Childhood, Adolescents, and Young Adults ($\leq$25 y) Colorectal Cancer: Study of Anatolian Society of Medical Oncology

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Purpose: To evaluate the clinicopathologic characteristics and treatment outcomes of young patients with colorectal cancer (CRC).

Methods: Between May 2003 and June 2010, 76 patients were found eligible for this retrospective study. Age, sex, presenting symptoms, patients with acute presentation, family history, presence of polyps, histologic features, localization and stage of the tumor, treatment outcomes, time and site of recurrence, sites of metastasis, and survival outcomes were recorded from the patient files.

Results: Seventy-six patients (55.3% male) with a median age of 23 years were evaluated. Patients were evaluated in 2 groups as follows: child-adolescent (0 to 19 y, n = 20) and young adult (20 to 25 y, n = 56). Sex and symptoms (abdominal pain and rectal bleeding) were significantly differed between the groups and acute presentation was close to statistical significance. Overall survival significantly increased in patients undergoing curative surgery ($P < 0.001$). Other parameters affecting the survival was stage of disease ($P = 0.004$). Response to palliative chemotherapy in metastatic patients ($P = 0.042$) and postoperative adjuvant chemotherapy had a statistically significant survival advantage ($P = 0.028$).

Conclusions: Diagnosis of CRC should not be excluded solely on the basis of age. CRC features in young-adult patients are more similar to adults compared with that of child-adolescent patients according to the symptoms and presentation. In patients with CRC in this age group, curative surgery, adjuvant chemotherapy, and palliative chemotherapy provide survival advantage.

Key Words: colorectal cancer, young, adolescent, childhood

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Although colorectal cancer (CRC) is one of the most common tumors in adults, it is rarely found in childhood, adolescents, and young adults. The incidence is 19 per 100,000 people for those younger than 65 years and 337 per 100,000 among those older than 65 years.[1] We know that 0.5% to 4.8% of all childhood malignancies arise from the gastrointestinal tract,[2–4] most of all gastrointestinal malignancies (45.7% to 91.5%) in children originate in the colon.[4–6] In contrast, investigators found that 1% to 4% of CRC occurred in people under the age of 25 to 30 years.[7–10]

Most of the previous studies investigating CRC in younger patients had an insufficient number of patients. Moreover, data regarding treatment outcomes were either absent or insufficient in many of them. As it is difficult to conduct prospective studies on this group of patients, the importance of retrospective studies in large patient series is clear. The current article is based on one of the largest series published, and this study aims to close the gap in the literature. Furthermore, although young-adult and child-adolescent patients are generally evaluated together in the literature, we aimed to find out whether the 2 groups have differences or not in our study.

METHOD

The records of patients under the age of 25 years, who were diagnosed with CRC between May 2003 and June 2010 at the referral medical oncology centers in Turkey, were reviewed retrospectively. Age, sex, symptoms at the time of diagnosis, interval between presentation to diagnosis, presentation status, family history, presence of polyposis coli, histopathologic features, tumor localization, tumor stage at the time of diagnosis, treatment modalities (including surgery, radiotherapy, and chemotherapy), site and time of recurrence, site of metastasis, survival time, and outcomes of the patients were recorded from the patient files. Stage of disease was determined using the modified Dukes staging scheme. Patients presenting with ileus and/or rigid abdomen admitted to emergency room were recorded as patients with acute presentation. Adjuvant chemotherapy was used in R0-resected patients. First-line palliative chemotherapy was used in patients with metastasis (without curative surgery) at the time of diagnosis or in patients with recurrence after their curative surgery. Second-line palliative chemotherapy was administered after progression after first-line palliative chemotherapy. Patients not receiving palliative chemotherapy were either those with poor performance or those refusing treatment. In

patients with measurable disease, tumor response was monitored using the Response Evaluation Criteria in Solid Tumors. Patients with partial or complete remission after first-line chemotherapy were defined as patients with a response to palliative chemotherapy. Overall survival was defined as the time from the date of diagnosis to death. Event-free survival (EFS) was defined as the interval between diagnosis of CRC and recurrence or progression, second malignancy, death from any cause, or last contact. Cases were evaluated in 2 groups: child-adolescent (0 to 19 y of age) and young-adult (20 to 25 y of age).

Overall survival and EFS were calculated according to the Kaplan-Meier method, and both populations were compared using the Mann Whitney U test, χ^2 test, or the Fisher exact test, as necessary. A multivariate analysis was performed using Cox model. Potential prognostic factors for curative surgery performed on CRC patients were included in the model.

RESULTS

Patient Characteristics

Seventy-six eligible patients were identified through screening of 7298 CRC cases from 9 referral centers in Turkey. Of the 76 patients (1.04% of all CRC patients), 42 (55.3%) were male and 34 (44.7%) were female. The mean age was 21.6 ± 3.3 years and the median age was 23 years (range, 10 to 25 y), in the entire group. Twenty patients were in the child-adolescent group and 56 patients were in the young-adult group (Table 1). Six of the 20 patients were prepubertal in the child-adolescent group.

The proportion of males were significantly higher in the child-adolescent group (75%, n = 15) compared with that in the young-adult group, (48.2%, n = 27; $P = 0.039$). Information on family history was available in the file of 69 patients. Of them, 15 patients had a family history of CRC (21.7%) and there was no significant difference between young-adult and child-adeloscent group in terms of family history ($P = 0.741$). İnformation about genetic disease of the colon cancer such as hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis could not be given due to lack of detailed information about family history in patients' files.

TABLE 1. Clinical Characteristics of Young Colorectal Cancer

	n (%)		
	Child-Adolescent (n = 20)	Young-Adult (n = 56)	Total (n = 76)
Sex			
Male	15 (75)	27 (48.2)	42 (55.3)
Female	5 (25)	29 (51.2)	34 (44.7)
Family history			
Positive	3 (18.8)	12 (22.6)	15 (21.7)
Polyposis coli			
Positive	0 (0)	5 (9.3)	5 (6.8)
Symptom			
Abdominal pain	15 (88.2)	23 (42.6)	38 (53.5)
Rectal bleeding	2 (11.8)	20 (37.0)	22 (31.0)
Change in bowel habit	5 (29.4)	22 (40.7)	27 (38.0)
Nausea/ vomiting	5 (29.4)	7 (13.0)	12 (16.9)
Weight loss	3 (17.6)	11 (20.4)	14 (19.7)
Acute presentation			
Positive	7 (35.0)	11 (20.0)	18 (24.0)

Symptoms and Presentation

Available data for 71 patients showed that the most common symptom was abdominal pain (53.5%, n = 38) followed by change in bowel habits (38.0%, n = 27), rectal bleeding (31.0%, n = 22), weight loss (19.7%, n = 14), and nausea and vomiting (16.9%, n = 12), in the entire group. Abdominal pain was significantly more common (88.2% vs. 42.6%, $P = 0.001$), and rectal bleeding was significantly less in the child-adolescent group than in the young-adult group (11.8% vs. 37.0%, $P = 0.049$). Change in bowel habits ($P = 0.401$), and weight loss ($P = 0.806$) were similar in child-adolescent and young-adult group. Although there was no significant difference in terms of nausea and vomiting between child-adolescent and young-adult group, it was numerically higher in the child-adolescent group (Table 1, 29.4% vs. 13.0%, $P = 0.143$).

We investigated the relationship between the symptoms of the patients and tumor stage. There was no significant difference in terms of abdominal pain (53.8% vs. 52.6%), change in bowel habits (34.6% vs. 47.4%), and nausea and vomiting (13.5% vs. 26.3%) between the patients with and without metastasis. Weight loss was significantly higher (47.4% vs. 9.6% $P = 0.001$) and rectal bleeding was borderline significantly less in metastatic patients than in non-metastatic patients (15.8% vs. 36.5%, $P = 0.094$).

The number of patients with acute presentation was 7 (35.0%) in the child-adolescent group and 11 (20.0%) in the young-adult group. Although there was a numerical difference between child-adolescent and young-adult group, no statistically significant difference in acute presentation was noted (Table 1, 35.0% vs. 20.0%, $P = 0.179$).

The median interval between symptoms and diagnosis was 2 months (range, 0 to 35 mo) in the child-adolescent group and 3 months (range, 0 to 48 mo) in the young-adult group, with no statistically significant difference between the 2 groups ($P = 0.282$).

Tumor Localization

As shown in Table 2, the primary site of the tumor was rectum in 31 patients (40.8%), descending colon in 18 patients (23.7%), transverse colon in 3 patients (3.9%), and ascending colon in 24 patients (31.6%). The most common primary tumor site was ascending colon (45%) in the child-adolescent group, and rectum (46.4%) in the young-adult group. There was no significant difference between the child-adolescent and young-adult group in terms of tumor site ($P = 0.302$).

Pathology and Staging

Mucinous or signet-ring type adenocarcinoma was seen in 47.4% (n = 36) of all patients, with no significant difference between the child-adolescent group (45.0%, n = 9) and the young-adult group (48.2%, n = 27, $P = 0.805$). Thirty-five (72.9%) of 48 patients with available data had intermediate and poorly differentiated histologic subtype: 60.0% in the child-adolescent group and 78.8% in young-adult group (Table 2, $P = 0.396$).

Fourteen patients had Dukes stage B (18.4%), 42 had Dukes stage C (55.3%), and 20 had Dukes stage D (26.3%) disease, none of the patients had Dukes stage A disease at the time of diagnosis. The proportion of Dukes stage B, C,

TABLE 2. Histopathologic Characteristics of Young Colorectal Cancer Patients

	n (%)		
	Child-Adolescent (n = 20)	Young-Adult (n = 56)	Total (n = 76)
Tumor localization			
Rectum	5 (25.0)	26 (46.4)	31 (40.8)
Descending colon	6 (30.0)	12 (21.4)	18 (23.7)
Transverse colon	0 (0)	3 (5.4)	3 (3.9)
Ascending colon	9 (45.0)	15 (26.8)	24 (31.6)
Stage			
Dukes A	0 (0)	0 (0)	0 (0)
Dukes B	5 (25.0)	9 (16.1)	14 (18.4)
Dukes C	12 (60.0)	30 (53.6)	42 (55.3)
Dukes D	3 (15.0)	17 (30.4)	20 (26.3)
Histopathologic subgroups			
Nonmucinous adenocarcinoma	11 (55.0)	29 (51.8)	40 (52.6)
Mucinous adenocarcinoma	9 (45.0)	27 (48.2)	36 (47.4)
Differentiation (n = 48)			
Good	8 (40.0)	5 (21.2)	13 (27.1)
Intermediate-poor	12 (60.0)	23 (78.8)	35 (62.9)
Metastatic site (n = 44)			
Peritoneum	3 (37.5)	12 (33.3)	15 (34.1)
Liver	2 (25.0)	12 (33.3)	14 (31.8)
Lung	1 (12.5)	3 (8.3)	4 (9.1)
Ovary	1 (12.5)	3 (8.3)	3 (6.8)
Bone	1 (12.5)	2 (5.6)	3 (6.8)
Other	0 (0)	4 (11.1)	5 (11.4)
Relapse site (n = 25)			
Local	1 (12.5)	6 (35.3)	7 (28.0)
Distant	7 (87.5)	11 (64.7)	18 (72.0)

and D patients were 25%, 60%, and 15% in the child-adolescent group and 16.1%, 53.6%, and 30.4% in the young-adult group, respectively. There was no statistical significant difference between child-adolescent and young-adult group (Table 2, $P = 0.355$).

Peritoneum was the most common metastatic site (n = 15, 34.1%) followed by liver (n = 14, 31.8%), lung (n = 4, 9.1%), ovary (n = 3, 6.8%), and bones (n = 3, 6.8%). Other metastatic sites included (1 case for each) adrenal glands, ureter, bone marrow, gallbladder, and small intestine (Table 2).

Treatment

Complete surgical resection was performed in 58 cases (76.3%). Of those, 17 patients (85%) were in the child-adolescent group and 41 patients (73.2%) were in the young-adult group ($P = 0.532$). Surgery (R0) rate was higher in the mucinous group than the nonmucinous group (83.3% vs. 70%, $P = 0.177$). Adjuvant chemotherapy was administered to 52 patients. Six patients refused to undergo chemotherapy. Radiotherapy was administered to 24 cases (adjuvant 11, neoadjuvant 9, and palliative 4; Table 3). Toxic death was observed in 1 patient (age = 16) who received concomitant chemoradiotherapy. Twenty-five of the 58 patients with operable disease experienced recurrence, at a median of 12.9 months (range, 1 to 99.6 mo) after diagnosis. Local recurrence was detected in 7 patients and distant recurrence was observed in 18 patients.

Patients with metastases (without curative surgery) at the time of diagnosis and patients with recurrence after curative surgery were a candidate for palliative treatment (n = 43). Twenty-four of whom were administered first-line palliative chemotherapy. Eleven out of 24 patients were administered second-line palliative chemotherapy after disease progression after first-line palliative chemotherapy. In the first-line treatment, irinotecan-based regimen (irinotecan/5-fluorouracil/folinic acid), oxaliplatin-based regimen (oxaliplatin/5-fluorouracil/folinic acid), and fluoropyrimidine-based regimen (5-fluorouracil/folinic acid) were received by 16, 6, and 2 patients, respectively. In the second line treatment, irinotecan-based regimen and oxaliplatin-based regimen were received by 6 and 5 patients, respectively.

TABLE 3. Treatment Characteristics of Young Colorectal Cancer Patients

	n (%)		
	Child-Adolescent (n = 20)	Young-Adult (n = 56)	Total (n = 76)
Surgery			
No residual disease (R0)	17 (85.0)	41 (73.2)	58 (76.3)
Microscopic residual (R1)	1 (5.0)	7 (12.5)	8 (10.5)
Gross residual (R2)	2 (10.0)	8 (14.3)	10 (13.2)
Radiotherapy			
Adjuvant	4 (20.0)	7 (12.5)	11 (14.5)
Neoadjuvant	1 (5.0)	8 (14.3)	9 (11.9)
Palliative	1 (5.0)	3 (5.4)	4 (5.3)
Palliative chemotherapy (n = 24)			
Complete remission	0 (0.0)	0 (0.0)	0 (0.0)
Partial remission	4 (57.1)	6 (35.3)	10 (41.7)
Stable disease	0 (0.0)	6 (35.3)	6 (25.0)
Progressive disease	3 (42.9)	5 (29.4)	8 (33.3)

Median overall survival was 16.3 months (range, 1 to 107 mo). Histologic subgroup (mucinous or nonmucinous) did not affect the overall survival, statistically, in our study (36.9 vs. 53.2 mo, $P = 0.674$, Fig. 1). Stage of disease was

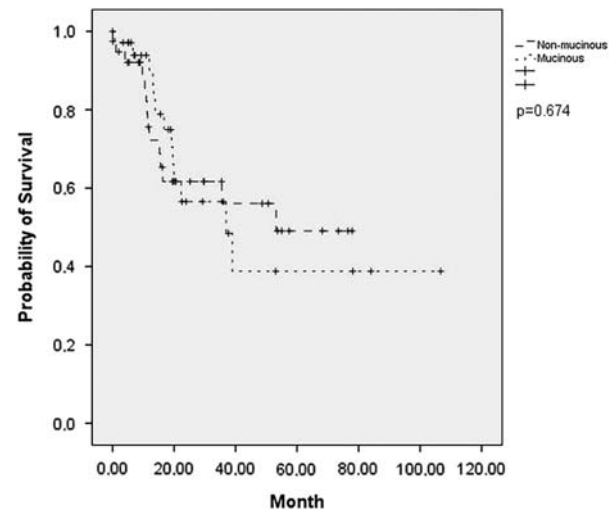

FIGURE 1. Kaplan-Meier survival curve: overall survival according to histologic subtype (muscinous or nonmuscinous).

TABLE 4. Prognostic Factors Affecting Survival

Parameters	No. Patients	Median Survival (mo)	*P*
Dukes stages*			
Dukes B	14	24.5	0.004
Dukes C	42	19.4	
Dukes D	20	11.7	
Surgery*			
No residual disease (R0)	58	19.6	< 0.001
Microscopic residual (R1)	8	16.5	
Gross residual (R2)	10	3.7	
Adjuvant chemotherapy†			
Done	52	29.9	0.028
Not done	6	9.3	
Response to palliative chemotherapy†			
Yes (CR, PR)	11	15.8	0.042
No (SD, PD)	11	9.4	

*Evaluated with overall survival.
†Evaluated with EFS.
CR indicates complete remission; EFS, event-free survival; PD, progressive disease; PR, partial remission; SD, stable disease.

a significant prognostic predictor of survival (Table 4). Dukes C and D patients had a median survival of 36.9 and 15.6 months, respectively, and in Dukes B patients median survival time was not reached (Fig. 2, $P = 0.004$). The second prognostic predictor of survival was resectability of the tumor (Table 4). For patients who underwent surgery, the median time of survival was not reached in R0 (no residual disease), 16.8 months in R1 (microscopic residual disease), and 10.4 months in R2 (macroscopic residual disease)-resected patients, respectively (Fig. 3, $P < 0.001$). Median EFS was 29.9 months in patients who were administered adjuvant chemotherapy and 9.3 months in those who did not receive adjuvant chemotherapy (Fig. 4, $P = 0.028$). In the R0-resected patients (n = 58) the following factors were analyzed in the multivariate analyses: sex (male vs. female), adjuvant chemotherapy (received vs. not), tumoral

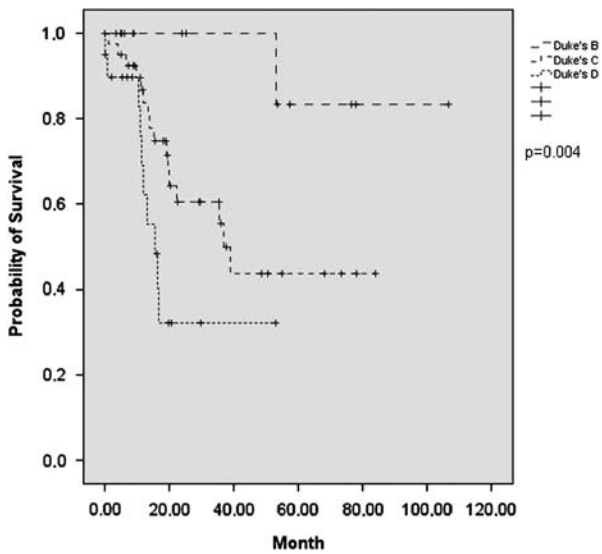

FIGURE 2. Kaplan-Meier survival curve: overall survival according to stage of the disease.

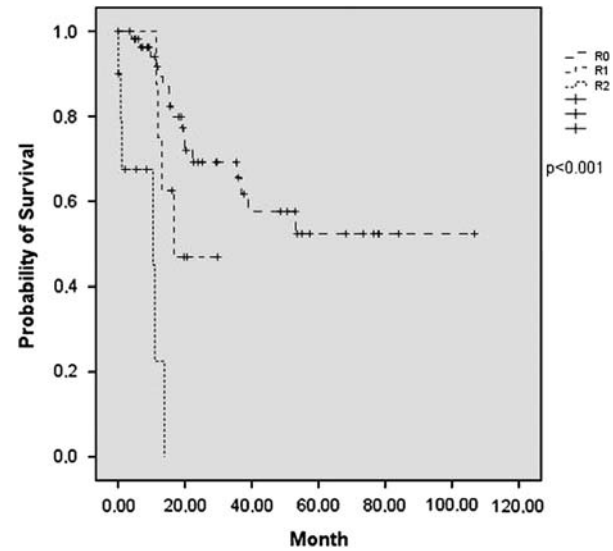

FIGURE 3. Kaplan-Meier survival curve: overall survival according to resection margin status.

invasion (serosal invasion positive vs. negative), lymph node involvement (positive vs. negative), and histologic subtype (mucinous vs. nonmucinous). Tumoral invasion [odds ratio (OR), 3.91; 95% confidence interval (CI), 1.35-11.3; $P = 0.012$], and lymph node positivity (OR, 4.51; 95% CI, 1.61-12.64; $P = 0.004$) were associated with significantly decreased EFS, whereas adjuvant chemotherapy usage (OR, 0.22; 95% CI, 0.07-0.65, $P = 0.006$) was associated with significantly enhanced EFS. Sex (OR, 0.77; 95% CI, 0.36-1.68; $P = 0.511$) and histologic subtype (OR, 1.65; 95% CI, 0.73-3.51; $P = 0.237$) was not significantly associated with EFS. The final prognostic predictor of survival was response to palliative chemotherapy in metastatic

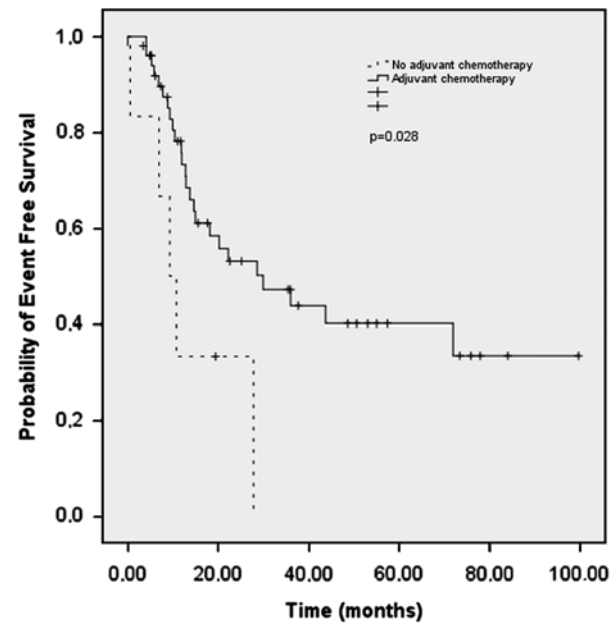

FIGURE 4. Kaplan-Meier survival curve: event-free survival according adjuvant chemotherapy (received or not) in R0-resected patients.

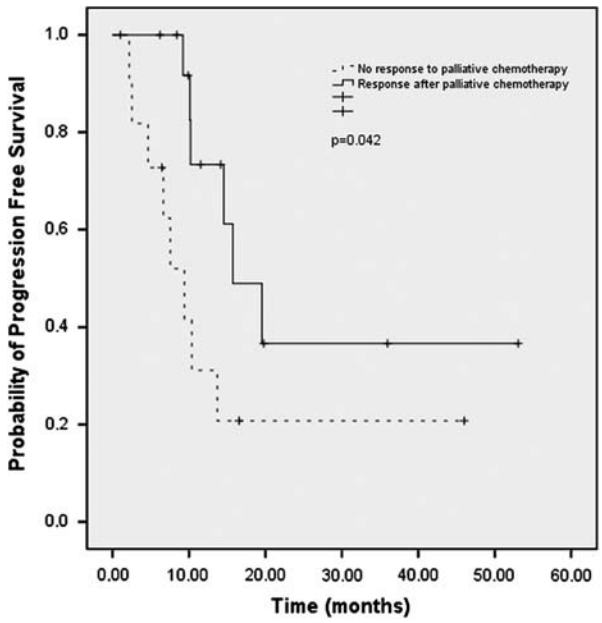

FIGURE 5. Kaplan-Meier survival curve: event-free survival according to palliative chemotherapy (received or not) in patients with metastasis (without curative surgery) at the time of diagnosis or patients with recurrence after their curative surgery.

patients (Table 4). Patients with a response to first-line palliative chemotherapy had a median EFS of 15.8 months compared to a 9.4-month survival for those not responding to chemotherapy (Fig. 5, $P = 0.042$).

DISCUSSION

CRC is extremely rare in children, adolescents, and young adults, and has significant differences in terms of symptoms, presentation, histologic subgroups, localization, stage, and prognosis in comparison with the disease in adults.[10–12] This study is one of the largest series of young patients with CRC. Furthermore, this is the most advanced study comparing the disease between child-adolescent and young-adult patients, to our knowledge. Furthermore, our study has several limitations as to lack of adequate data of patients such as, toxicity of the treatment, history of the disease, or family history due to the retrospective nature of the current study.

Clinical Features

Most studies suggest a male predominance in young CRC patients. Male-female ratio is noted as 1.5-2.1.[6,12–23] There is no sex predominance or only a slight female predominance for adult CRC patients.[24,25] Although the male-female ratio was approximately 1.3:1 among all patients, it was interesting to note a ratio of approximately 3:1 in the child-adolescent group in this study. There was a significant difference in sex distribution between the 2 groups.

Symptoms and Presentation

Abdominal pain was the most commonly reported symptom in previous studies, usually $>50\%$,[14,15,22] and exceeding 80% in some of the studies.[12,13,17,18,21] Only in a small study, rectal bleeding was reported as the most common symptom.[16] Change in bowel habits, nausea-vomiting, rectal bleeding, and weight loss were observed less frequently and their rates were usually $<50\%$.[12–15,17,22] In our study, the predominant symptom was abdominal pain, followed by change in bowel habits, nausea-vomiting, rectal bleeding, and weight loss. Abdominal pain (statistically significant) and nausea-vomiting (not statistically significant) were observed more frequently, but rectal bleeding was observed less frequently (statistically significant) in the child-adolescent group than in the young-adult group. Most of these symptoms are similar to those found in common childhood problems such as gastroenteritis, which may lead to a delay in diagnosis. When the relationship between the symptoms of the patients and the stage of disease was evaluated, it was observed that patients with rectal bleeding presented with early stage disease whereas patients with weight loss presented with more advanced disease.

Compared with adult patients, acute presentation is more frequent in young patients. Some previous studies reported rates $>20\%$ for acute presentation.[12,17,20] In our study, 24.6% of the patients were admitted with acute presentation. Acute presentation was more common in the child-adolescent group than in the young-adult group (41.2% vs. 18.2%). In light of this data, it may be predicted that the young-adult patients show more similarity to adult patients than the child-adolescent group in terms of symptoms and presentation.

Family History and Predisposing Factors

Although predisposing factors may be present in young CRC patients, the disease usually occurs sporadically.[26–28] Family history was reported in 0% to 23% of cases in previous reports.[12,14,15,17,22] In our study, 21.7% of the patients had a family history and the rate of family history was similar in both groups. Polyposis coli was detected in 5 patients (6.8%), all in the young-adult patient group.

Pathology and Staging

Mucinous histology was reported in only 11% to 13% of adult colorectal adenocarcinoma cases.[29–33] Mucinous carcinoma rates in young patients was reported to be 45% to 83%.[12,13,15–18,20,22] In our study, mucinous adenocarcinoma was observed in 47.4% of the patients. Previous studies documented an association between mucinous histology and high stage at presentation and poor outcome in adults.[29,31,32] A study in child-adolescent patients demonstrated a significant survival advantage in patients with nonmucinous tumors.[13] In our study there is no statistical difference between the mucinous and nonmucinous histology in terms of overall survival (39 vs. 53 mo, respectively). There may not be statistical difference due to RO resection performed on a larger number of patients in mucinous group as well as the scarcity of case number.

Stage

Approximately 25% of patients with CRC initially present with distant metastases at the time of diagnosis.[34] Most studies on young CRC patients reported that $>50\%$ of them had metastatic disease at the time of diagnosis.[12,13,18,20] Only 2 studies, 1 of them published recently,[14] reported a lower incidence of metastatic disease.[14,17] In our study, metastatic disease rate (26.3%) was similar to that in adult cases. Although further studies are warranted to support this assumption, it can be estimated that delayed diagnosis may no longer be regarded as a risk

factor in this age group. About 30% to 70% of adult patients with metastatic CRC have liver metastasis, 20% to 40% have lung metastasis, and 5% to 10% have bone metastasis.[35] In contrast, unlike adults, peritoneum has been reported as the most common site of metastasis in young CRC patients, as in our series.[12]

Localization

CRC is most commonly localized in the rectum and sigmoid in adult patients.[12] Although the right and the transverse colon were reported as the common tumor sites in some studies,[13,15,18] the left colon is usually the most common site of tumor.[12,16,17,20] Similar to adult patients, left colon was found to be the most frequent site of location of the primary tumor (64.5%) in our study. Localization in the left colon was observed in 55% of child-adolescent patients and 67.8% of young-adult patients.

Treatment and Outcomes

Most of the previous series suggest that curative surgery is the most effective treatment for young CRC patients.[18,36,37] Consistent with this observation, surgery provided a survival advantage in our study. Although older reports had lower resectability rates (< 50%) and poor outcomes,[12,17,18,20,37–40] more recent studies had higher resectability rates ($\geq$ 70%),[13,14,16,17] and the resectability rate in our study was 76.3%. Although surgical treatment rates are still lower in young CRC patients compared with adults, resectability rates are higher than past. These data may indicate that rate of early diagnosis is increasing in this patient group.

Because of the lack of prospective studies in this age group, it seems difficult to assess the benefits of treatment such as surgery and chemotherapy. Benefits of surgery and chemotherapy were identified in some retrospective series.[13,18] In our series, we found that surgery, and adjuvant and palliative chemotherapy provided an additional contribution to improved survival for young CRC patients. In addition, in R0-resected patients, adjuvant chemotherapy usage was found as independent prognostic factor according to the multivariate analysis.

In conclusion, our findings suggest that CRC had behavioral differences between young and adult patients. The differences in children-adolescent patients are more than that in the young-adult patients in terms of symptoms (abdominal pain and rectal bleeding) and acute presentation, when compared with adults. We believe that if clinicians are aware of young CRC, it may be possible to reduce the rate of metastatic patients in young adults similar to that of adults, as seen in our study. Our study suggests that surgery, adjuvant chemotherapy, and palliative chemotherapy may make contribution to clinicians in the management of young CRC patients' treatment.

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