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Title: Colorectal Cancer in Patients 30 Years Old and Younger: A 17-Year Experience

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ABSTRACT

Background: Although its incidence has been increasing, colorectal cancer is rare in young patients. There are conflicting reports on the prognosis of young patients with colorectal cancers.

Aims: The goal of this study is to investigate the prognostic factors in young patients with colorectal cancer.

Study Design: An observational population-based, retrospective study.

Methods: The clinicopathological characteristics, treatment approaches, and survival data of patients with colorectal cancers aged 30 years and younger were retrospectively analysed.

Results: A total of 32 patients were identified. Haematochezia and abdominal pain were the major signs of colorectal cancer. Left-sided tumors (rectum 53.1%, and left colon 25%) were found to be more common than right-sided (18.8%) and transverse colon tumors (3.1%). Curative surgery was performed in 81.3% of patients. Histologically, 43.8% of cancers found were poorly differentiated. According to subtype, 21.9% were signet ring cell and 25% were mucinous (colloid). Patients were evaluated as Stage III in 46.9% and stage IV in 31.3%. Three-year progression-free (PFS) was 38.7% and 3-year overall survival (OS) was 53.2%. Stage IV disease and disease without curative surgery were poor prognostic factors both OS and PFS.

Conclusion: Prognosis was poor in young patients with colorectal cancer. In this institutional study, advanced stage, left-sided localization, and poor histological feature were frequently detected. Stage and complete surgery were predictive factors for long term survival. In this respect, it is important for physicians to heighten their awareness of the increased incidence of colon cancer in younger patients.

Key words: Colorectal Cancer; Young Patients; Demographics; Prognosis.

INTRODUCTION

Colorectal cancer is the third most common cancer in males, and the second most in females. It constitutes not only 10% of all cancers but also 8% of cancer-related deaths (1). Diagnoses increase after 50 years of age, and 70% of the patients are over 65 years old. Median age at diagnosis is 68 (2). Thus, screening for colorectal cancer for people of average risk is recommended at 50 years of age. In the general population, screening programs have been implemented to detect colonic polyps which, depending on features, could undergo malignant transformation. Treatment at earlier stages may decrease the mortality and morbidity of colorectal cancers (3). Although the incidence of colon cancer has been increasing in the young adult group, only 1.6% of all colon cancers are diagnosed in patients 35 years of age and younger (2). By the year 2030, the incidence of colorectal cancers will have increased 90% and 124.2%, respectively for patients 20 and 34 years of age (4).

Conflicting results about colorectal cancer are detected in few studies. Some studies have reported poorer outcomes in young patients due to the aggressive nature of colon cancers (5,6). Other studies have reported better outcomes (7,8). Thus, we evaluated the clinical, pathological, treatment and survival features in colorectal carcinoma patients aged 30 years of age and younger. Our aim is to investigate the prognostic features on survival in young adult colon cancer patients in our centre and compare them with the literature.

MATERIALS AND METHODS

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Subjects

Eight hundred ninety-two colorectal cancer patients were treated at the Departments of Paediatric and Medical Oncology between 2000 and 2017. Out of those 892, 32 colorectal cancer patients were 30 years of age and younger. Approval for this retrospective study was obtained from the Institutional Ethics Committee (11.10.2017/1516). Demographics, clinical and histopathological characteristics of these patients were analysed. Standard TNM classification was used for the staging of tumors.

Statistics

SPSS for Windows (SPSS Inc., Version 15, Chicago, USA) was used for statistical analyses. Median and mean values were used for presenting quantitative variables. Kaplan-Meier survival estimates were calculated. The log rank test was used for the statistical comparisons. Definitions used for survival terms were the following: 1. Overall survival (OS) was calculated from the start of the treatment to death from any cause; 2. Progression-free survival (PFS) was calculated from the date to start of the treatment into the date of first progression. The possible prognostic factors were identified by univariate analyses. Cox regression analysis was performed to determine independent predictors of survival (9). Type-I error level was set at 5% to infer statistical significance.

RESULTS

Among 892 colorectal cancer cases, 32 (3.6%) patients were 30 years old and younger. The mean age of the patients was 22.7 (range: 12-30) and only one of them was female, the others were male. Family history and presence of polyposis coli were negative in all the

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patients. The complaints of the patients were abdominal pain in 12 (37.5%), hematochezia in 16 (50%), pallor in 3 (9.4%) and chronic diarrhea in 1 (3.1%). There were acute abdominal findings and intestinal obstruction in 5 of 6 (18.7%) patients who presented acutely. The primary tumor was located in 18.8% (6) of the patients in the right colon, 25% (8) in the left colon, 3.1% (1) in the transverse colon and 53.1% (18) in the rectum. The other clinical and treatment features of colorectal cancer were summarized in Tables 1 and 2.

With a median follow-up of 29 months, PFS and OS rates for 32 patients were 38.7% and 53.2% at 3 years, respectively (Figures 1a and 1b). Mean and median time of PFS and OS were shorter in stage IV patients than others (other stages: PFS; 55 and 23 months, OS; 72 and 45 months: Stage IV: PFS; 7 and 7 months, OS; 12 and 11 months).

According to histology, three-year OS and PFS rates were 18% and 14% in signet ring cell, whereas these were 47% and 38% in mucinous type, and 55.4% and 51.3% in other adenocarcinomas, respectively (OS p=0.482; PFS p=0.283). The OS and PFS rates of poor differentiated were worse than those with moderate differentiation (OS: moderate: 57.8% vs. poor: 33.6%, p=0.393; PFS: moderate: 46.7 vs poor: 27.3%, p=0.775).

The presence of T4 tumors (p=0.089, HR=2.6), metastasis (p<0.001, HR=10.5), no curative surgery (p<0.001, HR=10.5), and Stage IV disease (p=0.006, HR=22.6) were possible significant predictors for PFS in univariate analysis. After multivariate analysis, no curative surgery (p=0.040, HR=10.4) and Stage IV disease (p<0.001, HR=11.3) were the significant predictors on PFS (Table 3). Three-year PFS was significantly higher in patients with curative surgery and tumor stage less than Stage IV, respectively (PFS: Curative

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surgery=45.7% vs No curative surgery=0%, p<0.001; Stage IV=0% vs others=57.1%, p<0.001) (Figures 2a-b and 3a-b).

The presence of T4 tumors (p=0.042, HR=3.9), metastasis (p<0.001, HR=19.2), no curative surgery (p<0.001, HR=24.9), underwent adjuvant treatment (p=0.030, HR=3.1), Stage IV rather than the others (p< 0.001, HR=43.5) were possible significant predictors and were the effective parameters in the univariate analysis for OS. Stage IV disease (p=0.003, HR=30.2) and no curative surgery (p=0.037, HR=6.5) were the significant predictors on survival in a multivariate analysis (Table 3). Three-year OS was significantly higher in patients with curative surgery and tumor stage less than Stage IV (OS: Curative surgery=63.9% vs No curative surgery=0%, p<0.001; Stage IV=0% vs others=71.1%, p<0.001) (Figures 2a-b and 3a-b).

DISCUSSION

Although their numbers have increased over the years, adolescent and young adult colon cancers only account for a very small proportion of all colon cancers. Colon cancer in those less than 35 years of age has been reported to comprise 1.6% of all colon cancer patients (2). This rate was 3.26% in our study (32/982 patients with colon cancer) for 30 years of age or younger and compatible with disease frequency of the world. In addition, 31 patients were male, and one patient was female. Males were more affected than females due to the nature of the medical center where this study was performed.

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Most colon cancers are sporadic, but 20% to 30% of them have hereditary component. However, genetic basis is detected only in 3% to 5% of hereditary type (10). Individuals with hereditary colorectal cancer syndromes have an increased risk of developing colon cancer at earlier age (11). Kaplan et al (12) have reported a 21.7% of family history of colorectal cancer. There was no significant difference between young-adult (20 to 25 year) and child-adolescent (0 to 19 year) group in terms of family history (p=0.741). In the evaluation of accessible pathologic reports of patients and family history, the genetic transition and additional syndromic disease could not be found. It was thought that the number of patients was low, and it could not be detected due to the evaluation of a small part of the population.

Change in bowel habits and haematochezia are more frequent in left colon and rectal cancers. Iron deficiency anaemia is more commonly seen with right colon tumors. Tenesmus and rectal pain are seen with rectal tumors. However, partial obstruction and abdominal pain due to peritoneal irritation or involvement can be observed in all localization of colon cancer (13). In our study, 37.5% of the patients had abdominal pain and 50% of the patients had haematochezia. Of the patients presenting with haematochezia, 81% had rectal cancer, 12.5% had left colon cancer, and 6.5 % had transverse colon cancers. Abdominal pain was found in 33.3% of the left colon, right colon and rectum separately for each, while 18.8% of the patients were admitted with acute abdominal complaints, and 81.2% had chronic complaints.

The median lag time was 127 days. Scott et al (14) have reported the lag time as 29.5 days in patients over 50 years and 217 days in patients less than 50 years. The reason for this delay in diagnosis is that patients do not pay enough attention to their complaints or are

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evaluated inadequately by their physicians using diagnostic methods. Additionally, many symptoms of colorectal cancer like abdominal pain and anaemia can mimic benign disease.

Distal colon tumors are more common in the young adult population. In the study performed by Teng et al (15), 25.4% of patients were left-sided and 41.2% were rectal. Lee et al (16) have reported incidence of rectal cancer and left colon cancers as 40% and 26%, respectively. Zhao et al (17) reported rectal cancer as 44% and left colon tumor as 25%. Saluja et al (18) found rectosigmoid cancer in 59% of cases, and left colon tumor has been observed in 12% of cases. Consequently, rectal cancer is more common than left colon cancer. In our study, 53% of the patients had rectum and 25% had left side. This rate was compatible with previous rates.

Younger patients with colorectal cancers have poorer differentiation (19). The rate of poorly differentiated adenocarcinoma was determined by Teng et al (15) and Zhao et al (17) as 27.9% and 14.7% in their studies, respectively. However, the rate of signet ring cell adenocarcinoma was 4.1% in the study conducted by Teng et al (15) and 4.8% in the study with metastatic disease performed by Lee et al (16). In our study, 43.8% of the patients were poorly differentiated, and histologically 21.9% were signet ring cell. The more aggressive histologic features of our patients in the study group can be related to worse response to systemic chemotherapy.

Young patients are diagnosed at advanced stage in admission time compared to elders (20). Teng et al (15) have reported 43.9% of the patients as local advanced stage, while 27.9% has been diagnosed in metastatic stage. Similarly, 40% of the patients were stage III and 21%

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were stage IV in Lee et al (16). In another study involving the entire population, 36% of patients were diagnosed at the local advanced stage and 20% at the metastatic stage (21). In our study, 46.8% of patients were stage III, while 31.2% were stage IV. In this age group, physicians examining patients for further diagnosis should be more careful, and patients with cautionary symptoms should be evaluated with appropriate diagnostic methods, especially if there is a family history of colon cancer. It is suggested to be evaluated by proctosigmoidoscopy because the majority of the cases are in the rectum and left colon.

According to Teng et al (15), 5-year DFS was 64.8% and 5-year OS was 62.1% in 7530 colorectal cancers under 40 years of age. In our study, 5-year OS of muscular and signet ring cell adenocarcinoma were 59.3% and 27%, respectively, while it was 64.6% in adenocarcinoma. Yang et al (22) has reported that 5-year and 10-year DFS were 61% and 57% in children and adolescent group with colorectal cancer, respectively. The 5-year DFS in local disease is 92%, while the 5-year DFS in metastatic disease is 15.8%. In addition, 5-year DFS is 18.5% in signet ring cell tumor and 31.3% in high grade tumors. In a study conducted by Lee et al (16), median DFS is 38.4 months, while median OS is not reached in 40-year-old and younger patients with stage I, II, and III. In patients with metastatic disease, median PFS is 9.1 months and median OS is 19 months. According to median our study follow-up time of 29 months, 3-year PFS and OS were 38.7% and 53.2%, respectively. According to histology, the 3-year OS and PFS of signet ring type were 18% and 14%, which were 47% and 38% in mucinous type and 55.4% and 51.3% in other adenocarcinomas, respectively. The 3-year OS and PFS for poor differentiated tumors were 33.6% and 27.3%, while these were 57.8% and

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46.7% for moderately differentiated type, respectively. These rates were consistent with previous works. In our study, we found that PFS and OS rates were worse than other studies because of the high ratio of patients with mucinous and signet ring types and poor differentiation. The fact that targeted cancer therapy was not used at the time of treatment was among the factors affecting PFS and OS.

Some clinical factors may be important in prognosis of colon cancer treatment. Teng et al (15) has reported stage IV at diagnosis, male sex, poorly differentiated tumor, mucinous and signet ring cell types, low socioeconomic status, and black race as poor prognostic factors affecting OS and DFS negatively. According to Yang et al (22), end-stage tumor, stage IV, signet ring cell type and non-surgical factors were found as poor factors affecting DFS. Zhao et al (17) has found that less than 35-year old, advanced disease, poorly differentiated tumor, and preoperative CEA elevation are factors that affect OS and DFS. The fact that our patients did not have curative surgery and Stage IV had a negative effect on PFS and OS. Performing curative surgery and early detection of patients will prevent progression and further prolong survival.

There are some limitations to our study. This study was retrospective and conducted in a single centre. The majority were men since it was a military hospital, and this fact can create a bias in terms of gender distribution. Hereditary colorectal cancer was not observed and can be attributed to the fact that the working group is small.

In conclusion, the incidence of colorectal cancer is increasing. First, stage is the most important factor affecting the progression and survival at diagnosis. Often, these patients are

diagnosed late. Consequently, the rates of survival and progression-free are low in advanced stage disease. Curative surgery is the second prognostic factor for survival and progression. A patient without curative surgery is at risk for lower survival and a higher progression rate. Therefore, early stage diagnosis and curative surgery are essential for survival. Finally, physicians to whom these patients are referred should have a heightened suspicion of red flag symptoms like change in bowel habits and haematochezia. In these patients, it is suggested to perform a thorough and expeditious diagnostic workup to avoid further delays in treatment.

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Figures 1 a-b.

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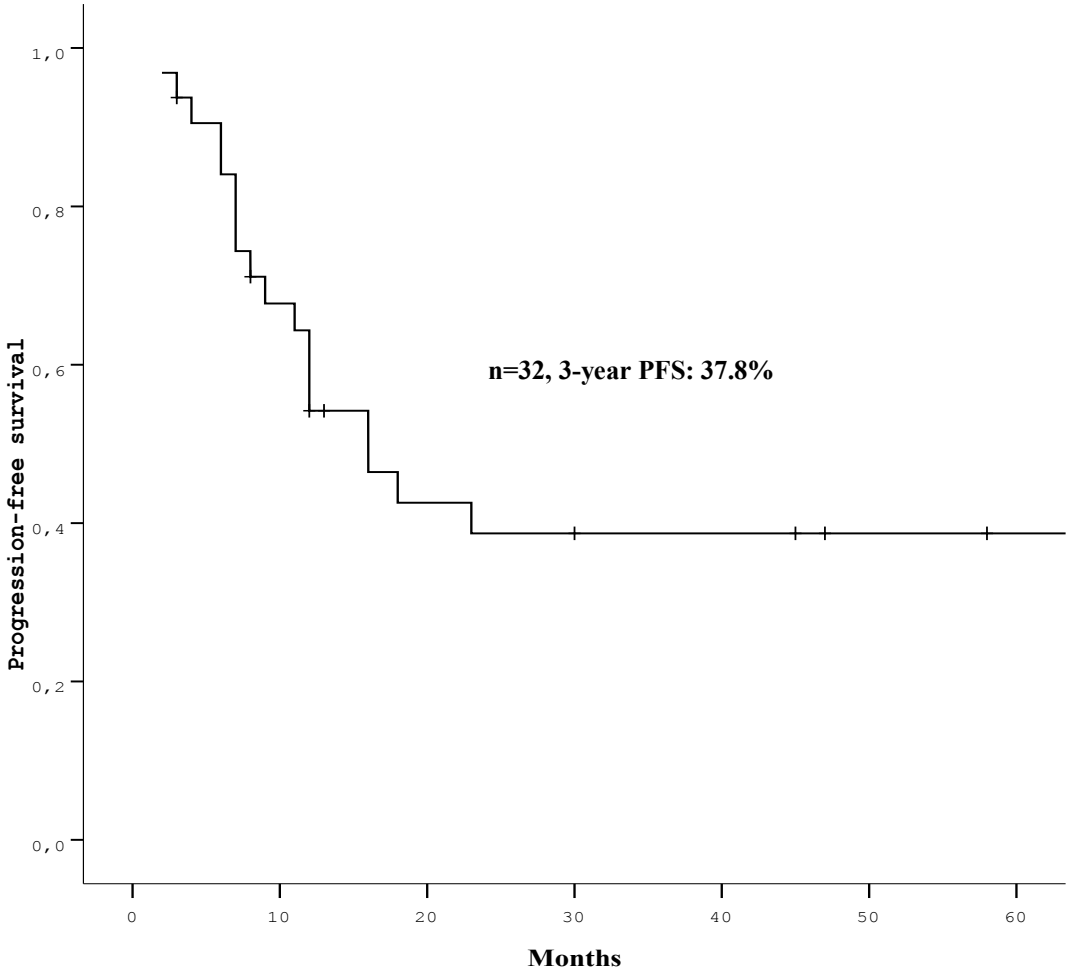

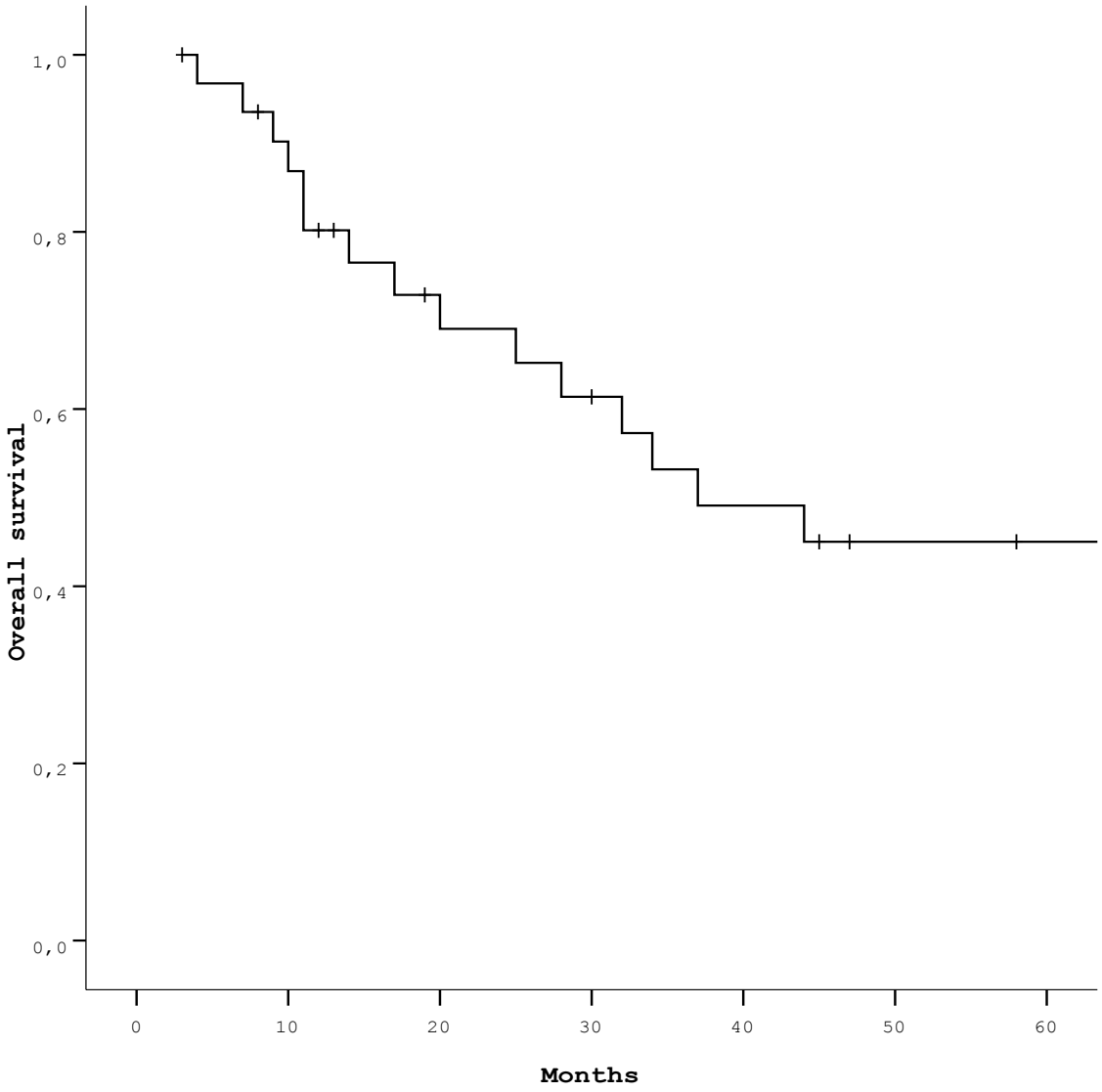

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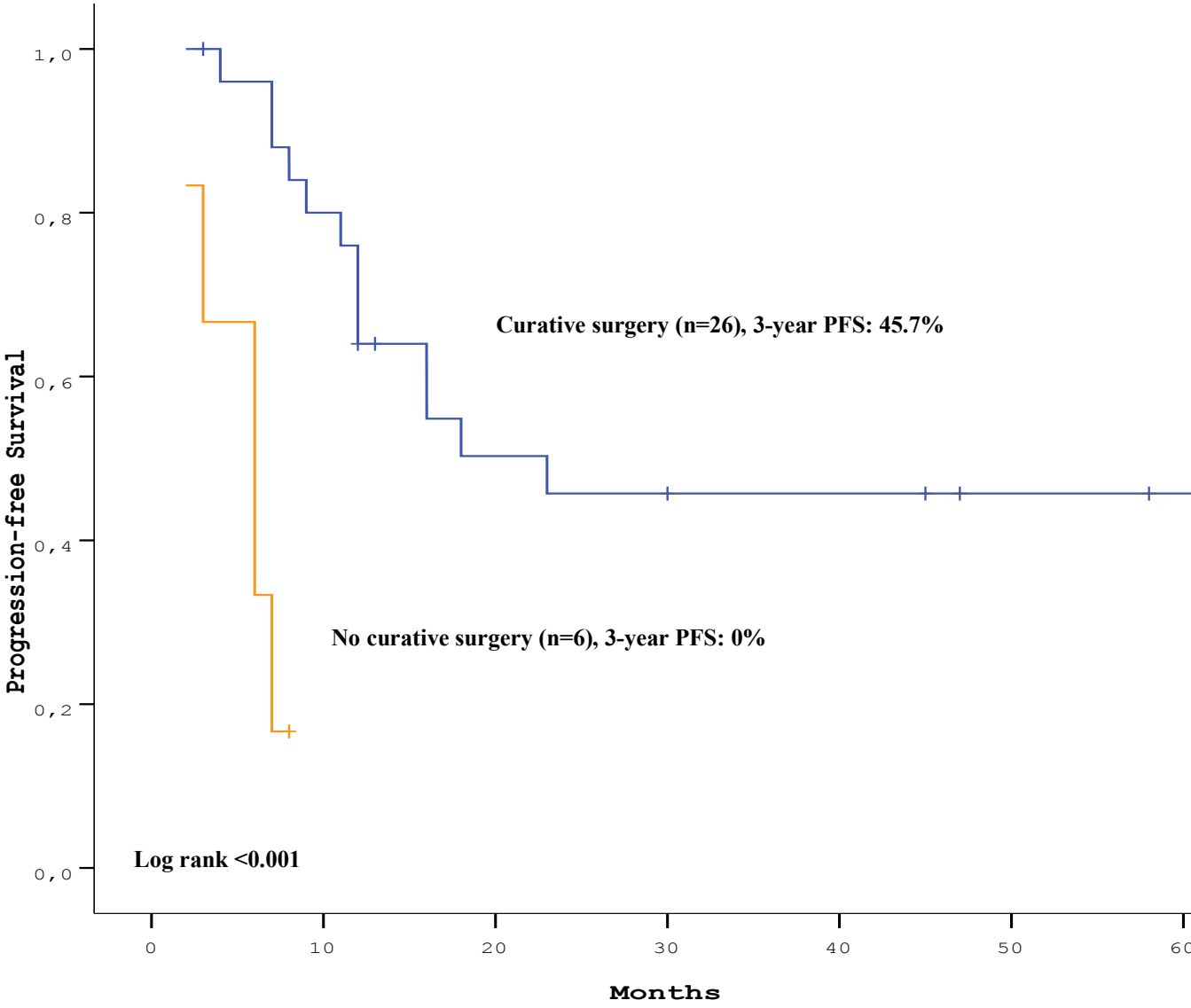

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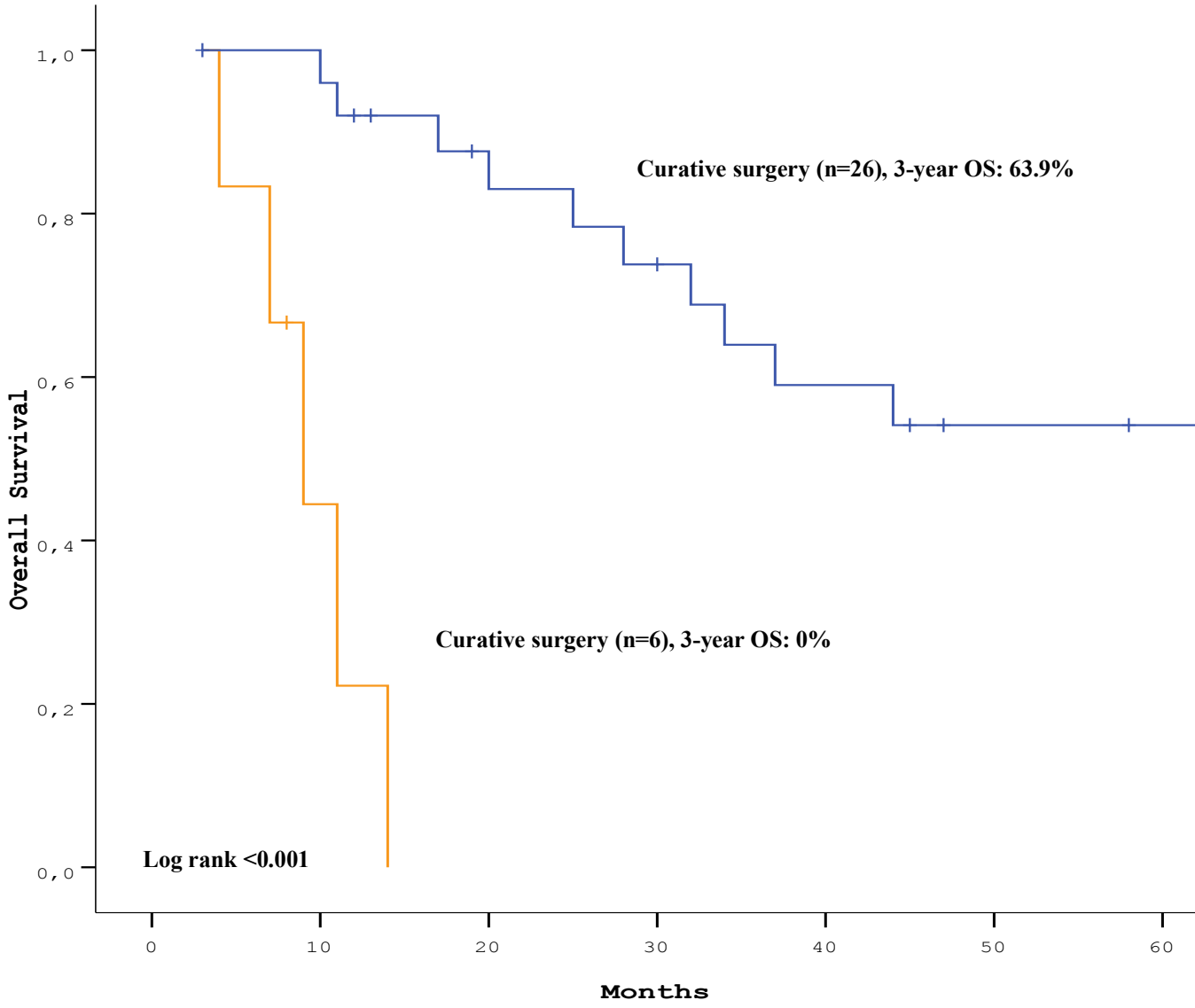

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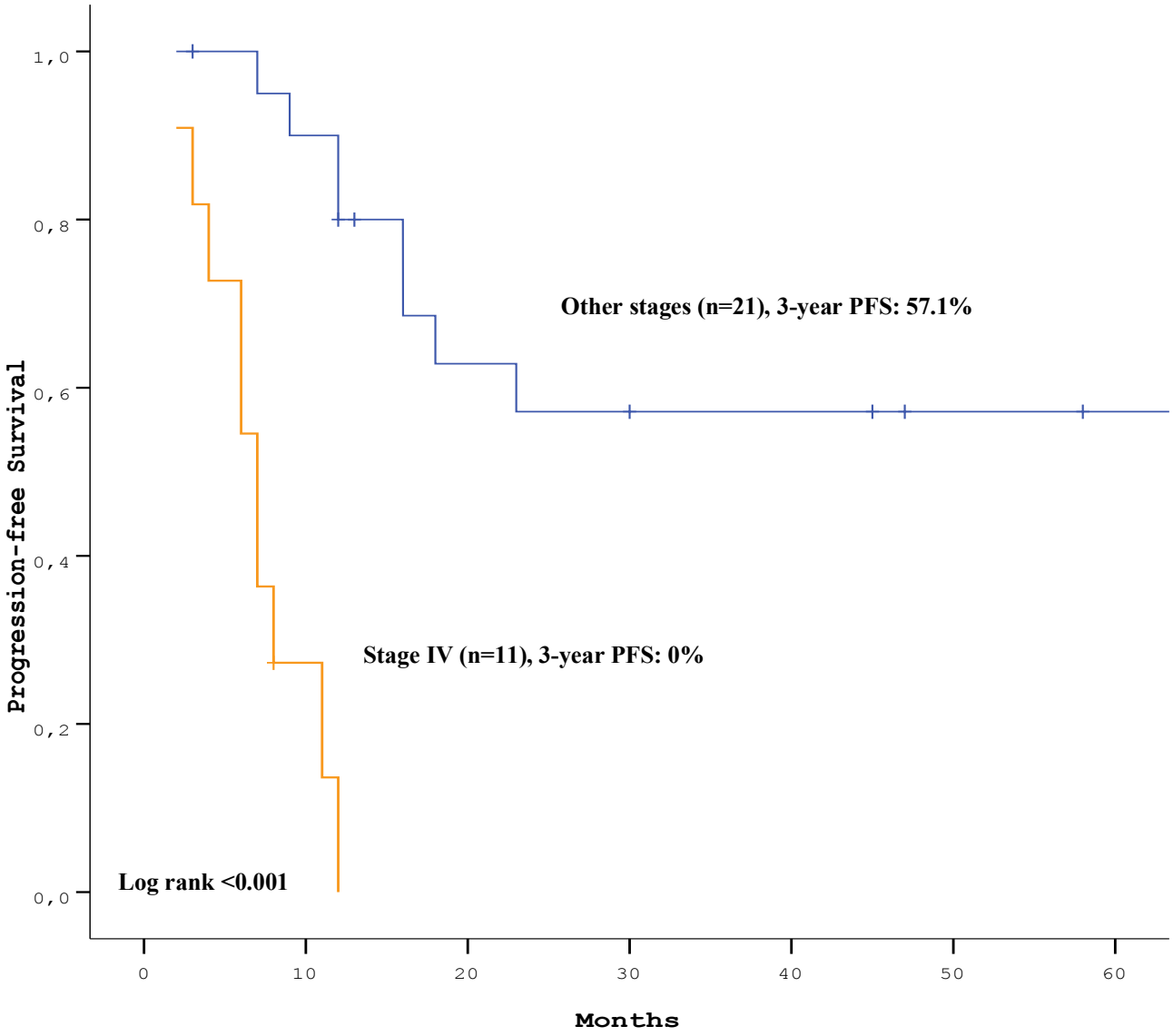
Figures 3 a-b



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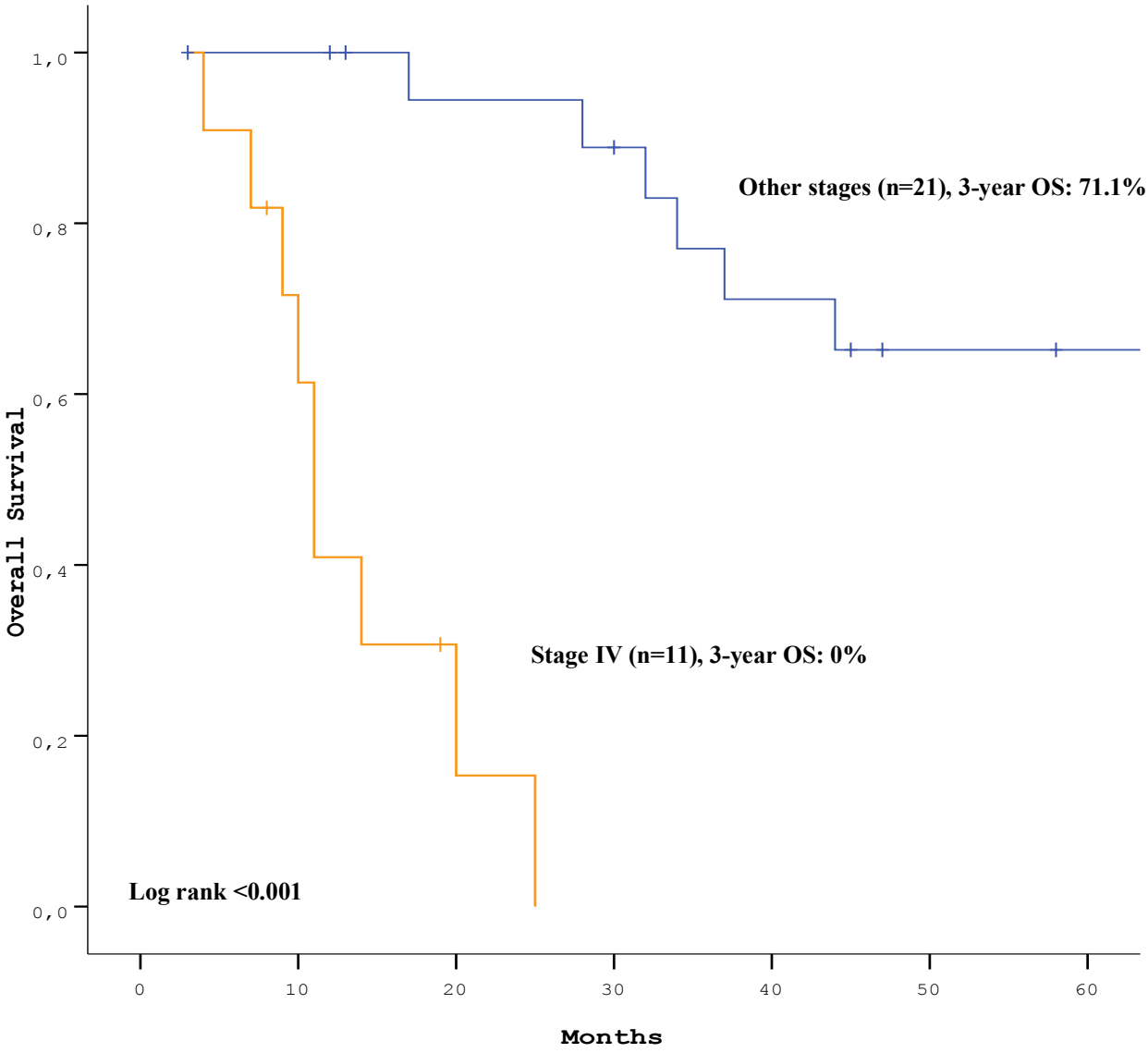

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TABLES

Table 1: Clinical features of patients with colorectal carcinoma.

Features	Units	Mean ± SD/Median (Range)
Age at diagnosis	years	22.7±3.2/22 (12-30)
Lag time	day	127±148/90 (2-730)
Total lymph node	n	16±13/14 (0-40)
Metastatic lymph node	n	4.7±6.1/2 (0-19)
	Category	n (%)
Sex	Male/Female	31 (96.9%)/1 (3.1%)
Family history	Yes/No	0 (0%)/32 (100%)
History of polyposis coli	Yes/No	0 (0%)/32 (100%)
Complaints	Abdominal pain	12 (37.5%)
	Haematochezia	16 (50%)
	Pallor	3 (9.4%)
	Chronic diarrhoea	1 (3.1%)
Acute presentation	Yes/No	6 (18.7%) / 26 (81.3%)
• Acute abdomen		5
• Obstruction		1
Localizations of primary tumour	Right colon	6 (18.8%)
	Left colon	8 (25%)
	Transverse	1 (3.1%)
	Rectum	17 (53.1%)
Histology	Adenocarcinoma	17 (53.1%)
	Signet ring	7 (21.9%)
	Mucinous (colloid)	8 (25%)
Differentiation	Moderate /Poor	18 (56.3%)/14 (43.8%)
Surgery	Curative/Others (Paliative-No surgery)	26 (81.3%)/6 (18.8%) (2-4)
Localization of metastasis	Liver	6
	Peritoneum	3
	Liver+Peritoneum	1
Stage	II/IIIa/IIIb	7 (21.9%)/1(3.1%)/ 6 (18.8%)
	IIIc/IV	8 (25%)/ 10 (31.3%)

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Table 2: Treatment features of patients with colorectal carcinoma.

Features	Category	n (%)
Neoadjuvant RT	Yes/No	13 (40.6%) / 19 (59.4%)
Patients with local disease at diagnosis		23 (71.9%)
Adjuvant chemotherapy	• FOLFOX	10 (31.3%)
	• FUFA	12 (37.5%)
	• FOLFIRI	1 (3.1%)
Relapse	Local/Distant	1/11
	• Peritoneum	6
	• Rectum (Local)	1
	• Liver	2
	• Pancreas	1
	• Duodenum-peritoneum	1
	• Liver-peritoneum	1
Patients with local/distant relapse or metastatic at diagnosis		19 (59.4%)
• First line	• FOLFIRI	14
	• FOLFOX-4	2
	• FUFA	1
	• FOLFIRI+bevacizumab	1
	• FOLFIRI+panitumumab	1
• Second line	• Irinotecan+cetuximab	1
	• Capecitabine +oxaliplatin	1
	• FOLFOX-6	1
	• FOLFOX-4	1
	• FOLFIRI	1
	• Docetaxel. cisplatin. 5-FU	1
• Third line	• Capecıtabıne	1
	• Irinotecan	1
Survival parameters	Units	Mean ± SD/Median (Range)
• PFS	months	39±59/12 (2-261)
• OS	months	52±61/29 (3-261)

FOLFOX:5- fluorouracil. folinic acid. oxaliplatin; FOLFIRI: 5-fluorouracil. folinic acid. irinotecan; 5-FU: 5-fluorouracil; FUFA: 5-fluorouracil. folinic acid; OS: Overall survival; PFS : Progression free survival; RT: Radiotherapy; SD: Standart deviation

Table 3: Prognostic factors of colorectal cancer in uni-multivariate analysis.

			Univariate analysis			Multivariate analysis		
	Prognostic factors	Category	HR	95% CI	p	HR	95% CI	p
Overall survival	Gender	Male/Female	0.04	0.0001-1183	0.551			
	Age	(years)	0.90	0.76-1.1	0.235			
	Complaint		0.47	0.2-1.2	0.088			
	Lag time	(days)	0.99	0.99-1.1	0.660			
	Acute presentation	Yes/No	1.9	0.5-7.5	0.322			
	Histology	Adeno/Musinous/Signet ring	1.2	0.67-2.1	0.509			
	Differentiation	Poor/Modorate	1.5	0.55-4.4	0.398			
	Localization	Colon/Rectum	1.2	0.41-3.2	0.788			
	T	4/ Others	3.9	1.1-14.2	0.042			
	N	Yes/No	0.68	0.24-1.9	0.465			
	M	Yes/No	19.2	3.8-95.7	<0.001			
	Curative surgery	No/Yes	24.9	4.6-134.2	<0.001	6.5	1.1-38.2	0.037
	Adjuvant treatment	Yes/No	3.1	1.1-9.1	0.030			
	Neoadjuvant treatment	Yes/No	0.9	0.32-2.5	0.850			
	Relapse	Yes/No	1.9	0.69-5.3	0.209			
	Stage	IV/Others	43.5	5.2-364	<0.001	30.2	3.2-285	0.003

CI: Confidence interval; HR: Hazard ratio; N: Node; M; Metastasis. T: Tumour

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