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ORIGINAL ARTICLE

Efficacy, safety and prognostic features of resected colon carcinoma treated in "real world" practice: a retrospective cohort-study

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Summary

Purpose: *Treatment outcomes and prognostic features of a specific cancer generally come from prospective randomized studies. It seems reasonable to ask the question whether the results of prospective randomized studies entirely reflect the results of the population treated in "real world" practice. Therefore we performed a retrospective cohort analysis in order to find out the efficacy of adjuvant chemotherapy as well as the prognostic factors of our patient population treated in daily practice, and compared these findings with those defined in the prospective studies.*

Methods: *Data of patients with high risk stage II and all stage III colon cancers treated with adjuvant chemotherapy were retrospectively analyzed.*

Results: *A total of 190 patients were retrospectively analyzed. The rates of T2, T3, and T4 tumors were 4.2, 77.9, and 17.9%, respectively. Over 35% of the patients had stage II disease. Of the 5-fluorouracil (5-FU)-based chemotherapy group (n=141), 15% had a dose reduction because of toxicity and 73% were given the total planned dose and cycles, whereas these rates were 18.5 and 66% for oxaliplatin+5-FU treated group, respectively (p=0.66 and 0.44, respectively). The 3-year disease-free survival (DFS) and 5-year cancer-specific overall survival (OS) for all patients were 69.4 and 73%, respectively. In multivariate analysis, cancer-specific OS showed significant correlation with T stage (p=0.015) and with perineural invasion (p=0.024). Also patients ≥ 65 years old had significantly lower OS (p= 0.003)*

Conclusion: *This study is the first to report the efficacy of adjuvant treatment in a curatively resected Turkish colon carcinoma population treated in "real world" practice. Our study showed that the treatment results and the prognostic parameters of Turkish colon carcinoma patients treated in "real world" practice are not different from those of selected patients treated in randomized prospective studies.*

Key words: adjuvant treatment, colon cancer, fluorouracil, oxaliplatin, real world

Introduction

Colorectal cancer is a common and potentially lethal disease. Nearly 150,000 new cases of large bowel cancer were expected in 2008 in the United States, with a colon to rectal cancer ratio of approximately 2: 1 [1]. It is the third most common cause of death due to cancer after lung and breast cancer in women and after lung and prostate cancer in men [2].

In about three quarters of patients diagnosed with colorectal cancer, the disease is limited to the bowel wall or surrounding lymph nodes and for this surgery is indicated as a curative therapy. Currently, unless otherwise contraindicated, adjuvant chemotherapy is recommended after curative resection in those patients with stage II colon cancer who have high risk criteria, and in all patients with stage III disease, to decrease the recurrence of disease due to occult micrometastases believed to have been present at the time of surgery [3].

There are several factors that have been defined in prospective studies as associated with an increased risk of tumor recurrence. These include the TNM stage, poorly differentiated histology (grade), lymphovascular invasion (LVI), perineural invasion (PNI), T4 tumor,

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presence of clinical bowel obstruction or perforation, preoperative high serum carcinoembryonic antigen (CEA) levels, and close, indeterminate or positive surgical margins [4-7]. Several other, molecular features such as hypermethylation of DNA mismatch repair genes, microsatellite instability [8] or loss of heterozygosity at chromosome 18q [9] have also been found to bear prognostic significance. For judging the adequacy of surgical technique as a predictor of outcome, examination of <13 lymph nodes has been linked with increased mortality in T3N0 colon cancer [10].

No single randomized clinical trial has demonstrated a survival benefit for adjuvant therapy in patients with stage II colon cancer. However, the colon cancer treatment practice guideline of the current National Comprehensive Cancer Network (NCCN) recommends administering adjuvant chemotherapy to patients with stage II colon cancer who have high risk criteria for relapse, such as inadequate lymph node dissection, T4 lesion, perforation, obstruction, lymphovascular involvement or poorly differentiated histology after other co-morbidities and the anticipated life expectancy have been assessed [11].

The superiority of 5-FU modulated by leucovorin (LV) in the adjuvant setting was shown in the NSABP [National Surgical Breast and Bowel Project] C-03 protocol in 1993 [12]. For patients who are considered for 5-FU-based treatments, the best adjuvant regimen has not been conclusively established yet, but the Mayo regimen [13], a weekly Roswell Park Memorial Institute (RPMI) regimen [14] or protracted infusion of 5-FU alone can be chosen. However, it has been shown that the efficacy of oral fluoropyrimidines (capecitabine [15] and UFT [16]), are also comparable to bolus administration of 5-FU/LV. Recently, evidence of additive effects have been demonstrated when oxaliplatin, formerly approved for metastatic colorectal cancer, was added to the 5-FU+LV backbone in the adjuvant setting [17,18].

Contemporary recommendations for the treatment of curatively resected colon cancer in the adjuvant setting come from large, multicenter and randomized prospective studies. We know that prospective studies analyzing the efficacy of anticancer treatments include selected patient populations with better clinical and laboratory parameters. Obviously, these groups constitute a small percentage of patients with related diseases. It seems reasonable to ask the question whether the results of prospective randomized studies entirely reflect the results of the population treated in "real world" practice. Therefore we performed a retrospective cohort analysis in order to find out the efficacy of adjuvant chemotherapy as well as the prognostic factors of our patient population treated in daily practice, and compared these findings with those defined in the prospective studies.

Methods

Eligibility criteria

Patients who had histologic proof of adenocarcinoma of the colon and had undergone complete resection of the primary tumor without gross or microscopic evidence of residual disease were screened for eligibility. The entire tumor had to be above the peritoneal reflection and all known tumors had to be resected *en bloc*. There had to be no evidence of any distant metastasis as determined by the surgeon at operation, at a computed tomography (CT) scan of the thorax, or at a CT/MRI (magnetic resonance imaging) of the abdomen and pelvis. Full evaluation of the colon and rectum by colonoscopy was required to exclude other synchronous, unresected primary cancers. Patients had to have the following: evidence of adequate organ function as measured by the Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, serum bilirubin ≤ 2x IULN (institutional upper limits of normal), aspartate aminotransferase (AST) ≤ 2x IULN, alkaline phosphatase (ALP) ≤ 2x IULN, and serum creatinine (Cre) ≤ 2x IULN; white blood cell count (WBC) more than 3,000/μL; and platelets (PLT) ≥ institutional lower limit of normal. Patients were ineligible if they had been treated for any other cancer within the previous 5 years (except for superficial squamous or basal cell skin cancer or *in situ* carcinoma of the cervix) or if they had any other severe concomitant disease that would limit life expectancy. All patients who were given adjuvant chemotherapy within 3 months after definitive surgery were included in the study.

Data of 190 eligible patients, who had been treated consecutively in our institution between January 1997-January 2008 with adjuvant chemotherapy after curative resection with a final diagnosis of high risk stage II or stage III colon cancer were retrospectively analyzed. Patients who were given even one cycle of chemotherapy were included in the analysis.

Treatment & aims

Regarding the adjuvant treatment, patients were administered either 5-FU-based or oxaliplatin + 5-FU-based regimens. The total cycles of chemotherapy per patient and the total dose per cycle for each anti-neoplastic agent were analyzed.

The primary aims of this study were to evaluate the efficacy of adjuvant treatment and the prognostic factor(s) related to outcomes in a Turkish population with curatively resected colon carcinoma patients in routine daily practice, irrespective of the chemotherapy regimen given. Comparison of the outcomes of 5-FU-

based regimens with oxaliplatin + 5-FU-based regimens and assessment of life-threatening/disturbing treatment-related toxicities were secondary aims of the study.

The potential effects of factors like age, sex, tumor diameter, stage of disease, T stage, nodal stage, grade of differentiation, lymphatic invasion (LI), vascular invasion (VI) and PNI, total number of dissected lymph nodes, tumor localization, mucine presence and choice of treatment (5-FU-based vs. oxaliplatin+5-FU-based) on the 3-year DFS and 5-year cancer-specific OS were investigated.

Evaluation of efficacy

Patients were followed-up every 3 months for the first 2 years and every 6 months thereafter as the guideline proposes [11]. Complete blood counts (CBC), routine biochemical tests and serum CEA levels were measured at every visit and also in situations when clinically indicated. Imaging follow-up with CT and MRI was done according to contemporary guidelines. In cases where relapse was controversial a final decision regarding the disease status of the patient was made by a council consisting of medical oncologists, general surgeons, radiologists and specialists of nuclear medicine.

DFS was defined as the time between the date of the operation and the first relapse, the occurrence of a second primary colon cancer, death from any cause with no recorded evidence of relapse, or the last date at which the patient was known to be free of disease. OS was defined as the time from the date of the operation to death or to the date at which the patient was last confirmed to be alive.

Evaluation of safety

All treatment-related adverse events that were noted in the patient files were taken into account. Treatment-related adverse effects were graded according to Common Toxicity Criteria 2.0 (CTC) [19]. Adjustments of the doses of anti-cancer treatments caused by experienced toxicities were also recorded. For every patient, the highest grade of toxicity encountered during all the treatment cycles was noted once under a specific toxicity title.

Statistical analysis

Two-sided statistical tests were performed on the DFS, OS, and toxicities. Survival curves were estimated by the Kaplan-Meier method. Records of patients who were lost to follow-up or alive at the time of analysis were censored at the last documented visit. The differences in DFS and OS were evaluated using log-rank test, or an unadjusted proportional hazards regression model to assess hazard ratios and their 95% CIs. Proportional hazard regression models of DFS and OS were used to identify significant prognostic covariates. A p value <0.05 was accepted as significant.

Results

Study population

The median follow-up of 190 eligible patients was 34.8 months (range 1.94-147.6). One hundred and forty-one patients received 5-FU-based treatments and 49 oxaliplatin+5-FU-based regimens. The baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics of all patients with adjuvant treatment for colon adenocarcinoma

Characteristics	*n (%)*
Age (years)	
Median (range)	62 (26-82)
Age < 65 yrs	111 (58)
Sex	
Male	103 (54.2)
Female	87 (45.8)
Localization	
Sigmoid	92 (48.4)
Descending	25 (13.2)
Transverse	12 (6.3)
Caecum & ascending	61 (32.1)
TNM stage	
IIA	51 (26.7)
IIB	16 (8.4)
IIIA	5 (2.6)
IIIB	98 (51.8)
IIIC	20 (10.5)
Depth of invasion	
T2	8 (4.2)
T3	148 (77.9)
T4	34 (17.9)
Nodal involvement	
N0	68 (35.8)
N1	102 (53.7)
N2	20 (10.5)
Tumor diameter (cm)	
Median	5
Histological grade	
Well	10 (5.3)
Intermediate	123 (64.7)
Poor	38 (20)
Mucinous adenocarcinoma	14 (7.4)
Unknown	5 (2.6)
Lymphatic invasion (+)	95 (50)
Vascular invasion (+)	61 (32.6)
Perineural invasion (+)	44 (23.7)
Mucine (+)	42 (22.1)

Thirty-five percent of patients (n=67) had stage II disease with high risk factors for relapse, and 65% (n=123) had stage III colon adenocarcinoma. Percentages for the type of surgery were as follows: left hemicolectomy 61%, transverse colectomy 5.6%, right hemicolectomy 32.8%, and total colectomy 0.6% of the cases.

Chemotherapy

Of the 5-FU-based chemotherapy group, 15.2% of the patients had a dose reduction because of toxicity and 73% of the patients were given the total planned dose and cycles. In the oxaliplatin+5-FU-based group, 18.5% of patients had a dose reduction because of toxicity and 66% of patients were given the total planned dose and cycles of chemotherapy (p=0.56 for dose reduction and p=0.44 for completeness of treatment schedule between 5-FU and 5-FU+oxaliplatin groups).

Overall, 16.5% of the patients had a dose reduction because of treatment-related toxicities and 70% were given the total planned dose and cycles of chemotherapy. In general, more than 90% of the planned chemotherapy dose was actually given.

High risk factors for stage II disease

Seventy-four percent of patients had an inadequate lymph node dissection, 36% had bowel obstruction, 27.5% had T4 tumor, 26% had poorly differentiated tumor histology and 12% had perforation.

Adverse effects

Nausea, vomiting, diarrhea, stomatitis and asthenia were the most frequent grade 3-4 adverse effects which caused dose reduction, whereas among all the patients, asthenia, diarrhea, nausea and vomiting were the most frequent adverse effects (Table 2). The incidence of thromboembolic events among patients who received at least one cycle of the assigned regimen was 4.2% (8 of 190 patients: 2 pulmonary embolisms and 6 deep vein thromboses). Although 44.4% of the patients treated with oxaliplatin+5-FU developed peripheral neuropathy during treatment, 90% of these cases were of grade 1 or 2 (Table 2). One patient (0.8%) died within 1 month after the start of treatment and 12 patients (6%) required hospitalization because of the adverse effects of chemotherapy.

Disease-free survival

At the time of analysis (median follow-up 34.8 months), 38 (20%) patients in the group given 5-FU-based chemotherapy relapsed, as compared with 5 (2.6%) in the oxaliplatin+5-FU-based group. The probability of DFS at 3 years was 69.4% in the group given 5-FU-based regimen and 83.6% in the oxaliplatin+5-FU group (stratified log-rank test, p=0.36) (Table 3 and Figure 1).

There was no statistical difference at 3-year DFS between patients with high risk stage II and stage III disease (75.9 vs. 65.9%, respectively; p=0.18). Among

Table 2. Adverse events in all patients with adjuvant treatment

Adverse event	*Grade 1-2 (%)*	*Grade 3-4 (%)*	*Total (%)*
Fever	8.4	–	8.4
Neutropenic fever	NA	2.5	2.5
Hematologic toxicity	10.9	1.6	12.5
Nausea	47.1	5	55.1
Vomiting	22.8	5	27.8
Diarrhea	37.8	6.7	44.5
Constipation	4.2	–	4.2
Stomatitis	13.4	3.3	16.7
Asthenia	44.5	4.2	48.7
Anorexia	9.2	–	9.2
Thyroid function abnormality	3.4	–	3.4
Neuropathy	15.9	1.7	17.6
Cardiac adverse effect	1	0.5	1.5
Pain	5	–	5
Thrombosis	NA	4.2	4.2
Hospitalization	NA	NA	6
Death	NA	NA	0.8

NA: not applicable, – : not observed

Table 3. Analysis of disease free survival at 3 years & cancer-specific and overall survival at 5 years

Variable	*All patients (n=190)*	*Patients with 5-FU based treatment (n=141)*	*Patients with oxaliplatin+5-FU based treatment (n=49)*
Follow-up (months)			
Median	34.8	42.3	22.1
Range	1.94-147.6	6.0-147.6	1.94-37.8
Event - no. (%)			
Relapse	43 (23)	38	5
Metastasis	31 (16)	27	4
Local recurrence	15 (8)	14	1
Probability of DFS at 3 yrs (%)	69.4	67.6	83.6
Event - no. (%)			
Death	32 (17)	30	2
Cancer related	23 (12)	22	1
Cancer unrelated	9 (5)	8	1
Probability of cancer specific-survival at 5 yrs (%)	78	77.5	NA
Probability of OS at 5 yrs (%)	73	72	NA

DFS: disease-free survival, OS: overall survival, NA: not available due to short follow-up of the oxaliplatin+5-FU group, yrs: years

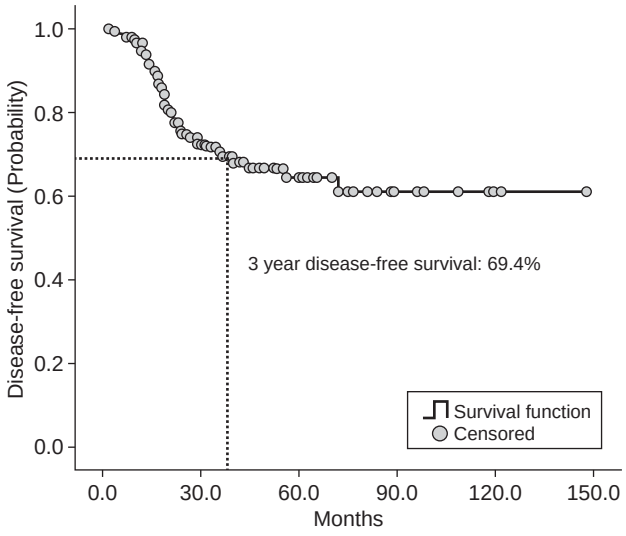

Figure 1. Three-year disease-free survival of the study population.

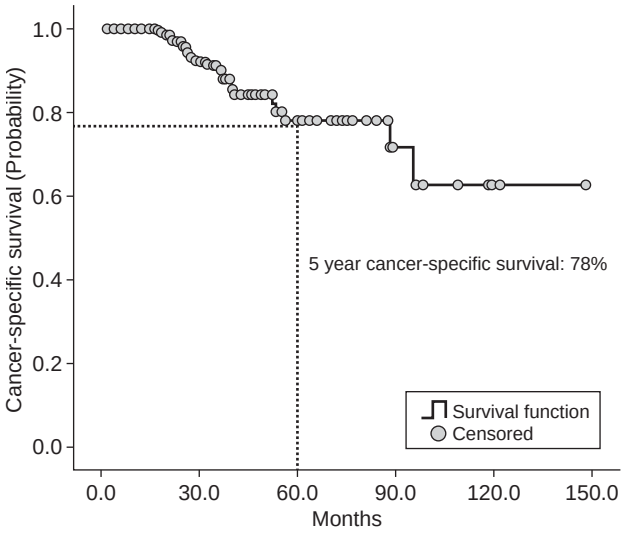

Figure 2. Five-year cancer-specific survival of the study population.

patients with high risk stage II disease, the 3-year DFS rates of patients in 5-FU-based and oxaliplatin+5-FU-based groups were 75.8 and 82.5%, respectively (p=0.81). Regarding the patients with stage III disease, the 3-year DFS rates of patients in the 5-FU-based and oxaliplatin+5-FU-based groups were 63.1 and 84.6%, respectively) (p=0.21).

Cancer-specific and overall survival

Thirty-two (16.7%) patients in the study population died; of these, 23 (12%) deaths were due to cancer and 9 (5%) to unrelated causes. We could not report the 5-year OS of the oxaliplatin group since the median follow-up time (22 months) was short for that group. For all patients, cancer-specific and overall probabilities of survival at 5 years were 78 and 73%, respectively (Table 3 and Figure 2).

The 5-year cancer-specific survival rates of patients with high risk stage II and stage III disease were 69 and 80%, respectively (p=0.73).

Patients ≥ 65 years old

Over 41% (n=79) of the study population was ≥ 65 years old. Three-year DFS of this older age group was significantly worse compared with the younger age group (59.5 vs. 75.8% respectively; p=0.023). The efficacy of adjuvant chemotherapy in terms of 5-year cancer-specific survival rates was not different between the groups (p > 0.05), whereas a significant difference was observed in the 5-year OS rates between the groups (< 65 years, 80.4%; ≥65 years 60%; p=0.003) (Table 4).

Prognostic factors

In the univariate analysis, we found that T stage (p=0.04), N stage (p=0.004), presence of mucine (p=0.002), and PNI (p=0.027) were the parameters affecting DFS. Additionally for all patients, a ratio of the number of metastatic lymph nodes to the total number of the dissected lymph nodes of > 0.2 also showed a significant relationship to DFS (p=0.001). However, in the multivariate Cox regression analysis, only T stage (p=0.038, HR: 3.49, 95% CI, 1.074-11.397) and presence of PNI (p=0.044, HR: 3.49, 95% CI 1.037-11.795) had a significant impact on DFS (Table 5).

As for DFS, the univariate analysis for cancer-specific survival also showed T stage (p=0.045), N stage (p=0.007), presence of mucine (p=0.008), and PNI (p=0.027) as prognostic factors. In the multivariate Cox

Table 4. Comparison of survival functions of patients < 65 and ≥ 65 years old

Variable	*< 65 years (n=111)*	*≥ 65 years (n=79)*	*p-value*
Follow-up - median (months)	35.8	31	
Event - no (%)			
Death	13 (11.7)	19 (24)	
Cancer related	12 (10.8)	11 (14)	
Cancer unrelated	1 (0.9)	8 (10)	
Probability of disease free-survival at 3 yrs (%)	75.8	59.5	0.023
Probability of cancer-specific survival at 5 yrs (%)	81	70.5	0.133
Probability of overall survival at 5 yrs (%)	80.4	60	0.003

yrs: years

Table 5. Results of analysis of disease-free survival and cancer-specific survival by individual baseline factors

	Disease-free survival at 3 years		*Cancer-specific survival at 5 years*	
Factors	*Univariate analysis*	*Multivariate analysis Hazard ratio (95% CI)*	*Univariate analysis*	*Multivariate analysis Hazard Ratio (95% CI)*
Age	NS	NS	NS	NS
Sex	NS	NS	NS	NS
Localization	NS	NS	NS	NS
Tumor diameter	NS	NS	NS	NS
Disease stage	NS	NS	NS	NS
T stage	p=0.046	p=0.038 3.49 (1.074-11.397)	p=0.045	p=0.015 9.83 (1.558-62.024)
N stage	p=0.004	NS	p=0.007	NS
LNR > 0.2	p=0.013	NS	NS	NS
LI	NS	NS	NS	NS
VI	NS	NS	NS	NS
PNI	p=0.027	p=0.044 3.49 (1.037-11.795)	p=0.027	p=0.024 8.60 (1.332-55.605)
Mucine	p=0.002	NS	p=0.008	NS
Grade	NS	NS	NS	NS
Total number of LN dissected	NS	NS	NS	NS

LNR: ratio of metastatic to total number of dissected lymph nodes, LI: lymphatic invasion, VI: vascular invasion, PNI: perineural invasion, LN: lymph nodes, NS: non significant

regression analysis, again T stage (p=0.015, HR: 9.83, 95% CI 1.558-62.02) and the presence of PNI (p=0.024, HR: 8.60, 95% CI 1.332-55.60) stood out statistically relative to the others (Table 5).

Discussion

Contemporary recommendations for the treatment of curatively resected colon cancer in the adjuvant setting are well known from NCCN practice guidelines that are based on large, multicenter and prospective studies. Our study was primarily designed to investigate the efficacy of chemotherapy and the prognostic factors in a curatively resected colon carcinoma population treated in daily practice setting, irrespective of the chemotherapy regimen. Hence, the survival outcome measures (such as DFS, cancer-specific survival and OS) and patient and tumor characteristics at presentation were analyzed.

Our 3-year DFS, 5-year cancer-specific survival and 5-year OS rates were 69.4, 77.8 and 72.6%, respectively. The 3-year DFS was 73% in the 5-FU/LV arm of NSABP C03 [12] and 5-year OS was 74% in the NCCTG trials [20]. The results of these two studies showed bolus 5-FU/LV to be the standard adjuvant regimen for resected stage III colon cancer. When oxaliplatin was added to the adjuvant treatment, the 3-year DFS was 78.2%, whereas it was 72.2% in the 5-FU arm in the MOSAIC study [17]. In an update of this study, the 5-year OS was 79% in the oxaliplatin group [21]. For our 5-FU subgroup (n=141, median follow-up 42.3 months) the 3-year DFS, 5-year cancer-specific and 5-year OS rates were 72, 77.5 and 72%, respectively. The 3-year DFS of the oxaliplatin+5-FU group (n=49, median follow-up of 22.1 months) was 85%. Since the number of patients was less and the duration of follow-up was short for the latter group, it would be inappropriate to compare the efficacy of both regimens at present. Nevertheless, we prefer oxaliplatin+5-FU as an adjuvant treatment for patients with high risk stage II disease and for all patients with stage III disease on the basis of the results of the MOSAIC study, published in 2004 [17]. We found that the results of our retrospective cohort treated in "real world practice" in terms of survival outcomes were comparable to that reported in prospective studies.

One third of the patients who were given oxaliplatin+5-FU were ≥65 years. In patients ≥65 years, 5-FU-based regimens predominated (n=63, 79.7%) but one should remember that oxaliplatin was not added to the adjuvant treatments until after 2004. When we compared the anti-cancer treatment efficacy of chemotherapy in young (<65 years) and old (≥65 years) patients, there was no statistical difference in the 5-year cancer-specific survival rates. The differences observed were in the 3-year DFS and in the 5-year OS, which may be attributable to a greater number of deaths unrelated to cancer in the older age group. For a given patient, treatment decisions were made according to ECOG performance status and under-

lying comorbidities. Pooled data analyses have repeatedly demonstrated a consistent and equivalent survival benefit for adjuvant therapy for all age groups [22-25]. As has been emphasized in a recent review concerning cancer chemotherapy in elderly patients by Bostankolu et al. [26], our findings also imply that patients' performance status is far more important than their chronological age during the evaluation for the adjuvant treatment.

The 5-year cancer-specific survival was 69% in the high risk stage II patients and 80% in the stage III patients ($p>0.05$). Despite the better survival expectancy for stage II disease, we found a shorter survival time, which, however, was not statistically significant. Notably, 74% of the high risk stage II patients (n=68) had inadequate lymph node dissections on the basis of a cut off value of 12. This shows that the majority of our stage II patients might have been inappropriately under-staged due to a lack of adequate lymph node dissection. Another conclusion that can be extrapolated from this result is that high risk stage II colon carcinoma constitutes a group that merits adjuvant treatment no less than stage III disease.

Many correlative studies have explored the prognostic significance of various histological, molecular, and clinical features, but currently the pathologic stage at diagnosis remains the best indicator of long-term prognosis for colon cancer [27]. The most important characteristics for curatively resected patients are the local tumor extent (T), nodal positivity (N stage, particularly the number of involved lymph nodes) and residual disease. Further stratification of outcome can be achieved by the identification of patients with LVI and high preoperative serum CEA levels. Molecular features like microsatellite instability [28] and DCC (Deleted in Colorectal carcinoma gene) loss [29] may also influence the outcome, independently of stage. In this study, we analyzed the potential effects of various factors evident in the patient at presentation, both for the 3-year DFS and the 5-year cancer-specific survival. Univariate analysis showed that local tumor extension, involvement of regional lymph nodes, presence of PNI and presence of mucine are worse for both outcome measures. However, only local tumor extension and presence of PNI showed a statistical significance in the multivariate analysis. It was demonstrated that preoperative CEA serum levels ≥ 5.0 ng/mL have an adverse impact on survival that is independent of tumor stage [30]. Since many of the patients included in our study were referred to an oncology clinic postoperatively, the preoperative CEA serum levels were lacking, thus we could not examine the prognostic value of CEA.

In order to avoid bias and to have the exact rates of the planned numbers of cycles and dose completion, all patients who received at least one cycle of chemotherapy were included in the study. Indeed, it would be valuable to report those patients who were assigned for adjuvant treatment but could not receive it for some reason. The main reason for a deficient treatment course was dose reduction due to toxicity (in 16.5% of patients). Another 13.5% of patients had incomplete courses of treatment, mostly due to toxicity and patient reluctance.

The following, in decreasing order, were the most common adverse effects: asthenia, diarrhea, nausea, vomiting, neuropathy and stomatitis. The most common grade 3-4 toxicities were diarrhea, nausea, vomiting, asthenia, and neutropenic fever. The method of noting toxicities was different from that used in prospective studies, so that it would be inappropriate to make a comparison between incidences of toxicities. Nevertheless, as in the MOSAIC study [17], hematological and neurosensorial toxicities were more common in the oxaliplatin+5-FU group than in the 5-FU group (hematological 28 vs. 7%, $p=0.002$; neurosensory 46 vs. 7%, $p=0.000$), but stomatitis was more common in the 5-FU group (3 vs. 23%, $p=0.007$). Since every patient was noted once, with the highest grade of toxicity, under a specific toxicity title, this caused underestimation of grade 1 and grade 2 toxicities experienced during the chemotherapy courses. Since this underestimation of grade 1 and grade 2 toxicities were not indications for dose modifications they were not clinically important unless, as in the case of neuropathy, it becomes irreversible and deteriorates the quality of life.

None of the specific toxicity types was statistically higher in older patients ($\geq$65 years) except thromboembolism, which in all cases occurred in the older group. Moreover, the rates of completion of the planned cycles of chemotherapy or rates of having deficient chemotherapy courses also showed no differences. Interestingly, fewer patients experienced adverse effects such as nausea, vomiting and asthenia in the older age group. This observation can be explained as follows: first, we mostly prescribed the lower range of the drug doses to older patients, and second, the older patients almost always got weekly regimens (Roswell Park and FLOX) which are thought to be less toxic than their counterparts. But these are no more than unproven hypotheses, at least for now.

Owing to the nature of this study, it has all the handicaps of retrospective studies such as selection or observation biases. We tried to defeat a potential selection bias by inclusion of patients who received at least one cycle of adjuvant chemotherapy. To avoid an observation bias we made phone calls, but these were not always successful. Patients with an ECOG performance score ≤ 2 were given adjuvant treatment but whether further stratification according to the ECOG score has any effect on outcome measures is not demonstrable; this is another weak point of our study. Since the follow-up periods of the treatment arms are far apart, it would be im-

proper to compare the efficacy of both, at least for now.

In conclusion, despite some handicaps relating to the retrospective nature, this study is the first one, with a respectable number of patients and detailed analyses, reporting the efficacy of adjuvant treatment in a curatively resected Turkish colon carcinoma population treated in "real world" practice. Since it will be unethical to reconduct identical phase III studies for evaluating the efficacy of currently approved regimens, the only way to analyze the efficacy of these regimens in a developing country is to perform a retrospective cohort study. Our results showed that the treatment outcomes and the prognostic parameters of patients treated in daily practice in Turkey are not different from those of selected patients treated in prospective randomized studies.

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