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ORIGINAL ARTICLE

Clinical significance of serum interleukin-17 levels in colorectal cancer patients

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Summary

Purpose: *The proinflammatory cytokine, interleukin-17 (IL-17) plays a potent role in T-cell mediated angiogenesis and promotes tumorigenicity. The objective of this study was to determine the clinical outcomes of colorectal cancer (CRC) patients in relation to serum IL-17 levels.*

Methods: *Ninety-six CRC patients were enrolled in this study. Pre-treatment serum IL-17 levels were determined by enzyme-linked immunosorbent assay (ELISA). Thirty age - and sex-matched healthy controls were included in the analysis.*

Results: *The median patient age was 60 years (range: 24-84) and the most frequent localization was colon (N=59;61%). Median follow-up time was 14 months, 27 patients (28%) experienced disease progression, and 20 of the remaining patients (20%) died. The estimated and 1-year progression-free survival (PFS) and 2-year overall survival (OS) rates for the whole patient group were 26.9% (95% confidence interval [CI]=9.9-44.0) and 71% (95% CI=56.0-85.0), respectively. The number of patients who received neoadjuvant treatment was 25. Of the patients who received palliative treatment, 11 had oxaliplatin whereas 18 and 7 had irinotecan and FU/capecitabine, chemotherapy (CTx). Twenty-four and nine of the patients who received targeted therapy had bevacizumab and cetuximab, respectively. Thirty-three percent of 36 metastatic patients who received palliative CTx were CTx-responsive. The baseline median serum IL-17 levels were significantly lower in patients with CRC than in the healthy control group (p=0.01). Moreover, known clinical variables including older age, poor grade and low albumin levels were found to be correlated with high serum IL-17 concentrations (p=0.02, p=0.02, and p=0.04, respectively). No statistically significant serum IL-17 concentrations were noted regarding PFS and OS.*

Conclusion: *Serum levels of IL-17 may be diagnostic marker in CRC patients. However, no predictive and prognostic values were determined.*

Key words: *colorectal cancer, diagnostic, IL-17, serum, survival*

Introduction

CRC is a common and life-threatening disease. CRC incidence and mortality rates vary markedly around the world. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with over 1,2 million new cases and 608,700 deaths estimated to have occurred in 2008 [1].

Infiltration of inflammatory cells into CRC tissue is considered important for tumor progression [2. The proinflammatory cytokine IL-17 is predominantly produced and secreted by activated CD4 T-cells [3] but data in humans have shown that CD8 T-cells can also produce IL-17 [4]. In ad-

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dition to the proinflammatory response, IL-17 is able to regulate tight junction formation [5] and has an anti-mitotic effect on the intestinal epithelial cells [6].

IL-17 family of cytokines play important and sometimes contradictory roles in human malignancies [7]. It is linked to rapid progression of CRC, therapy resistance and exerts its pro-tumorigenic activity through its type A receptor (IL-17RA) but how it promotes colonic tumorigenesis is unknown [8]. IL-17 may promote angiogenesis by enhancing vascular endothelial growth factor (VEGF) [9]. A correlation between vascularity and invasive behavior in CRC has also been demonstrated [10].

Until today, there has been little information available about IL-17 in cancer, especially in human CRC. It has been suggested that IL-17 plays a minor or partial role in CRC, for instance in connection with T-cell mediated angiogenesis and IL1-β/IL-6 derived tumor growth [11]. In another study IL-17 expression correlated to well differentiated and early stage CRC. Although some authors reported that positive IL-17 expression was connected with better OS [12], some others indicated that high IL-17 expression tumor tissues was a predictor for poor survival in CRC patients [13].

Moreover, IL-17 has been shown to be expressed in a considerable proportion of ovarian cancers and promotes tumor angiogenesis [14]. IL-17 may also be involved in the progression of gastric cancer by promoting angiogenesis [15] and accumulation of intratumoral IL-17A producing cells may promote gastric cancer progression directly or by inducing key signal transduction pathways implicated in gastric carcinogenesis [16].

Serum IL-17 has been shown to be a diagnostic and prognostic marker for non-small cell lung cancer [17] and it is found elevated in pleural effusion [13]. IL-17 is a diagnostic marker and outcome predictor in lung cancer patients [18]. For bladder cancer, Th17-related cytokines can be used as indicators for following the course and clinical stages of bladder carcinoma progress and immune response to cancer [19]. Based on all these data, the objective of this study was to determine the clinical outcomes of CRC patients in relation to serum IL-17 levels.

Methods

Study design and eligibility criteria

Serum samples of the 140 consecutive patients with CRC referred to Istanbul University Institute of Oncology and Bakirkoy Dr. Sadi Konuk Training and Research Hospital from 2011 to 2014 were obtained. Median age of the patients was 60 years (range: 24-84). All patients were staged using the 7th edition of the American Joint Committee on Cancer (AJCC) TNM system.

All of the patients were treated with multidisciplinary approach. Patients with colon cancer who had undergone surgery including segmental colon resection were treated with adjuvant CTx if they had stage 2 or 3 disease. Patients with rectal cancer, who received neoadjuvant radiochemotherapy (RCTx) or radiotherapy (RT), were subjected to low anterior resection or abdominoperineal resection. Some patients underwent palliative surgery and stage IV patients received palliative CTx with or without targeted therapy (bevacizumab or cetuximab).The pretreatment evaluation included detailed clinical history and physical examination with a series of biochemistry tests and complete blood cell counts. Selection for treatment required an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0-2, and appropriate bone marrow (hemoglobin >9g/dl, absolute neutrophil count >1500/μL, and platelet count >100,000/μL), cardiac, renal and hepatic function.

Patients were treated with various CTx regimens including single agent or combination therapy. Regimens of single or combination CTx were selected according to the PS of the patients and extension of disease to stage 4. Patients received one of the following regimens: simplified LV5FU2 (leucovorin 400 mg/m^2, followed by 5-fluorouracil as a 400 mg/m^2 bolus and a 2400 mg/m^2 infusion over 46 hrs every 2 weeks); capecitabine (1000 mg/m^2, b.i.d., p.o. for 14 days in 21-day cycles); modified FOLFOX (simplified LV5FU2 regimen plus oxaliplatin 85 mg/m^2 every 2 weeks); FOLFIRI (simplified LV5FU2 regimen plus irinotecan 180 mg/m^2 every 2 weeks), XELOX (capecitabine 1000 mg/m^2, b.i.d., p.o., for 14 days plus oxaliplatin 130 mg/m^2 every 3 weeks); or XELIRI (capecitabine 1000 mg/m^2, b.i.d., p.o. for 14 days plus irinotecan 240 mg/m^2 every 3 weeks). Bevacizumab was given at a dose schedule of either 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. Cetuximab 500 mg/m^2 was administered intravenously every 2 weeks.

All of the patients had pretreatment imaging of primary tumors with magnetic resonance imaging (MRI) or computed tomography (CT). For patients with evaluable imaging studies before and after treatment, radiologic response was recorded according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and classified as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The tumor response after 2 months of CTx was used for statistical analysis. Follow-up programs of metastatic disease consisted of clinical, laboratory, and CT or MRI, depending on which imaging methods were used at baseline and performed at 8-week intervals during CTx or every 12 weeks for patients who couldn't

receive anticancer treatment. Patients with either CR or PR were classified as responders, and patients with SD or PD were considered as non-responders.

The study was approved by the Institutional Review Board of Istanbul University, Institute of Oncology. Baseline demographic, clinical, and laboratory data including age, gender, ECOG PS, CEA and CA 19.9 tumor marker levels, KRAS mutation status, and treatment details were collected retrospectively for all patients using uniform database templates to ensure consistent data collection. The comorbid diseases of patients were cardiac and metabolic diseases.

The control group consisted of age- and sex-matched healthy people (N=30) with no previous history of malignancy or autoimmune disorders. Blood samples were obtained from patients with CRC at first admission, one month after surgery, and two weeks before adjuvant or palliative CTx. Blood samples of healthy controls were taken into dry tubes and sera were separated from cellular elements by centrifugation (at 4000 rpm for 10 min) within half an hour after blood samples were stored at -80°C until analysis. All of the samples were collected under the approval of the Institutional Review Board and with adequate informed consents.

Measurement of serum IL-17 levels

IL-17 ELISA (Diaclone SAS F-25020 Besancon Cedex, France) uses a double-antibody sandwich to determine the level of human IL-17 in samples. Serum samples and standards were added to the wells of the microtiter stip plate which were pre-coated with human IL-17 monoclonal antibody (Diaclone SAS F-25020 Besancon Cedex, France). Following a 2-hr incubation, IL-17 antibody labeled with biotin and combined with Streptavidin-HRP was added to form immune complex and were incubated for 2 hrs. Unbound material was washed away and then TMB (3, 3', 5, 5'-tetramethylbenzidine) substrate solution was added for the conversion of the colorless solution to a blue solution (5-15 min), the intensity of which is proportional to the amount of IL-17 in the sample. Acidic stop solution turned the color to yellow. The colored reaction product was measured using an automated ELISA reader (ChroMate® 4300 Microplate Reader, Awareness Technology Inc., Palm City, FL, USA). The results were expressed in pg/mL.

Statistics

The Stastistical Package for Social Sciences (SPSS) for Windows, version 21.0 (SPSS Inc., Chicago, ILL, USA) was employed for data analysis. Continuous variables were categorized using median values as cut-off points. For group comparison of categorical variables, Chi-square test or One-Way ANOVA test were used and for comparison of continuous variables, Mann–Whitney U test or Kruskall-Wallis test were performed. PFS was calculated from the date of admission to the date of first radiologic progression with/without elevated serum tumor markers. OS was calculated from the date of first admission to the clinic to disease-related death or date of last contact with the patient or any family member. Kaplan-Meier method was used for estimation of survival distribution and differences in PFS and OS were assessed by the log-rank test. All statistical tests were two-sided and a p value <0.05 was considered statistically significant.

Results

Ninety-six patients who were pathologically diagnosed with CRC from March 2012 to August 2014 were included in the current study. Their baseline demographic features and histopathological/laboratory characteristics are listed in Tables 1 and 2. Median age at diagnosis was 60 years

Table 1. Patient and disease characteristics

Characteristics	*N*
No. of patients	96
Age (years)	
Median (range)	60 (24-84)
Gender	
Male/female	72/24
Performance status (PS)[1]	
0/1/2	53/35/5
Smoking[1]	
Yes/no	48/44
Alcohol intake[1]	
Yes/no	22/66
Comorbidity[1]	
Yes/no	39/52
Obstruction	
Yes/no	11/85
Type of operation	
Colectomy	40
Low anterior resection	23
Abdominoperineal resection	9
Palliative	8
Pathologic tumor (pT) stage[2]	
0/1/2/3/4	7/2/9/30/7
Pathologic node (pN) stage[2]	
0/1/2	28/14/11
Clinical disease stage	
2/3/4	12/45/39
Site of lesion	
Colon/rectum	59/37
Response to chemotherapy (CTx)[3]	
CR/PR/SD/PD/Unknown	1/11/6/14/4
Metastasis	
Yes/no	39/57

[1]Patients with unknown data concerning the variables are not included in the analysis; [2]57 nonmetastatic patients with unknown data concerning the variables are not included in the analysis; [3] In 39 patients with metastatic colorectal cancer

Table 2. Pathological features of tumors and laboratory parameters

Features	*N*
Histology	
Adenocarcinoma/mucinous	89/7
Grade[1]	
1/2/3	6/38/3
Angiolymphatic invasion[2]	
Yes/no	19/16
Vascular invasion[2]	
Yes/no	9/25
Perineural invasion[2]	
Yes/no	12/22
Regression score[3]	
1/2/3/4	1/7/3/6
KRAS mutation status[4]	
Mutant/wild	18/17
Lactate dehydrogenase (LDH)[1]	
Normal (<450 IU/ml)/high (>450 IU/ml)	69/9
Albumin[1]	
Normal (>4 g/dl)/low (<4 g/dl)	41/39
CEA[1]	
Normal (<5 ng/ml)/high (>5 ng/ml)	52/9
CA 19-9[1]	
Normal (<38 U/ml)/high (>38 U/ml)	54/17

[1] Patients with unknown data concerning the variables are not included in the analysis; [2] 57 non-metastatic disease patients with unknown data concerning the variables are not included in the analysis; [3] In 39 patients with metastatic colorectal cancer; [4]In25 patients with rectal cancer who received neoadjuvant treatment

(range 24-84) and males constituted the majority of the group (N=72;75%). Thirty patients had a family history of cancer including 6 lung cancers and 11 CRC. The tumor localization was the rectum plus rectosignoid in 39% (N=37) and colon in 61% (N=59) of the patients (right colon, N=11, hepatic flexure, N=3, transverse colon, N=5, descendending colon, N=10, sigmoid colon, N=28, multiple synchronous colon tumors, N=2, rectosigmoid junction tumor, N=3 and rectum N=34. Liver (n=31;79.4%) and peritoneum (N=6;15.3%) were the most frequent metastatic sites in 39 patients with metastases. Fifty-nine percent of all metastases were synchronous (N=23), whereas metachronous metastases were 41% (N=16).

Of the 34 patients with rectal cancer, 19 received fluoropyrimidine-based RCTx whereas in 6 a short-course of RT was delivered. Fifty-two patients who had adjuvant CTx received one of the following treatment regimens: simplified LV5FU2 or capecitabine (N=12), mFOLFOX (N=21) or XELOX (N=19). Oxaliplatin-based, irinotecan-based combination CTx regimens and single-agent fluoropyrimidine were administered to 11, 18, and 7 patients, respectively. Bevacizumab were given to 24 patients whereas 9 patients had cetuximab as targeted agents. Response to CTx was observed in 33% of 36 metastatic patients who received palliative CTx.

The levels of serum IL-17 in CRC patients and healthy controls are shown in Table 3. The baseline serum IL-17 levels were significantly lower in the control group (20.91 vs 23.47 pg/mL, p=0.01) (Figure 1). Tables 4 and 5 show the correlation between the serum levels IL-17 and clinico-pathological factors. Older age and low albumin levels were found to be correlated with high serum IL-17 concentrations (p=0.02 and p=0.04, respectively). The median serum IL-17 levels of patients with baseline poor grade cancer were significantly higher compared to good grade disease (41.70 vs 23.47 pg/mL, p=0.002). More analytically, the results showed poor grade vs intermediate grade: 41.70 vs 32.50 pg/mL, p=0.49; and intermediate grade vs good grade: 32.50 vs 23.47 pg/mL, p=0.55.

Median follow-up time was 14.0 months (range 1-33), while 23 patients (24%) experienced disease progression, and 20 of the remaining patients (21%) died. Mean PFS and OS of the whole

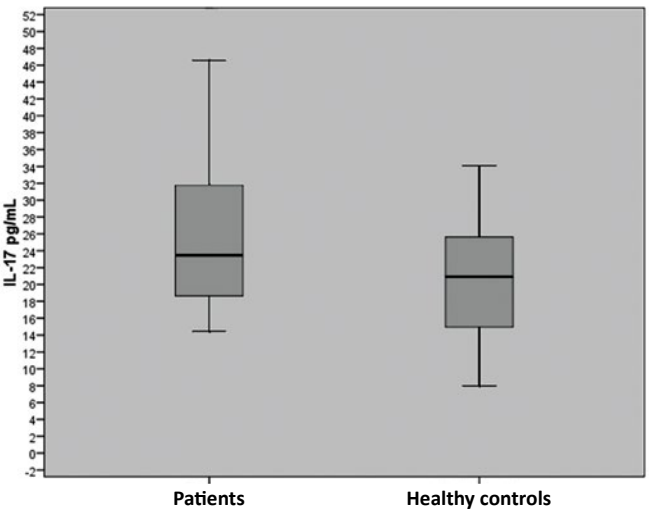

Figure 1. Serum IL-17 levels in colorectal cancer patients and healthy controls (p=0.01).

Table 3. Serum IL-17 levels in CRC patients and healthy controls

	Patients (N=96)		*Controls (N=30)*		
IL-17 level (pg/mL)	*Median*	*Range*	*Median*	*Range*	*p value*
	23.47	14.43-151.58	20.91	7.95-34.09	0.01

Table 4. Results of comparisons between the serum IL-17 levels and various demographic and disease characteristics

Variables	*N*	*IL-17 (pg/mL) Median (range)*	*p value*
Age, years			
<50	16	19.60 (15.23-38.98)	0.02
≥50	80	24.89 (14.43-151.58)	
Gender			
Male	72	23.30 (14.43-55.11)	0.49
Female	24	25.00 (15.57-151.58)	
PS			
0	53	23.41 (14.43-151.58)	0.80
1-2	40	24.09 (14.54-70.11)	
Smoking			
Yes	48	22.90 (14.43-151.58)	0.30
No	44	25.00 (15.11-70.11)	
Alcohol intake			
Yes	22	25.85 (14.54-55.11)	0.19
No	66	22.84 (14.43-151.58)	
Comorbidity			
Yes	39	24.43 (14.43-151.8)	0.55
No	52	22.73 (14.54-70.11)	
Obstruction			
Yes	11	19.66 (15.34-38.98)	0.22
No	82	23.86 (14.43-151.58)	
Surgery			
Yes	80	22.27 (14.43-42.95)	0.17
No	16	23.86 (14.54-151.58)	
pT stage			
0-2	18	23.86 (14.54-151.58)	0.67
3-4	37	25.23 (14.77-55.11)	
pN stage			
0	28	23.86 (14.77-52.72)	0.62
1-2	25	25.34 (14.54-151.58)	
Metastasis			
Yes	39	24.43 (14.54-151.58)	0.60
No	57	22.61 (14.43-70.11)	
Response to CTx			
Yes (CR+PR)	12	20.63 (14.43-59.66)	0.14
No (SD+PD)	20	23.98 (16.25-70.11)	
Site of lesion			
Colon	59	22.61 (14.54-38.98)	0.17
Rectum	37	25.00 (14.43-151.58)	

Table 5. Comparisons of serum IL-17 levels and various histopathological features and laboratory parameters

Features	*N*	*IL-17 (pg/mL) Median (range)*	*p value*
Histology			
Adenocarcinoma	89	23.52 (14.43-151.58)	0.94
Mucinous	7	23.18 (17.27-34.54)	
Grade			
Good	6	23.47 (15.23-59.66)	0.02
Intermediate	38	32.50 (17.84-35.57)	
Poor	3	41.70 (23.36-151.58)	
Angio-lymphatic invasion			
Yes	19	25.34 (16.82-151.58)	0.61
No	16	25.12 (14.77-53.97)	
Vascular invasion			
Yes	9	27.38 (16.82-151.58)	0.32
No	25	25.23 (14.77-53.97)	
Perineural invasion			
Yes	12	25.06 (15.11-151.58)	0.76
No	22	25.29 (14.77-55.11)	
Regression score			
0-2	8	21.48 (14.54-38.63)	0.61
3-4	9	22.16 (15.23-27.84)	
KRAS mutation status			
Mutant	18	22.61 (14.43-70.11)	0.20
Wild	17	22.10 (16.36-42.95)	
LDH			
Normal	69	23.52 (14.54-151.58)	0.84
High	9	23.41 (14.43-42.95)	
Albumin			
Normal	41	21.25 (14.43-70.11)	0.04
Low	39	25.34 (15.11-151.58)	
CEA			
Normal	52	25.00 (14.54-55.11)	0.89
High	9	22.61 (15.23-59.66)	
CA19-9			
Normal	54	24.60 (14.43-151.58)	0.14
High	17	20.00 (14.77-40.45)	

group were 7.3±1.1 months (95% CI=5-10) and 26.4±1.3 months (95% CI=24-29), respectively, while 1-year PFS was 26.9% (95% CI=9.9-44.0), 1- and 2-year OS were 82.6% (95% CI=74.8-90.4) and 70.7% (95% CI=56.0-85.0), respectively. There was a significant relationship between having no surgical resection (p=0.005), chemotherapy unresponsiveness (p=0.009), 19-9 (p=0.01) and poor PFS (Tables 6 and 7). Also, a significant relationship was noticed between localization in the rectum (p=0.04), presence of metastasis (p<0.001), low ECOG PS (p=0.01), having no surgical resection (p<0.001), chemotherapy unresponsiveness (p=0.007), high serum levels of lactate dehydrogenase (LDH) (p=0.004), CEA (p<0.001), CA 19-9 (p<0.001), low albumin serum levels (p=0.01) and poor OS (Tables 8 and 9). However, serum IL-17 levels showed no significantly adverse impact on PFS and OS (p=0.42 and p=0.72, respectively) (Tables 7, 9 and Figures 2,3, respectively).

Table 6. Univariate analysis of PFS according to patient and disease characteristics

Variables	*N of events/Total N*	*Progression-free survival Median (±SE) (months)*	*p value*
All patients	27/96	7.3 (1.1)	
Age, years			
<50	5/16	11.0 (2.1)	0.46
≥50	22/80	6.6 (1.2)	
Gender			
Male	21/72	7.8 (1.2)	0.14
Female	6/24	5.4 (3.2)	
PS			
0	8/53	9.3 (2.5)	0.17
1-3	16/40	6.6 (1.3)	
Obstruction			
Yes	3/11	7.5	0.88
No	23/82	6.7 (1.1)	
Surgery			
Yes	18/80	8.9 (1.4)	0.005
No	9/16	4.2 (1.5)	
Metastasis			
Yes	22/39	6.7 (1.2)	0.30
No	5/57	9.8 (3.1)	
Response to CTx			
Yes (CR+PR)	3/12	14.3 (3.2)	0.009
No (SD+PD)	15/20	4.2 (0.9)	
Site of lesion			
Colon	15/59	7.8 (1.9)	0.48
Rectum	12/37	6.9 (1.4)	
Histology			
Adenocarcinoma	23/89	11.0 (3.6)	0.29
Mucinous	4/7	6.8 (1.2)	
Grade			
Good	1/6	9.0	0.38
Intermediate	7/38	4.9 (2.2)	
Poor	1/3	8.0	
Angio-lymphatic invasion			
Yes	4/19	8.3 (3.4)	NR
No	0/16	NR	
Vascular invasion			
Yes	2/9	6.0	0.23
No	1/25	18.0	
Perineural invasion			
Yes	4/12	11.5 (3.3)	NR
No	0/22	NR	
KRAS mutation status			
Mutant	12/18	4.8 (1.8)	0.09
Wild	8/17	8.4 (1.8)	

NR: not reached

Discussion

Elevation of proinflammatory cytokines is considered to be associated with CRC. IL-17 which is one of the most important cytokines, promotes angiogenesis and tumor growth [20,21]. It induces the production of many other cytokines and chemokines, attracts neutrophils to the site of inflammation and enhances the inflammatory cascade. Inflammation is closely associated with cancer initiation and progression, including CRC [12].

Table 7. Univariate analysis of PFS according to laboratory parameters

Variables	*N of events/ Total N*	*Progression-free survival Median (±SE) (months)*	*p value*
LDH			
Normal	15/69	11.0 (5.0)	0.59
High	5/9	8.1 (1.6)	
Albumin			
Normal	9/41	9.6 (2.5)	0.19
Low	11/39	6.6 (1.6)	
CEA			
Normal	9/52	10.6 (2.0)	0.11
High	5/9	6.0 (3.5)	
CA 19-9			
Normal	10/54	11.3 (1.8)	0.01
High	11/17	5.0 (1.5)	
IL-17			
<median	18/65	7.9 (1.4)	0.42
>median	9/59	5.9 (1.8)	

Up to date, studies have shown that IL-17 is associated with CRC, its progression and prognosis [8,10,22]. In the present study the baseline serum IL-17 levels were significantly lower in the control group and older age, whereas low albumin levels were found to be correlated with high serum IL-17 concentrations. The median serum IL-17 levels of patients with baseline poor grade tumor were significantly higher compared to good grade, but there was no association between IL-17 and survival.

In a study there was no correlation between serum IL-17 levels and CRC but detectable levels of IL-17 were found only in 12 out of 61 CRC patients [11]. In CRC tissues IL-17 protein expression was found to be higher and was associated with well differentiated and early stage disease [12]. However, a new study found that interleukin-17FT7488 allele was associated with a decreased risk of CRC and tumor progression [7].

In another study serum IL-17A levels were

Table 8. Univariate analysis of OS according to patient and disease characteristics

Variables	*N of events/Total N*	*Overall survival Median (±SE) (months)*	*1-year overall survival (%) (±SE) (months)*	*p value*
All patients	20/96	26.4 (1.3)	82.6 (4.0)	
Age,years				
<50	2/16	23.1 (1.4)	93.8 (6.1)	0.21
≥50	18/80	26.1 (1.4)	80.4 (4.6)	
Gender				
Male	15/72	26.1 (1.6)	83.9 (4.5)	0.82
Female	5/24	20.7 (1.7)	78.9 (8.4)	
PS				
0	6/53	24.3 (1.0)	90.0 (4.2)	0.01
1-3	14/40	22.7 (2.2)	71.6 (7.3)	
Obstruction				
Yes	2/11	22.4 (2.3)	90.0 (9.5)	0.61
No	17/82	26.2 (1.5)	82.4 (4.3)	
Surgery				
Yes	11/80	28.6 (1.2)	89.2 (3.6)	<0.001
No	9/16	11.5 (2.3)	50.0 (12.5)	
Metastasis				
Yes	19/39	15.4 (1.8)	58.7 (8.4)	<0.001
No	1/57	32.4 (0.6)	98.2 (1.7)	
Response to CTx				
Yes (CR+PR)	2/12	23.7 (2.1)	91.7 (8.0)	0.007
No (SD+PD)	11/20	10.4 (2.1)	34.7 (13.5)	
Site of lesion				
Colon	4/59	29.9 (1.5)	91.6 (4.6)	0.04
Rectum	16/37	19.3 (1.2)	77.0 (5.6)	
Histology				
Adenocarcinoma	18/89	26.5 (1.4)	83.7 (4.0)	0.55
Mucinous	2/7	17.9 (3.6)	68.6 (18.6)	

Continued on the next page

Grade				
Good	0/6	NR	100.0 (0.0)	0.29
Intermediate	3/38	NR	92.0 (4.4)	
Poor	1/3	NR	66.7 (27.2)	
Angio-lymphatic invasion				
Yes	1/19	NR	94.4 (5.4)	0.35
No	0/16	NR	100.0 (0.0)	
Vascular invasion				
Yes	1/9	NR	87.5 (11.7)	0.08
No	0/25	NR	100.0 (0.0)	
Perineural invasion				
Yes	1/12	NR	90.9 (8.7)	0.16
No	0/22	NR	100.0 (0.0)	
KRAS mutation status				
Mutant	8/18	15.1 (2.5)	55.0 (13.2)	0.41
Wild	6/17	18.7 (2.6)	75.8 (10.8)	

NR: not reached

Table 9. Univariate analysis of OS according to laboratory parameters

Variables	*N of events/ Total N*	*Overall survival Median (±SE) (months)*	*1-year overall survival (%) (±SE) (months)*	*p value*
LDH				
Normal	12/69	22.9 (1.1)	86.5 (4.2)	0.004
High	5/9	14.4 (3.9)	55.6 (16.6)	
Albumin				
Normal	5/41	24.2 (1.2)	89.9 (4.8)	0.01
Low	14/39	18.2 (1.7)	71.4 (7.3)	
CEA				
Normal	4/52	24.7 (0.6)	97.8 (2.2)	<0.001
High	3/9	18.8 (3.9)	66.7 (15.7)	
CA19-9				
Normal	6/54	24.9 (0.8)	96.1 (2.7)	<0.001
High	8/17	14.7 (2.6)	48.1 (13.2)	
IL-17				
<median	10/65	22.2 (1.3)	84.6 (5.4)	0.72
>median	10/59	26.7(1.8)	80.7 (5.8)	

similar in CRC patients and the elderly controls, although their serum levels were higher than those in young controls [23]. It is known that IL-17A modulates circulating tumor cells in tumor draining veins of CRCs contributing in the metastatic process and thus its serum levels were also correlated with DFS in patients with CRC [24].

Higher IL-17 serum levels in patients with CRC than in control subjects were found in a study with limited number of patients and there was an inverse correlation between p53 expression and the level of serum IL-17 [25]. To our knowledge this study was the first to show that IL-17 might also act as a valuable tumor marker in patients with CRC [25].

Limited data are to be found in the literature about the relationship of serum levels of IL-17 and CRC. In our study there were 96 patients and our findings revealed the clinical significance of serum IL-17 levels in CRC patients. Older age, low albumin levels and grade were factors related with IL-17 levels but survival was not. As a result serum levels of IL-17 may be used as diagnostic markers in CRC patients although no predictive and prognostic values were determined.

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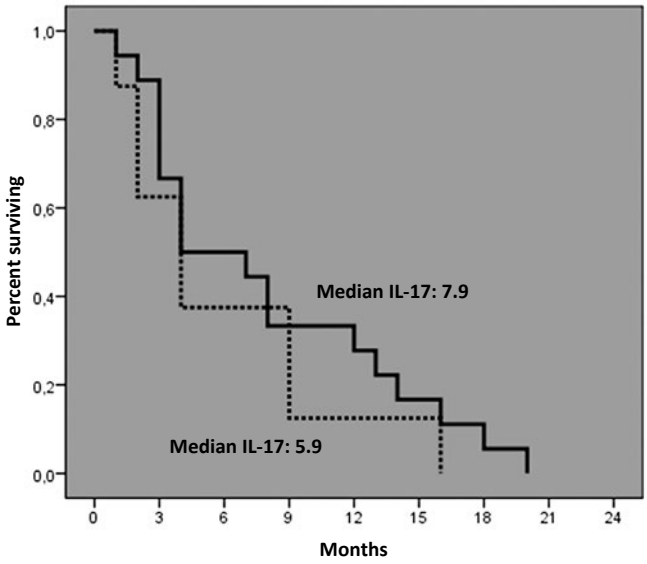

Figure 2. Progression-free survival in colorectal cancer patients according to serum IL-17 levels (p=0.42).

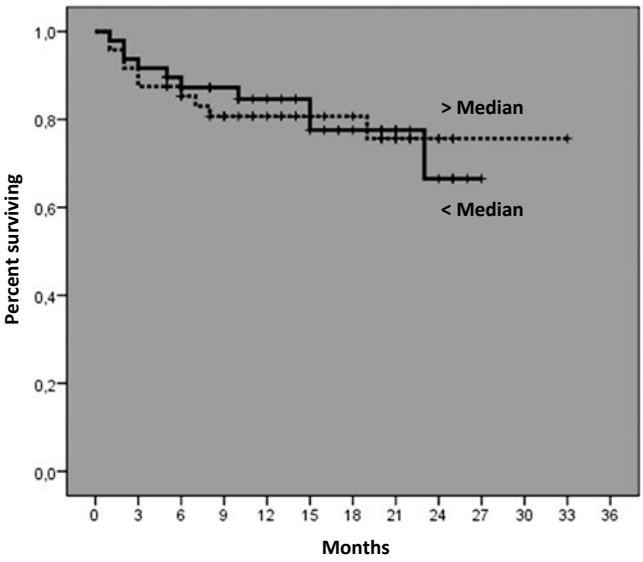

Figure 3. Overall survival in colorectal cancer patients according to serum IL-17 levels (p=0.72)

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