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The impact of operation center and the prognostic factors on the outcome of patients with stage II and stage III colorectal cancer

ABDULLAH BÜYÜKÇELİK[1], HAKAN AKBULUT[1], BÜLENT YALÇIN[1], ORHAN ŞENCAN[1], İBRAHİM TEK[1], ÖZGÜR DEMİR[2], AHMET DEMİRKAZIK[1], DİLEK DİNÇOL[1], HANDAN ONUR[1], FİKRİ İÇLİ[1]

Ankara University School of Medicine, Departments of [1]Medical Oncology and [2]Internal Medicine, Ankara-Turkey

ABSTRACT

University hospitals have mainly well-educated and practiced surgeons in Turkey as well as in other developing countries. The aim of the study was to delineate the impact of operation center on the outcome of patients with stage II and III colorectal cancer, in addition to the prognostic factors. One hundred fifty two consecutive patients with stage II and III colorectal cancer treated at Ankara University School of Medicine İbni Sina Hospital, Department of Medical Oncology were retrospectively analysed. The patients operated at a university hospital (group A) were compared with those (group B) operated at other hospitals (community, private hospitals etc.) in terms of prognostic factors, considering age, gender, the location, stage and the differentiation of tumor, the number of resected and involved local and regional lymph nodes, preoperative CEA levels and adjuvant chemotherapy schemas. Patient characteristics of group A and B were similar. The patients in group A had slightly better 5 year overall (51.8% vs. 48.3%) and disease free survival (49.9% vs. 45.7%) advantage over those in group B, but the difference was not statistically significant. We found that the TNM stage of tumor was the only independent prognostic factor in our patients group. Five year overall survivals in patients with stage II and stage III tumor were 72.1% and 42.6%, respectively (p=0.0009). Likewise, 5 year disease free survival in patients with stage II and III tumor were 70.9% and 39.7%, respectively (p=0.0004). Our results showed that the operation center had no significant impact on the outcome of patients with stage II and stage III colorectal cancer. TNM stage of tumor was the only prognostic factor for both disease-free survival and overall survival in our patients group. [Turk J Cancer 2008;38(4):175-183]

KEY WORDS:

Colorectal cancer, prognostic factor, surgical treatment, adjuvant treatment

INTRODUCTION

Surgery is the most important treatment modality in colorectal cancer. However, the risk of clinical failure after resection in colon cancer is mainly due to the progression of previously undetected distant metastases (1). The stage of the tumor at the time of resection remains the single most important prognostic factor to predict the likelihood of residual microscopic metastatic cancer (2). Nowadays, 5-fluorouracil/leucovorin (5-FU/Leu) and oxaliplatin combination is the standard of care for adjuvant treatment in stage III colon cancer. However, the benefit of adjuvant chemotherapy is still controversial in stage II colon cancer (3,4).

On the other hand, the local residual disease is responsible for local failure of treatment in rectal cancer. The sigmoid, rectosigmoid, and intraperitoneal (without gross invasion of a contiguous structure) rectal cancers have the low risk for local recurrence and treated with adjuvant chemotherapy as in colon cancers. However, rectum cancers located below peritoneal reflection, especially 12 cm or less from the anal canal are considered as true rectal cancer, and should be treated by multimodal approach, including surgery, chemotherapy and radiotherapy. The pelvis is the most common site of tumor recurrence which is a major cause of morbidity and mortality in patients with rectal cancer. The effectiveness of salvage treatment is usually limited and only offers temporary palliation (5). The major tumor-related risk factors for local recurrence are the number of involved regional lymph nodes, the extent of transmural penetration, and the tumor grade (6). The lateral (radial, circumferential, tangential) margin is the best predictor of local failure (7,8). The surgeon's operative technique and ability to achieve a negative circumferential marginly total mesorectal excision are strong determinants of local control for rectal cancer. That's why the frequency of local recurrence varies among individual surgeons from less than 10% to more than 50% (9).

University hospitals mainly have well-educated and practiced physicians in Turkey as well as in other developing countries. Therefore, we retrospectively analysed the patients with stage II and III colorectal cancer treated with adjuvant chemotherapy and/or radiotherapy in our center between December 1988 and April 2000 for prognostic factors in this study. We also analysed the patients for local recurrence and survival, to delineate whether operation centers (university hospitals vs. community hospitals) had an impact on the outcome of patients with stage II and III colorectal cancer or not.

MATERIALS AND METHODS

Patient selection and operation centers

One hundred fifty two consecutive patients treated with adjuvant chemotherapy and/or radiotherapy for colorectal cancer between December 1988 and April 2000 were included. Only the patients with adenocarcinoma of the colon and rectum were included in the study. Patients were mainly divided into two groups according to the operation center. The patients who were operated at university hospitals were in group A, and those operated at other hospitals (i.e., private, state and regional hospitals etc.) were in group B. The patients were also analysed for the rate of local recurrence of the disease.

Location of tumor and surgical treatment

Rectal cancer was defined as the cancer within 12 cm from anal canal verge. The cancer beyond this border was defined as colon cancer. Therefore, sigmoid colon was included in colon group.

All patients with rectal cancer had low anterior resection or abdominoperineal resection in conjunction with extensive local and regional lymph node dissection. Patients with colon cancer had undergone segmentary colon resection and local and regional lymph node dissection. The patients treated by other surgical methods (i.e., only tumor resection, partial resection or palliative resection) as the treatment of colorectal cancer were not included in the study. All patients had tumor free surgical margins, including proximal, distal sides, and the side toward depth of invasion.

Prognostic factors, staging of the tumor and survivals

Patients were analysed for prognostic factors, considering age, gender, the location, stage and the differentiation of tumor, the number of resected and involved local and regional lymph nodes, preoperative carcinoembryonic antigen (CEA) level, operation centers and adjuvant chemotherapy schedules. The tumor size which had been previously reported not to be related to the outcome in patients with colorectal cancer (10) was not used as a prognostic factor in the analysis. The surgical resection margins, including proximal, distal sides, and the side toward depth of invasion were tumor free in all patients. CEA levels were measured by radioimmunoassay, and were considered to be high if more than 3.5 ng/mL in nonsmokers and 5 ng/mL in smokers.

TNM staging system (pathological staging) defined elsewhere was used for the tumor staging (11).

Overall survival (OS) and disease-free survival (DFS) were calculated from the date of operation to the date of death due to any cause and to the time of first evidence of disease recurrence, respectively.

Adjuvant treatments

All of one hundred fifty two patients received at least two cycles of 5-FU/Leu or 8 weeks of 5-fluorouracil and levamisole (5-FU/Lev) combinations (12,13). The schedule of 5-FU/Leu was Leu 20 mg/m^2 intravenous bolus half an hour before 5-FU infusion for 5 days, and 5-FU 425 mg/m^2 intravenous bolus for 5 days. 5-FU/Leu was repeated every 28 days, and it was continued up to 6 cycles if white blood cell count was $\geq 4x10^9$/L, neutrophils were $\geq 2x10^9$/L, platelets were $\geq 100x10^9$/L, and patient had adequate renal and hepatic functions. One week delay of adjuvant chemotherapy due to hematological toxicity was allowed. The schedule of 5FU/Lev was 5-FU 450 mg/m^2 intravenous bolus 1-5 days, then weekly from day 29, and Lev 50 mg, per oral, three times a day for 3 days every other week. 5-FU/Lev was continued for 1 year if bone marrow, renal and hepatic functions were adequate as defined above. Hematopoietic growth factors such as granulocyte-colony stimulating factor or granulocyte/macrophage-colony stimulating factor were not used prophylactically. Patients with stage III or locally invasive rectum cancer were also given local and regional radiotherapy.

Statistical analysis

Student's t test and chi-square test were used in the comparison of parametric and non-parametric data among the groups, respectively. Kaplan-Meier curve was used to calculate the survivals, and differences were analysed using log rank test. Cox-regression analysis was used to determine independent prognostic factors. The p value less than 0.05 was considered as statistically significant. All statistics were done with the SPSS for Windows 9.05 statistics package.

RESULTS

Patient characteristics and operation centers

Patient characteristics are summarized in Table 1. Median age was 55 years (17-79), and the female/male ratio was 0.7. TNM stages of tumor were II in 38.2% and III in 61.8% of the patients. The locations of the tumor were colon in 58 patients and rectum in 94 patients. The tumor was well-differentiated in 51.3%, moderately differentiated in 46.1% and undifferentiated in 2.6% of the patients. Adjuvant chemotherapies were 5-FU/Leu in 112 patients and 5-FU/Lev in 40 patients. Adjuvant radiotherapy was applied to 60 patients (63.8 percent of patients with rectal cancer) with rectal cancer. CEA levels were measured preoperatively in only 64 patients; it was elevated in 33 of 64 patients. The number of resected regional lymph nodes was 10 or less in 53 of 152 patients (34.9%), and was more than 10 in 99 of them (65.1%). The status of involved local and regional lymph nodes were 0 (N0) in 58, 1-3 (N1) in 60, and ≥4 (N2) in 34 of the patients. Operation centers were university hospital (group A) in 66 of those 152 patients and other hospitals (group B) in 86 of them.

Prognostic factors and survivals

Considering the median age, gender, TNM stage, differentiation and location of the tumor, adjuvant chemotherapy regimen and relapse site, preoperative CEA level, the number of resected locoregional lymph nodes and the number of involved local and regional lymph nodes, there was no statistically significant difference between the group A and group B (Table 1).

Median follow-up interval was 44 (6-232) months. Median DFS and OS have not been reached yet for all patients. DFS and OS at 5 year were 51.8 and 52.9 percent in all patients, respectively. There was no statistically significant difference in both DFS and OS between group A and B (Table 2, Figure 1A and 1B). It was also found that the location of tumor, age, gender, the number of resected regional lymph nodes, adjuvant chemotherapy regimen (5-FU/Leu vs. 5-FU/Lev), location of tumor and preoperative CEA level had no impact on both DFS and OS (Table 2). However, OS in patients with undifferentiated tumor at 5 year was 0% but the number of patients (4 patients) with undifferentiated tumor was quite small (p=0.0032, Table 2).

TNM stage of tumor was a significant predictor for both DFS and OS. OS were 72.1% and 42.6% at 5 year for patients with TNM stage II and stage III tumor, respectively (p=0.0009, Table 2, Figure 2A). Likewise, the 5 year

Table 1
Patient characteristics

	Group A n = 66 (%)	Group B n = 86 (%)	p value
Median age	65(17-79)	48 (30-69)	0.734
Female/male ratio	27/39	38/48	0.686
TNM stage			
II	24 (36.4)	34 (39.5)	0.845
III	42 (63.6)	52 (60.5)	
Tumor location			
Colon	25 (37.9)	33 (38.4)	0.912
Rectum	41 (62.1)	53 (61.6)	
Differentiation of the tumor			
Well-differentiated	36 (54.5)	42 (48.8)	0.659
Moderately differentiated	27 (41.0)	43 (50.0)	
Undifferentiated	3 (4.5)	1 (1.2)	
Adjuvant chemotherapy			
5-FU/Lev	14 (21.2)	26 (30.2)	0.696
5-FU/Leu	52 (78.8)	60 (69.8)	
Adjuvant radiotherapy*	28 (68.3)	32 (60.4)	0.678
Preoperative CEA level			
High**	19 (28.8)	14 (16.3)	0.861
Normal†	13 (19.7)	18 (21.0)	
Undetermined	34 (51.5)	54 (62.7)	
Relapse site			
Local	14 (21.2)	14 (16.3)	0.884
Distant	10 (15.2)	10 (11.6)	
Local and distant	8 (12.1)	7 (8.1)	
The number of resected LN			
≤10	22 (33.3)	31 (36.0)	0.936
>10	44 (66.7)	55 (64.0)	
The number of involved LN			
Negative	24 (36.4)	34 (39.5)	
1-3 (N1)	28 (42.4)	32 (37.2)	0.812
≥ 4 (N2)	14 (21.2)	20 (23.2)	

5-FU/Lev: 5-fluorouracil and levamisole; 5-FU/Leu: 5-fluorouracil and leucovorine; CEA: Carcinoembryonic antigen; LN: Lymph node
*Adjuvant radiotherapy was applied to patients with locally invasive or stage III rectal cancer
**More than 3.5 ng/mL in non-smokers and 5 ng/mL in smokers
†Less than 3.5 ng/mL in non-smokers and 5 ng/mL in smokers

DFS rates were 70.9% and 39.7% in patients with TNM stage II and stage III tumor, respectively (p=0.0004, Table 2, Figure 2B). Like TNM stage of tumor, the number of involved local and regional lymph nodes had also impact on DFS and OS (Table 2). The 5 year OS in patients with 0 (N0), 1-3 (N1) and ≥4 (N2) involved local and regional lymph nodes were 71.58%, 54.98% and 40%, respectively (Table 2, p=0.004). Again, the 5 year DFS in patients with N0, N1 and N2 disease were 69.53%, 47.05% and 30.49%, respectively (Table 2, p=0.001).

Recurrences of tumor (both local and distant) were observed in 63 patients (41.4%). The rate of local recurrence

Table 2
Results of univariate analysis for survivals

	5 year DFS (%)	p value	5 year OS (%)	p value
Operation center				
Group A	49.9	0.858	51.8	0.967
Group B	45.7		48.3	
TNM Stage				
II	70.9	0.0004	72.1	0.0009
III	39.7		42.6	
Differentiation of tumor				
Well differentiated	53.2		52.2	
Moderately differentiated	49.1	0.235	52.8	0.0032
Undifferentiated	33.3		0	
Gender				
Female	44.7	0.054	48.1	0.122
Male	57.4		57.3	
Age				
≤45 year	62.6	0.751	69.4	0.046
>45 year	44.8		43.1	
Location				
Colon	52.5	0.662	55.6	0.708
Rectum	50.1		50.3	
The number of resected LN				
≤10	54.9	0.746	49.1	0.827
>10	50.7		57.1	
The number of involved LN				
Negative (N0)	69.53		71.58	
1-3 (N1)	47.05	0.001	54.98	0.004
≥4 (N2)	30.49		40	
Adjuvant chemotherapy				
5-FU/Lev	51.2	0.862	55.6	0.71
5-FU/Leu	53.9		53.4	
Preoperative CEA level				
High*	43.4	0.834	55.7	0.124
Normal**	45.1		37.5	

5-FU/Lev: 5-fluorouracil and levamisole; 5-FU/Leu: 5-fluorouracil and leucovorine; CEA: Carcinoembryonic antigen; LN: Lymph node
*More than 3.5 ng/mL in non-smokers and 5 ng/mL in smokers
**Less than 3.5 ng/mL in non-smokers and 5 ng/mL in smokers

was 28.3% (43 patients) in all patients. The rates of local recurrence in patients with colon and those with rectum cancer were 25.9% (15 of 58 patients) and 29.8% (28 of 94 patients), respectively. Considering the relapse rates, there were no significant difference between group A and B (Table 1).

Cox-regression analysis showed the TNM stage of the tumor as the only independent prognostic factor for both DFS and OS (p=0.044). Although the patients operated at the university hospitals tend to have better OS and DFS, the difference between group A and B was not statistically significant (Table 2 and Figure 1A and 1B).

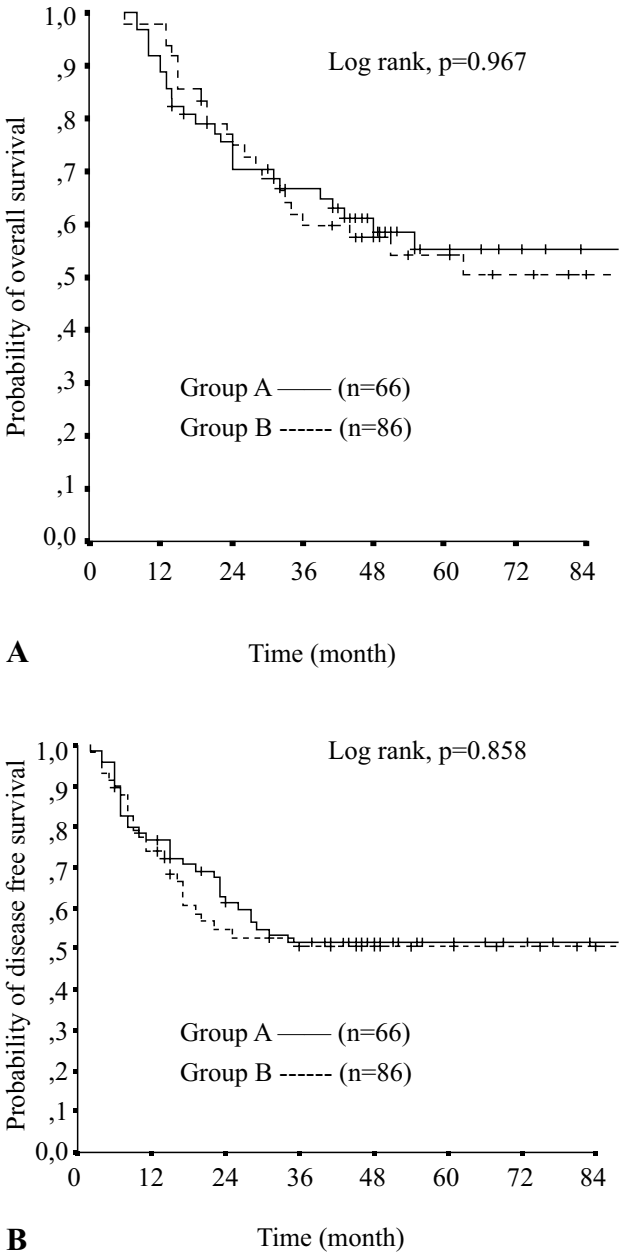

Fig 1(A,B). Kaplan-Meier curves according to the operation center. (A): for OS and (B): for DFS. There was not statistically significant difference in both OS and DFS between Group A and B

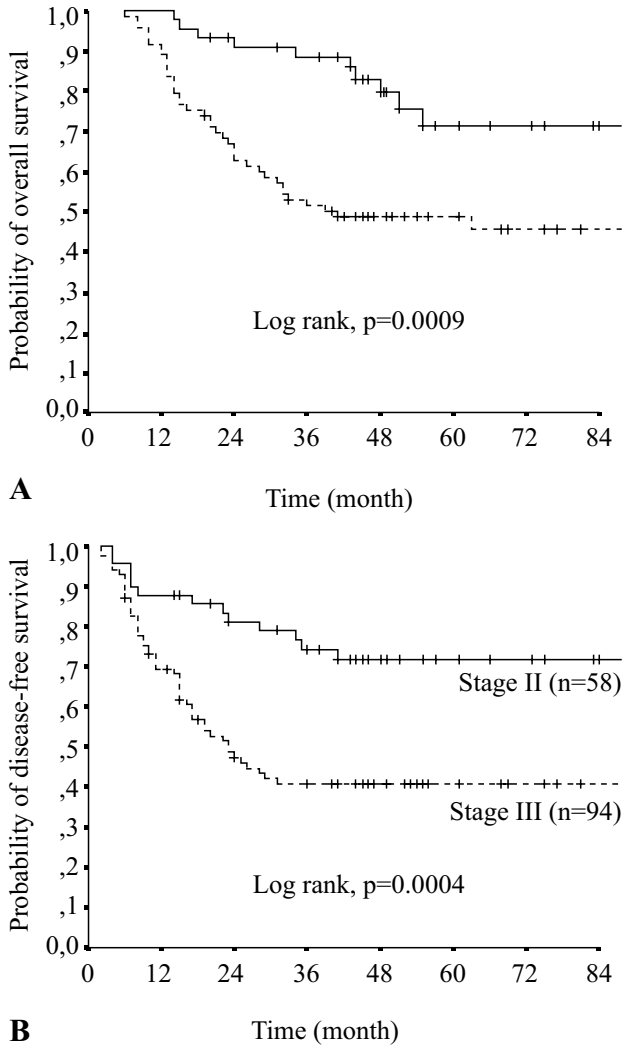

Fig 2(A,B). Kaplan-Meier curves according to TNM stage of tumor. (A): for OS and (B): for DFS. TNM stage was the only independent prognostic factor for both OS and DFS in our patients group

DISCUSSION

Colorectal cancer is the most common malignancy of gastrointestinal tract in the western countries. The majority of patients with colorectal cancer undergo surgical resection with curative intent. Although the improvement in surgical techniques, adjuvant chemotherapy and/or radiotherapy in the treatment of colorectal cancer has improved the survival of patients with colorectal cancer, many patients with colorectal cancer ultimately have recurrence of their disease and die of disease progression. Clearly, there remains need for further development of better treatments for early-stage colorectal cancer. In order to plan the most appropriate treatment modality for a patient with early colorectal cancer every physician should be aware of prognostic (related to likelihood of survival) and predictive factors (related to likelihood of response to therapy) for the disease.

The stage of the tumor at the time of resection remains the most important prognostic factor to predict the probability of residual disease (1,2). While stage I colorectal cancer have 90 percent cure rate by surgery alone, stage II and III disease have high risk of microscopic residual or

metastatic disease (1,2). Therefore, those patients should be considered for adjuvant treatment. Five year DFS rates in stage II and stage III colorectal cancer is 78-90% and 20-50%, respectively, with surgical treatment alone. Although the efficacy of adjuvant chemotherapy in stage II colon cancer is controversial, it significantly improves the outcome in patients with stage III colorectal cancer (3,4).

Besides the tumor stage, many factors such as the presence of obstruction or perforation, vascular or lymphatic invasion (or both), per neural invasion, peritumoral lymphocytic infiltration, the character of invasive margin and tumor type, presence and the number of mast cells, age and gender, tumor grade, DNA content, increased mitosis, low Bcl-2 expression, low apoptosis rate, vascular endothelial growth factor levels and allelic loss of chromosome 18q have been studied as a prognostic factor (14,15).

In the present study, the TNM stage of tumor was found to be an independent prognostic factor which is consistent with the previous studies. However, the results of our study were somewhat contradictory to the literature. The outcome of the patients younger than 40 years were reported to be poor in the literature. Also, females were found to have a survival advantage when compared to males in early studies, but this association was not confirmed by other studies (6,15). Interestingly, we found that patients younger than 45 years had better both DFS and OS, and although there was no statistically significant difference in OS between males and females, males had a borderline DFS advantage over females (p=0.054). It is likely that the retrospective nature of the study may be partially responsible for these results. Other explanation for the poor outcome in patients older than 45 years may be the insufficient treatment in this group of patients. The shorter DFS in patients older than 45 years may support this explanation. Females are less likely to undergo screening studies than males (15). Therefore female patients may have more advanced disease than male patients.

It has been found that the tumor arising at or below the peritoneal reflection (rectosigmoid and rectum) have worse prognosis than those arising above the reflection. With regard to colon primary tumors, the prognostic value of primary tumor location is inconclusive (14,15). We found that patients with colon cancer tend to have better outcomes than those with rectal cancer but the difference was quite small and was not statistically significant which may be related to small population size.

The degree of tumor differentiation is confirmed as a prognostic factor in several studies (16). The patient with well or moderately differentiated tumor had a survival advantage when compared to those with undifferentiated tumor, but the number of undifferentiated tumor was quite small to make a firm conclusion in the present study.

Although the number of lymph nodes present in any given operation specimen may be limited by anatomic variation, surgical technique and pathological examination, it has been shown that a minimum 12-15 regional lymph nodes should be examined pathologically to accurately predict regional lymph node negativity (17,18). We have also examined the impact of the number of resected regional lymph nodes on the outcome. There was no survival difference between the patients who had equal or less than ten and those who had more than ten resected regional lymph nodes. However, the number of involved local and regional lymph nodes had an impact on the outcome as in the TNM stage of tumor. The patients with N0 disease had significantly survival advantage over those with N1 and N2 disease. These findings are compatible with the knowledge of literature. No survival difference according to the adjuvant chemotherapy schedules (six months 5-FU/Leu, Mayo Clinic Regimen vs. 52 weeks 5-FU/Lev) was noticed.

Although CEA is the most reliable indicator for tumor recurrence in colorectal cancer after curative resection, the prognostic potential of preoperative CEA level is still unclear (15). It is possible that an elevated CEA level may be the reflection of a more advanced colorectal cancer. In our study, it was found that preoperative CEA level was not a prognostic factor in both univariate and multivariate analyses. However, it was not measured preoperatively in the majority of patients in the present study and its level was elevated in only thirty three patients.

The distant metastases and local failure are important issues for the treatment failure in patients with colorectal cancer. The local failure is more frequent in patients with rectal cancer than in those with colon cancer. The inadequate surgical resection is a major cause of pelvic

recurrence (9). Therefore, the surgeon's ability to achieve a negative surgical margin is a strong determinant for local control. The early studies have shown that patients treated with abdominoperineal resection as a primary surgical treatment had a higher recurrence rate than those treated with low anterior resection, but later studies did not confirm these results (19,20). Nowadays, total mesorectal excision in conjunction with low anterior resection or abdominoperineal resection is recommended as the optimal surgical treatment for rectal cancer (21). The local recurrence rate in patients treated with total mesorectal excision ranges 3.5-13 percent in various studies, according to the locoregional lymph node positivity (21-23). However, the local recurrence rate from one surgeon to another ranges from less than 10 percent to more than 50 percent (9). It has been shown that removing rectal cancer surgery from routine surgical teaching and concentrating training in total mesorectal excision among specialized surgeons could drop the local recurrence rate to 7 percent when compared to historic control with a local recurrence rate of 23 percent (24). In addition, the local recurrence rate and survival advantage in patients with rectal cancer is associated with surgeon colorectal surgery fellowship training (24). The hospital size, hospital type (university vs. community), and experience of the surgeon are also important factors for improving survival and local recurrence rate in rectal cancer patients (25). We found that the operation center had no impact on the outcomes in our patients group, though the patients operated at university hospitals had slightly better survival than those operated at other hospitals (i.e., community hospitals). Though there were no significant differences in patients' characteristics, in relapse rate and in other prognostic factors, local recurrence rate in our patients group was higher than those reported in the literature. Also, there was no significant difference in the rate of local relapse in patients with rectal cancer between group A and B. The colorectal surgery has been done as a routine surgical procedure in the majority of the hospitals, including many university hospitals in Turkey. It would be better that the individual surgeon's characteristics were analysed to delineate the impact of surgeon on the outcome of patients with operable colorectal cancer. Due to retrospective nature of our study, to clarify the surgeon's characteristics was very difficult. Therefore, we are planning a prospective study with a larger sample size to delineate the role of surgeon in the treatment of colorectal cancer.

In conclusion, TNM stage of the disease was the only independent prognostic factor in the current study. Operation at university hospitals had no impact on the outcomes in patients with stage II and stage III colorectal cancer, although patients operated university hospitals had slightly better outcome than those operated at community or other hospitals. Although our study does not represent the whole Turkish population, and it has relatively small sample size, it is informative. Prospective studies are necessary to clarify this issue in Turkey and World.

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