	0.87	0.45	1.68	*0.69*
Perineural invasion				
Negative (Ref.)				
Positive	1.2	0.61	2.36	*0.6*
Lymphovascular invasion				
Negative (Ref.)				
Positive	2.66	1.32	5.35	*0.01*
Grade				
1 (Ref.)				
2	1.3	0.89	1.9	*0.17*
3	1.6	0.95	2.7	*0.08*
Number of lymph nodes dissected				
<12 (Ref.)				
≥12	1.3	0.88	1.99	*0.18*
Anatomical tumor location				
Ascending (Ref.)				
Transvers	0.27	0.04	2.07	*0.21*
Descending	0.88	0.34	2.33	*0.8*
Sigmoid	0.75	0.34	1.68	*0.49*
Bowel obstruction				
Absent (Ref.)				
Present	1.94	0.97	3.85	*0.06*
Chemotherapy				
Without oxaliplatin (Ref.)				
With oxaliplatin	1.53	0.77	3.05	*0.23*
Duration of adjuvant chemotherapy				
3 months (Ref.)				
3-6 months	0.73	0.19	2.83	*0.65*
6 months	0.21	0.09	0.49	*<0.001*

Table 3. Multivariate Cox Regression analysis for overall survival.

	HR	95.0% CI for HR		*p*
Age of diagnosis				
65 years≤ (Ref.)				
65 years>	0.61	0.27	1.36	*0.22*
Lymphovascular invasion				
Negative (Ref.)				
Positive	3.87	1.71	8.78	*0.001*
Grade				
1 (Ref.)				
2	0.88	0.29	2.7	*0.82*
3	1.2	0.31	4.7	*0.8*
Number of lymph nodes dissected				
<12 (Ref.)				
≥12	0.92	0.32	2.71	*0.89*
Bowel obstruction				
Absent (Ref.)				
Present	1.61	0.77	3.34	*0.2*
Chemotherapy				
Without oxaliplatin (Ref.)				
With oxaliplatin	2.3	1.76	3.1	*<0.001*
Duration of adjuvant chemotherapy				
3 months (Ref.)				
3-6 months	0.79	0.2	3.2	*0.74*
6 months	0.16	0.06	0.43	*<0.001*

negative prognostic factors, such as histological grade 3 tumors, which were more common in the oxaliplatin-containing group. As a result, this relationship must be evaluated in further studies that include other prognostic factors and molecular subtypes.

Our study also has some limitations. First, it was a retrospective analysis of patients from various oncology departments and therefore consisted of a relatively small sample size. An analysis of the MSI, BRAF and RAS was not performed due to the unavailability of the data. During the considerably long enrolment period (from 2007 to 2019), multiple oncological and surgical innovations were introduced that may have affected the survival outcomes of our patients but were not accounted for. Also, potential limitations were the lack of information on eventual patient dropouts and side effects related to the chemotherapeutic treatments. However, our study is noteworthy because we evaluated the effectiveness of oxaliplatin specifically in stage IIB colon cancer patients and also considered the sidedness of the tumor.

Conclusion

Tumor sidedness and the addition of oxaliplatin to AC treatment were not found to be associated with the OS in stage IIB colon cancer patients in our study. Further large prospective studies that also include data about the MSI, RAS and BRAF status are therefore warranted in colon cancer patients.

Author contributions

Concept – MMA, BA, MD, AS; Design – AS, MMA, BA, OS, MA, MD, SA, RA; Supervision – AS, MMA, BA, OS, MA, RA,MO; Resources –BA, MD, MMA, RA, SA, MA, OS, GK, GTC, AKO; Materials – MMA, AS, BA, MD, ND, İC, NO; Data Collection and/or Processing–BA, MMA, SA, MD, İC, RA, OS, GK, GTC, AKO; Analysis and/or Interpretation – MD, AS, BA, OS, MMA, İC; Literature Search – BA, MMA, RA, ND, NO, İC; Writing Manuscript – MMA, BA, MD, AS, MO; Critical Review – MMA, OS, BA, MD, NO, GK, GTC, AKO,MO; Other – NO, ND, OS, GK, GTC, AKO,MO.

Disclosure statement

No potential conflict of interest was reported by the authors.

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