Do high-risk features support the use of adjuvant chemotherapy in stage II colon cancer? A Turkish Oncology Group study

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ABSTRACT

Background. A high-risk group of patients with stage II colon cancer has been identified by the results of studies in Western populations. The aim of this study was to investigate the prognostic factors of adjuvant chemotherapy in Turkish patients with stage II colon cancer.

Methods. A total of 554 stage II colon cancer patients were retrospectively enrolled in the study. Three hundred fifty-three patients had received adjuvant chemotherapy (5-FU-LV, FOLFOX or FLOX) and 201 had received no adjuvant chemotherapy. T4 tumor stage, lymphovascular invasion, perineural invasion, bowel obstruction and/or perforation, <12 harvested lymph nodes, and poor differentiation were defined as high-risk factors.

Results. The median age of the patients was 62 years (range 26-88). The median disease-free survival (DFS) was 58.1 months (95% CI, 47.6 months to 68.5 months) in the non-treatment group and has not been reached in the treatment group (P <0.01). In univariate analysis, patient age >60 years and T4 tumor stage were statistically significant factors that affected DFS as poor prognostic factors. Adjuvant chemotherapy reduced the risk of recurrence with statistical significance (P <0.01). In multivariate analysis, patient age >60 years and T4 tumor stage were independent risk factors affecting DFS. In addition, adjuvant chemotherapy was an independent favorable prognostic factor for DFS (P <0.01).

Conclusions. Clinical and pathological risk factors in patients with stage II colon cancer may be different in the Turkish population compared to other populations. Further prospective studies in colon cancer are needed to understand the differences in biology and risk factors between races.

Introduction

In 2013, the expected incidence of colon cancer worldwide will be more than 1.2 million[1]. In Turkey, the percentages of stage II and III colon cancer at diagnosis were estimated to be 26% and 35%, respectively[2]. The seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual[3] has subdivided stage II colon cancer into IIA (T3N0), IIB (T4aN0) and IIC (T4bN0) based on differential survival prognosis. Interestingly, the observed prognosis in the stage IIB and IIC subgroups has been worse than that of some stage III patients[4]. In addition to the AJCC classification, some other independent prognostic factors that are generally used in patient man-

agement include differentiation grade, lymphatic and perineural invasion, and DNA microsatellite instability[5]. However, despite significant progress in the molecular biology of colon cancer, no suitable biomarkers to guide the adjuvant treatment for stage II colon cancer have yet been identified.

In the past, stage II colon cancer was believed to be a step on the path from stage I to stage III disease, meaning that each of these stages represents a continuum of the same cancer with additional genetic abilities being acquired[6]. However, newer evidence shows that stage II colon cancer is genetically different from stage III colon cancer[7]. The benefit of adjuvant chemotherapy after surgery for stage III patients is well established[8,9]. In contrast, the role of adjuvant therapy in patients with stage II disease has been a source of debate. The efficacy of adjuvant chemotherapy for stage II colon cancer was established by the QUASAR study[10]. The adjuvant trials MOSAIC and NSABP C-07 did not show a significant overall survival (OS) benefit of oxaliplatin in combination with fluoropyrimidines in patients with stage II colon cancer. For oncologists the decision to administer adjuvant chemotherapy to stage II patients is based on clinical and pathological markers of risk[11]. High-risk stage II colon cancer has been defined as T4 tumor stage, poor histological grade, lymphovascular invasion, perineural invasion, bowel obstruction, and inadequate lymph node sampling (fewer than 12 nodes)[12,13]. According to the National Comprehensive Cancer Network (NCCN) guidelines, patients with high-risk stage II colon cancer should be considered for adjuvant chemotherapy[14]. However, a recent retrospective study did not show a survival advantage from adjuvant chemotherapy in stage II patients[15]. Unfortunately, information about some important prognostic factors was not available in this study. On the other hand, among patients in randomized phase III clinical trials, younger and older patients with stage II and III colon cancer had a similar adjuvant therapy benefit[16].

The aim of this study was therefore to evaluate the benefit of high-risk features for adjuvant chemotherapy in stage II colon cancer.

Materials and methods

Patients

Between August 1995 and December 2011, a total of 622 patients with stage II colon cancer from 7 centers in Turkey were identified. The inclusion criteria were a) resected colon cancer; b) pathological stage II (T3-T4, N0, M0); c) no neoadjuvant therapy; d) surgical treatment with or without adjuvant chemotherapy. The exclusion criteria were a) patient was lost to follow-up after surgery; b) diagnosis of other malignancies before colon cancer diagnosis. In accordance with the exclusion cri-

teria 68 patients were excluded from the study. The analysis was done on the remaining 554 patients.

Patients were followed post-surgery at 3-month intervals for 2 years. After 2 years they were observed at 6-month intervals with CT, CEA and physical examination, and after the fifth year they were observed annually. The study was approved by the ethics committee of the Medical Faculty of Necmettin Erbakan University, Meram, Turkey.

Clinicopathological characteristics

All patient data and tumor characteristics were collected from the medical records. High-risk factors were defined as the presence of the following: T4 tumor, lymphovascular invasion, perineural invasion, bowel perforation or obstruction, <12 retrieved lymph nodes, and poor differentiation. The adjuvant chemotherapy consisted of the 5-FU-LV MAYO regimen or the FOLFOX or FLOX regimen as previously described[8,9]. Pathological restaging was done according to the seventh edition of the AJCC Staging Manual[3].

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). The Kaplan-Meier method was used for the survival analysis. A log-rank analysis was performed for intergroup differences. The Cox proportional hazards model was used for univariate and multivariate analysis. The forward likelihood ratio was used for the multivariate selection process. A P value <0.05 was considered significant.

Results

The median age of the enrolled patients was 62 years (range 26-88). Three hundred thirty-two (59.9%) patients were male and 222 (40.0%) were female. Two hundred and one (36.2%) patients received no adjuvant chemotherapy and 353 (63.7%) received adjuvant chemotherapy. Forty-five patients (12.7%) received oxaliplatin-based therapies (FOLFOX or FLOX) and 308 (87.3%) received 5-FU-LV therapy. In the treatment group, T4 tumors were present in 76 patients; T4a in 73 patients and T4b in 3 patients. In the non-treatment group, T4 tumors were present in 28 patients; T4a in 24 patients and T4b in 4 patients. The proportion of T4 tumors was significantly higher in the treatment group (Table 1).

Poorly differentiated carcinomas and ≤12 harvested lymph nodes were features that were significantly more frequent in the treatment group than in the non-treatment group. Lymphovascular invasion and perineural invasion were also higher in the treatment than the non-treatment group, but these differences had no statistical significance. The proportion of mucinous-type

Table 1 - Clinical characteristics of patients

	Treatment	Non-treatment	P value
Number	353	201	
Male gender	212 (60.1)	120 (59.7)	0.93
Age (median)	59 (26-84)	67 (29-88)	<0.01
Age >60 years	153 (43.3)	141 (70.1)	<0.01
Tumor diameter (cm)	5 (2-18)	5 (1-19)	0.25
Tumor location			
Cecum	43 (12.2)	24 (11.9)	
Ascending colon	68 (19.3)	27 (13.4)	
Hepatic flexure	11 (3.1)	18 (9.0)	
Transverse colon	27 (7.6)	11 (5.5)	
Splenic flexure	12 (3.4)	11 (5.5)	
Descending colon	46 (13.0)	23 (11.4)	
Sigmoid	111 (31.5)	75 (37.3)	
Rectosigmoid	35 (9.9)	12 (6.0)	
T stage			
T3	277 (78.5)	173 (86.1)	0.02
T4a	73 (20.7)	24 (11.9)	
T4b	3 (0.8)	4 (2.0)	
Harvested LN	13 (0-80)	16 (0-60)	<0.01
Harvested LN ≤12	141 (39.9)	48 (23.8)	0.01
Poor differentiation	66 (18.6)	19 (9.4)	<0.01
LVI	75 (21.2)	32 (15.9)	0.25
PNI	66 (18.6)	23 (11.4)	0.07
Mucinous type	46 (13)	9 (4.4)	<0.01
Obstruction/perforation	76 (21.5)	24 (11.9)	<0.01

Values are presented as number (%) or median (range).
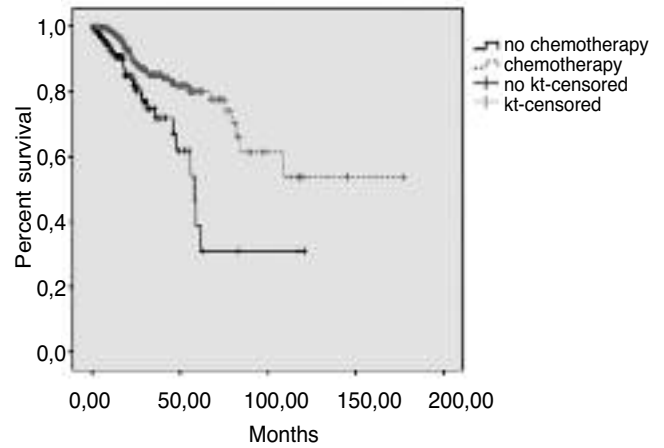LN, lymph nodes; LVI, lymphovascular invasion; PNI, perineural invasion.

Figure 1 - Disease-free survival in patients of the adjuvant chemotherapy and non-chemotherapy groups.
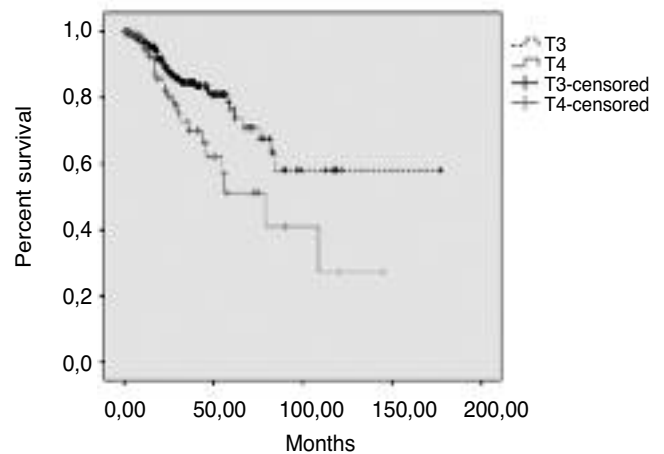
Figure 2 - Disease-free survival in patients with T3 *versus* T4 tumors.

carcinomas was significantly higher in the treatment than in the non-treatment group. Bowel obstruction and perforation were significantly more frequent in the treatment group than in the non-treatment group (Table 1).

The median follow-up time was 24.2 months (range, 1-177 months). Seventy-five patients had recurrences and the total number of deaths was 28. There were not enough events for the analysis of OS. The median disease-free survival (DFS) was 58.1 months (95% confidence interval [CI], 47.6-68.5 months) for the non-treatment group and has not been reached for the treatment group ($P < 0.01$) (Figure 1). The median DFS was 79.2 months (95% CI, 43.6-114.8 months) for T4 tumors and has not been reached for T3 tumors ($P < 0.01$) (Figure 2). The median DFS was 75.9 months (95% CI, 51.6-100.3 months) for patients older than 60 years and has not been reached for patients ≤60 years ($P < 0.01$) (Figure 3).

In univariate analysis, patient age >60 years and T4 tumor stage were statistically significant factors that affected DFS as poor prognostic factors. Adjuvant chemotherapy reduced the risk of recurrence with statistical signif-

Figure 3 - Disease-free survival in patients aged ≤60 years and >60 years.

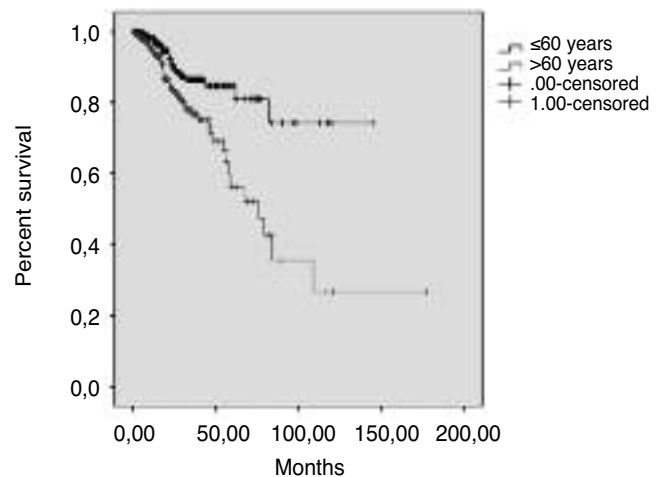icance. In multivariate analysis, patient age >60 years and T4 tumor stage were independent risk factors affecting DFS. Adjuvant chemotherapy was an independent favorable prognostic factor for DFS (Table 2).

Discussion

Controversy regarding the management of stage II colon cancer exists. This study showed that adjuvant chemotherapy reduced the risk of recurrence and was an independent favorable prognostic factor in Turkish patients with stage II colon cancer. In contrast to the ASCO and NCCN recommendations, only T4 tumor and patient age older than 60 were found to be independent risk factors for DFS. All other risk factors, defined as poor differentiation, lymphovascular invasion, perineural invasion, bowel obstruction and inadequately sampled lymph nodes (fewer than 12) were not found to be of prognostic significance.

The QUASAR trial showed the superiority of adjuvant treatment over curative surgery for patients with stage II colon cancer[10]. In contrast to the QUASAR trial, most studies on adjuvant 5-FU-LV treatment for stage II colon cancer gave negative results[15,17,18]. The differences between the results of these trials and our study could be due to differences in the gene expression of the tumors, which depends on race. The ability to tolerate 5-FU and the metabolism of drugs differ between races[19]. A retrospective study from Korea showed superior OS after adjuvant chemotherapy (5-FU-LV) compared to curative surgery alone in stage II colon cancer[20]. In that study, 5-year DFS in the adjuvant chemotherapy group was 87.9%, which was higher than in the MOSAIC trial, where 5-year DFS was 83.7% in patients treated with the FOLFOX regimen. These results show that there might be some biological differences

between races that can cause different responses to the same adjuvant treatment in colon cancer. Furthermore, East-Asian-American patients had a significantly better prognosis, while African-American patients had a worse prognosis than non-Hispanic white patients, despite the identical adjusted number of lymph nodes examined after surgery for colon cancer[21]. Similarly, African-American patients with resected stage II and stage III colon cancer who were treated with the same therapy as white patients experienced worse overall and recurrence-free survival than white patients[22]. A systematic review which included both Western and Eastern studies showed improved 5-year OS and DFS with adjuvant chemotherapy for stage II colon cancer[23]. In addition, adjuvant therapies with oral fluoropyrimidines improved the survival of stage II colon cancer patients in Japan[24]. Therefore, it would be useful to determine prognostic differences due to race/ethnicity after surgery for colon cancer.

The number of lymph nodes identified in the surgical specimen has routinely been correlated with clinical outcome in colon cancer[25]. Other high-risk factors such as bowel obstruction/perforation at presentation, undifferentiated histology, perineural infiltration, and lymphovascular invasion may be helpful to further characterize the prognosis of patients. Interestingly, not all of these parameters have been validated in multivariate analyses[26]. In the MOSAIC study, stage II patients with high-risk features had better DFS (HR, 0.76; 95% CI, 0.49-1.06) after the 6-year follow-up[27]. But a report based on a pooled analysis from the NSABP studies did not confirm these results of FOLFOX therapy in stage II colon cancer patients with high-risk features[28]. In addition, a recent subgroup analysis of the MOSAIC trial has shown that DFS and OS were not improved in high-risk stage II colon cancer patients and elderly patients[29]. A study from Japan showed improved prognosis

Table 2 - Factors associated with disease-free survival in stage II colon cancer

Factor	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age >60 years	2.38	1.45-3.90	<0.01	1.78	1.00-3.17	0.04
Male gender	1.37	0.86-2.19	0.17			
Stage (T4)	1.93	1.17-3.16	<0.01	2.32	1.36-3.97	<0.01
Mucinous histology	2.01	0.73-5.58	0.17			
Poor differentiation	0.87	0.66-1.16	0.35			
Tumor location	1.04	0.94-1.15	0.36			
Perforation/Obstruction	1.53	0.80-2.91	0.19			
Tumor diameter	0.89	0.79-1.00	0.06	0.91	0.81-1.02	0.13
Number of harvested nodes	0.99	0.96-1.01	0.52			
Number of harvested nodes ≤12	1.05	0.65-1.67	0.83			
PNI	1.59	0.85-2.97	0.14			
LVI	1.52	0.86-2.69	0.14			
Chemotherapy	0.41	0.26-0.67	<0.01	0.40	0.23-0.69	<0.01

HR, hazard ratio; CI, confidence interval; PNI, perineural invasion; LVI, lymphovascular invasion.

with adjuvant chemotherapy in patients with extensive venous invasion, fewer than 13 dissected lymph nodes, patients >50 years old, and male patients[30]. Particularly, patients with more than 2 of these risk factors had more benefit from adjuvant chemotherapy. In our study of Turkish colon cancer patients who were mostly treated with 5-FU-LV, adjuvant chemotherapy showed better results than in studies from Western countries. Conversely, the prognostic importance shown for high-risk factors in Western studies was not confirmed. Only T4 tumor stage and age over 60 years were found to be prognostic factors in multivariate analysis.

There are some limitations to this study. First of all, it is a retrospective study and the follow-up time is not enough to perform an analysis of OS. Second, the patient numbers in the treatment and non-treatment groups were not well balanced. Age was also not balanced. As the median age in our cohort was 62 years, we chose to dichotomize age around the value of 60. The association of age with outcome could be attributed to some other factors like comorbidities. The multivariate analysis that we carried out subsequently is expected to correct this to some extent. As this was a retrospective and multicenter study, performance status in the medical records unfortunately could not be sufficiently documented. Indeed, only 272 cases out of 554 had a recorded ECOG performance status. We therefore chose not to include performance status in the analysis. Nevertheless, the results of this study seem to have value, because the patients who received therapy had worse overall prognostic features yet a better DFS. This is actually a strong evidence to support adjuvant therapy in stage II colon cancer.

In conclusion, our results suggest that clinical and pathological risk factors in stage II colon cancer patients may be different in the Turkish population compared to other populations. We need more objective and reproducible risk factors like molecular biomarkers in colon cancer to identify which patients need adjuvant chemotherapy. Furthermore, prospective studies are needed in colon cancer to understand the difference of biology and risk factors between races.

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