Investigation of the Effect of Tumor Location in Patients with Stage III Colon Cancer Receiving Adjuvant Oxaliplatine-Based Adjuvant Chemotherapy

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ABSTRACT

Left-sided (LCC) and right-sided (RCC) colon cancers have different prognostic and predictive features in metastatic colon cancers, however there is insufficent data about tumor location in stage III disease. The aim of this study is to investigate the effect of tumor location on prognosis in patients with stage III colon cancer. From 2006 to 2012, medical records of 215 patients who underwent primary surgery and received adjuvant oxaliplatin based chemotherapy at 5 referral centers were collected, retrospectively. Disease-free survival (DFS) and overall survival were analysed using Kaplan-Meier and log-rank tests, and prognostic facrtors were identified by Cox regression methods. Clinicopathological characteristics of patients were similar between patients with right-and left-sided colon cancers. The 3-year DFS rate was similar (88% vs 78%, p= 0.07) but the RCC was significantly associated with a shorter 3-year OS than LCC (76% vs 87%, p= 0.03). The 3-year median OS was 125.8 months for all patients groups, 92.2 (±5.81) months for the RCCs and 132.2 (±5.52) months for the LCCs (p= 0.037). Multivariate analysis showed that stage (HR:0.32, p= 0.042 for OS) and venous invasion (HR: 0.28, p= 0.002 for OS) were the independent prognostic factors. Although there was no DFS difference between RCCs and LCCs, poorer survival of RCC indicated that the prognosis of RCC worsened after transitioning to the metastatic stage. Tumor location may be a prognostic factor in metastatic colon cancer but not in stage III disase.

Keywords: Colon cancer, Stage III, Left-sided colon cancers, Right-sided colon cancers

INTRODUCTION

Colorectal cancer (CRC) accounts for 10% of all tumour types worldwide and is the third most common cancer in men and the second in women.[1] Most newly diagnosed patients present with locoregional disease and can potantially be cured with a combination of chemotherapy and surgery.[2] Today, colon is not considered as a single entity, it is divided into two parts as right colon and left colon.[3,4] Cancer originating from cecum, ascending colon, hepatic flexura and transverse colon is defined as right-sided colon cancer (RCC); cancer from splenic flexura, descending colon and sigmoid colon and rectum is defined as left-sided colon cancer (LCC).[5,6] Increasing evidence demonstrated that cancers originating from different sides of the colon shows different characteristics such as molecular alterations, epidemiological incidence, physiological characteristics and different survival outcomes.[1,7-9]

Compared to LCC, RCC is more frequently poor differentiated and presents with locally advanced tumors that have several specific molecular features including a high level 5′C-phosphate-G-3′ (CpG) island methylator phenotype (CIMP), BRAF mutations, microsatellite instability (MSI) and worse survival outcomes.[7,8,10] There are many studies reporting that the oncological outcomes of colon cancer differ according to the location of the tumor. Most studies have reported worse oncologic outcomes in patients with RCC compared with patients with LCC.[11-15]

Despite these different characteristics, 6-months adjuvant chemotherapy with oxaliplatin and fluoropyrimidines is standard of care in patients with operated stage III colon cancer regardless of the tumor location.[16-22] Indeed, nearly 30% of patients can not complete the full planned course of adjuvant chemotherapy due to poor tolerance and therapeutic toxicity[17,21,23] and 25% to 30% of stage III colon cancer patients develop distant metastasis despite curative treatment.[24,25] Therefore, the management of stage III colon cancer is still challenging and better insight into the prognostic factors are important for personalization of adjuvant chemotherapy. Grothey et al. showed that stage III operated colon cancer patients with T4 or N2 had a very similar, poor prognosis than other groups and needs longer adjuvant treatment duration.[26] However, this study did not mention the effect of tumor location. Peng et al. reported that RCC patients with stage III colon cancer had a worse prognostic outcome and a full course of adjuvant chemotherapy should be offered to patients with RCC, but not to patients with LCC.[27] Because of the structural and prognostic differences between the left and right colon, it can be thought that the efficacy of oxaliplatin-containing adjuvant chemotherapy is not only influenced by tumor stage, but also by tumor location.

In these study, we aimed to examine the survival outcome of operated stage III colon cancers patients by tumor location and the importance of tumor location in order to optimize the adjuvan chemotherapy duration of these patients.

PATIENTS AND METHODS

Patients

This was a retrospective study conducted at five Turkish institutes and approved by the ethics committee of Acıbadem Healthcare Organizations Medical Research Ethics Committee (No 2020-02/37).

215 consecutive patients diagnosed with stage III colon cancer and underwent tumor resection followed by adjuvant chemotherapy from June 2006 to December 2016 were included in the study. The patients with rectal cancer were excluded. The patients medical records were reviewed to obtain data on clinic-pathologic variables. The pathological tumor-node-metastasis (TNM) classification was defined acccording to the criteria of the American Joint Commision on Cancer (AJCC) 8th edition.[28]

Tumors distal to the splenic flexura were classified as left colon, and tumors proximal to splenic flexura were classified as right colon. The reference duration of 6 months was chosen in accordance with pivotal trials in which the efficacy of the duration had been established. The patients who completed their treatment for 6 months were defined as the full treatment group, and those whose treatment was less than 6 months were defined as the short treatment group. The college of American Pathologist recommend examination of a minimum of 12 lymph nodes to accurately stage colon cancers,[29] therefore the 12 is used as a cut off value for lymph node dissection.

Since T4 and N2 stages were shown to be associated with poor prognosis in operated stage 3 colon cancer, the patients were classified as N2 versus N1 and T4 versus T1-3.

Treatment

All patients received modified FOLFOX [oxaliplatin (85 mg/m^2 intravenously over 2 h on day 1) plus LV (400 mg/m^2 intravenously over 2 h on day 1) and 5-fluorouracil (5-FU) (400 mg/m^2 bolus on day 1, followed by infusion of 2400 mg/m^2 over 46 h)] or XELOX (capecitabine 1000mg/m^2 BID po x14 days plus oxaliplatin 130 mg/m^2, every 21 days for 8 cycles) in adjuvant therapy.

Statistical Analysis

All of the data were analyzed using IBM SPSS statistics software, version 21.0. The correlations between clinicopathological variables and tumor lo-

cation were assessed using chi-squared test or Fisher's exact test. The 3-year DFS and OS rates were calculated with the Kaplan–Meier method, and the differences were compared with the log-rank test. Overall survival (OS) was defined as the interval (in months) from the date of surgery until death from any cause or the last follow up, whereas disease free survival (DFS) was defined as the interval (in months) from date of surgery to disease recurrence, death, or the last follow-up. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals for both univariate and multivariate analyses. P-values < 0.05 was considered significant.

RESULTS

Patient characteristics

The baseline characteristics of the patients are shown in Table 1. Their median age was 61 (range, 23-81years). 122 patients (56.7%) were men and 92 patients (43.35) were women. 9 (4.2%) patients were diagnosed with stage IIIA colon cancer, 161 (74.8%) with stage IIIB colon cancer, and 45 (21%) with stage IIIC colon cancer. 139 (64.6%) patients had LCC while 76 (35.4%) patients had RCC. The median number of resected lymph nodes and metastatic lymph nodes were 15 (range, 2-93) and 2 (range, 1-57) respectively. There was not statistically difference in baseline characteristics between the tumor location subgroups (Table 1).

Survival Analysis

The median follow-up period for all eligible patients was 63.34 (1.3-168.05) months. 64 (29.7%) patients experienced tumor metastasis, 60 (27.9%) patients died by cut-off date.

The median 3-year OS was 125.8 (±5.23) months for all patients. The median 3-year survival was 92.2 (±5.81) months for the RCC and 132.2 (±5.52) months for the LCC (p= 0.037) groups. DFS and OS rates were 81% and 83% in all patients. The 3-year DFS rate was 88% vs. 78% (p= 0.07) (Figure 1A), and 3-year OS rate was 76% vs. 87% (p= 0.03) (Figure 1B) for RCC and LCC patients respectively. In univariate analyses; age, N stage, TNM stage, risk group, venous invasion and tumor location affect survival, while multivariate analyses showed that TNM stage and venous invasion is effective on survival (Table 2). None of these variables affected DFS in univariate and multivariate analyses.

The total metastasis rate, liver metastasis and lung metastasis were not significiantly different between RCCs and LCCs (all p> 0.050) (Table 3). Peritoneal carcinomatosis was more common in RCCs than LCCs (23.4% vs. 15%, p= 0.038).

Toxicities

No significiant differences were identified for neutropenia, thrombocytopenia, neurotoxicity and nause and vomiting. Grade 3-4 neutropenia was 19.7% and 10.7%, grade 3-4 thrombocytopenia was 5.2% and 5.0%, grade 2-3 nause and vomiting was 11.8% and 13.9% and grade 2-3 neurotoxicity was 18.4% and 17.2% (grade 4 neurotoxicity not seen in any patient) for RCCs and LCCs (p< 0.005 for all) (Table 4).

DISCUSSION

Studies in the literature have discussed the demographic, biological, genetic, clinical and survival differences between left-sided and right-sided colon cancers.[30-34] Bufill demonstrated two distinct genetic categories of colon cancers (left-sided and right-sided colons) for the first time in 19903 and various studies have been conducted based on this concept.[35-39] However, it is still not clear whether the location of primary tumour is an independent factor in locoregional colon cancer. In a study by Wray et al.[11] sigmoid colon cancers were found to have a lower tumour grade, an earlier stage, and an independent decreased CRC-specific mortality compared to proximal tumors. Huang et al. demonstrated that patients with right-sided colon cancer had significiantly worse overall and cancer specific survival rates compared to patients with left-sided colon cancer and the differences were significant only in patients with stage III CRC.[12] Zhang et al. showed that both 5-year overall survival and recurrence-free survival were significantly different and survival gradually decreased for tumors from the cecum to the sigmoid colon in 895 stage III colon cancer patients treated with curative resection and subsequently received adjuvant chemotherapy with oxaliplatin.[13] So far, the strongest evidence was

Table 1. Clinicopathological characteristics of patients

Parameters	Overall cases (n, %)	Left sided (n, %)	Right sided (n, %)	p
Overall	215 (100)	139 (64.6)	76 (35.4)	
Age (years)				
< 65	140 (65)	100 (71.9)	40 (52.6)	0.23
≥ 65	75 (34.8)	39 (28.1)	36 (47.4)	
Gender				0.43
Male	122 (56.7)	75 (54)	47 (61.8)	
Female	92 (43.3)	64 (46)	29 (38.2)	
Tumor differantiation				0.92
Wel/modarate	178 (85.5)	121 (89.6)	57 (78.1)	
Poor/undifferentiated	30 (14.4)	14 (10.4)	16 (21.9)	
T stage				0.87
T1-T2	10 (4.6)	6 (4.3)	4 (5.3)	
T3	126 (58.6)	81 (58.3)	45 (59.2)	
T4	79 (36.7)	52 (37.4)	27 (35.5)	
N stage				
N1	152 (70.7)	103 (74.2)	49 (64.5)	
N2	63 (29.3)	36 (25.8)	27 (35.5)	
TNM stage				0.67
3A	9 (4.2)	5 (3.6)	4 (5.3)	
3B	161 (74.8)	108 (77.7)	53 (69.7)	
3C	45 (21)	26 (18.7)	19 (25)	
Risk stratification				0.77
Low risk	103 (48)	69 (49.6)	34 (44.7)	
High risk	112 (52)	70 (50.4)	42 (55.3)	
Lymph node dissection				0.48
≥ 12	156 (72.5)	97 (69.8)	59 (77.6)	
< 12	59 (27.5)	42 (30.2)	17 (22.4)	
Perineural invasion				0.53
Yes	82 (42)	55 (43.7)	27 (39.1)	
No	113 (58)	71 (56.3)	42 (60.9)	
Lymphatic invasion				0.12
Yes	133 (68.9)	80 (64)	53 (77.9)	
No	60 (31.1)	45 (36)	15 (22.1)	
Venous invasion				0.23
Yes	93 (47.7)	56 (44)	37 (54.4)	
No	102 (52.3)	71 (66)	31 (45.6)	
Adjuvant chemotherapy				0.92
Full	109 (50.7)	70 (50.3)	39 (51.3)	
Short	106 (49.3)	69 (49.7)	37 (48.7)	
Dose reduction				0.97
Yes	80 (41.7)	53 (42)	27 (41)	
No	112 (58.3)	73 (58)	39 (59)	

reported in a meta-analysis of 66 studies including about 1.5 million patients with all stages of colon cancer. This meta-analyses demonstrated that LCCs are associated with a significiantly lower risk of mortality compared to RCCs (HR 0.82; 95% CI: 0.79-0.84, p< 0.01) and this finding was independent of race, cancer stage and adjuvant chemotherapy.[14] Similarly, Brungs et al. found improved overall and cancer specific survival rates RCC patients with stage I and II, but RCC patients with stage III had a worse overall survival and a trend to worse cancer specific survival.[15] In their meta-analyses, RCC were more likely to have a more advanced grade, stage and more commonly occurred in older

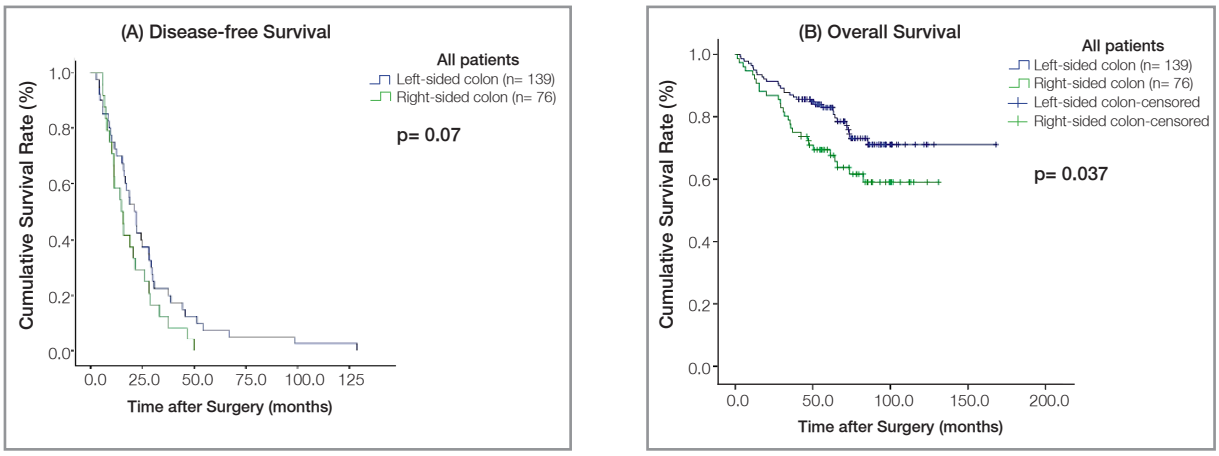

Figure 1. Kaplan-Meier curves of patients with stage III colon cancer grouped by right-and left-sided colon
A: Disease-free survival of all patients; **B**: Overall survival of all patients

patients with more comorbidities. In this study, we have demonstrated that TNM stage and venous invasion were independent poor prognostic factors for overall survival, but conversely tumor location was not. 3-year DFS rates were similar between the two groups; however, patients with RCC exhibited a worse 3-year overall survival than those with LCC. While the DFS rate was similar, the difference of overall survival suggests that the patients with right colon cancer are similar to the left colon in the early period, but they have an aggressive course when they progress to the metastatic stage. The incidence of peritoneal metastasis, which has been demonstrated as a risk factor resulting in the worst survival outcome, was significiantly higher in patients with RCC compared to those with LCC.[40] This may be one of the factors playing a role in short survival of patients with RCC.

Accumulating evidence has shown that the location of the primary tumor can be both a prognostic and predictive factor of response to EGFR inhibitors in metastatic colorectal cancers.[41-46] Many studies have shown that panitumumab and cetuximab confer little if not any benefit to patients with meta-

Table 2. Prognostic factors for overall survival

Variables	Univariate Analyses		Multivariate Analyses	
	HR	p	HR	p
Age. years (≥ 65 vs < 65)	0.42 (0.23-0.70)	0.001	1.78 (1.02-3.09)	0.040
Gender (Male vs. Female)	1.41 (0.62-1.73)	0.860		
Differention (Well vs Moderate vs Poor)	2.16 (1.16-4.03)	0.015	0.56 (0.29-1.08)	0.088
Tstage (T4 vs T1-3)	1.49 (0.89-2.47)	0.124		
Nstage(N2 vs N1)	2.43 (1.45-4.05)	0.001	0.88 (0.39-1.97)	0.764
Number of resected lymph nodes (< 12 vs. ≥ 12)	0.92 (0.52-1.64)	0.801		
Stage (3C vs 3B vs 3A)	2.63 (1.58-4.40)	< 0.001	0.37 (0.17-0.80)	0.043
Risk stratification (Low vs. High)	1.87 (1.10-3.18)	0.021	1.19 (0.56-2.56)	0.641
Perineural invasion (Yes vs. No)	1.42 (0.83-2.43)	0.192		
Lymphatic invasion (Yes vs.No)	1.37 (0.75-2.52)	0.29		
Venous invasion(Yes vs.No)	2.60 (1.48-4.57)	0.001	0.41 (0.23-0.74)	0.003
Tumor location	1.70 (1.02-2.83)	0.039	0.71 (0.41-1.25)	0.243
Adjuvant chemotherapy (Full vs Short)	1.45 (0.87-2.42)	0.149		
Dose reduction (Yes vs No)	0.74 (0.41-1.34)	0.331		

Table 3. Postoperative metastatic patterns of patients

Metastatic Patterns	Total (n: 215, %)	Left-sided (n: 139, %)	Right sided (n: 76, %)	p
Postoperative metastasis				
Yes	64 (29.7)	40 (28.7)	24 (31.5)	0.39
No	151 (70.3)	99 (71.3)	52 (68.5)	
Liver metastasis				
Yes	24 (37.5)	13 (32.5)	11 (45.8)	0.29
No	40 (62.5)	27 (67.5)	13 (54.2)	
Lung metastasis				
Yes	12 (18.75)	8 (20)	4 (16.6)	0.32
No	52 (81.25)	32 (80)	20 (83.4)	
Peritoneal carcinomatosis				
Yes	15 (23.4)	6 (15)	9 (37.5)	0.03
No	49 (76.6)	34 (85)	15 (62.5)	

static colorectal cancer, when the primary tumour originated from the right side.[41,42,44,46] However, the effect of tumor location on the selection of adjuvant chemotherapy is unclear. The different clinical and biological characteristics of LCC and RCC may contribute to different prognostic benefits obtained from adjuvant chemotherapy. Gervaz et al. proposed that tumor side should be considered in colon cancer before group stratification in future research on adjuvant chemotherapy.[37] Regardless of tumor location, adjuvant chemotherapy with fluoropyrimidines and oxaliplatin is the standart treatment in stage III colon cancer.[21,47,48] Although it has been shown that the duration of chemotherapy can be shortened in some subgroups of patients with opere stage III colon cancer, studies showing the effect of tumor location on adjuvant therapy are limited.[26,27] Grothey et al. demonstrated that 3 months adjuvant XELOX chemotherapy was sufficient in patients with low risk (T1-3, N2) opere stage III colon cancer. In high risk (T4, N2) patients, 6-months duration of therapy was superior to that for a 3-months duration,[26] but tumor sideness was not examined in this study. Should the tumor side affect the decision of adjuvan therapy duration in stage III operated colon cancers? In this study, we aimed to examine whether the duration of adjuvant chemotherapy and chemotherapy dose density affects DFS and overall survival in LCCs and RCCs. Approximately half of the patients (49.3%) could not complete treatment and dose was reduced in 41.7% of patients. It was observed that early discontinuation or dose reduction did not affect survival.

The limitations of this study can be listed as follows. First, this is a retrospective study and has a limited number of patients, there was not enough information about drug dose reductions and toxicities. Second, the short follow-up duration was insufficient to evaluate 5-year survival outcome. Finally, tumour molecular features such as MSI, BRAF and RAS mutations were not studied in the majority of patients, so could not be assessed. Thus these findings should be validated in further larger prospective studies.

Conclusion

Various studies have shown that RCC and LCC are considered as different tumor entities and RCC is more agressive than LCC. Tumor location is important in determining survival and choice of treatment in patients with stage IV colon cancer, but there are very limited studies evaluating the effect of tumor side on adjuvan chemotherapy in operated stage III colon cancer. Our findings suggest that prognostic features of patients with LCC and RCC were similar and the duration of treatment and dose intensity did not change survival of patients. Although 3-year DFS was similar, 3-year overal survival was longer in patients with LCC than those with RCC, suggest-

Table 4. Grade 3-4 treatment-releated toxicities during adjuvant chemotherapy

Toxicities	Right-sided colon cancer (n: 76, %)	Left-sided colon cancer (n: 139, %)	p
Neutropenia			
Total	35 (46)	63 (45.3)	0.932
Grade 1-2	20 (26.3)	40 (28.7)	0.952
Grade 3-4	15 (19.7)	23 (16.6)	0.778
Thrombocytopenia			
Total	23 (30.2)	40 (28.7)	0.812
Grade 1-2	19 (25)	33 (23.7)	0.765
Grade 3-4	4 (5.2)	7 (5)	0.963
Nause/vomiting			
Total	43 (56.5)	78 (56.1)	0.875
Grade 1-2	41 (53.9)	72 (51.7)	0.778
Grade 3-4	2 (2.6)	6 (4.4)	0.402
Neurotoxicity			
Total	31 (40.7)	57 (41)	0.819
Grade 1	18 (23.6)	32 (23)	0.781
Grade 2-3	13 (17.1)	25 (17.9)	0.892
Hand-foot syndrome			
Total	23 (30.2)	45 (32.3)	0.429
Grade1	20 (26.3)	36 (25.8)	0.342
Grade 2-3	3 (3.9)	9 (6.6)	0.212

ing that RCC has an aggressive course after progressing to the metastatic stage.

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