

## ORIGINAL ARTICLE

# Evaluation of erectile dysfunction risk factors in young male survivors of colorectal cancer

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## Summary

**Purpose:** Improved long-term survival of colorectal cancer patients (CRC) treated with surgery and/or chemotherapy ± radiotherapy (RT) has led to increased awareness of long-term side effects, including effecting sexual life, which can ultimately affect the quality of life in these patients. Because the absolute risk factors of erectile dysfunction (ED) have not been defined in CRC patients, the aim of this research was to identify the severity and the absolute risk factors of ED in male CRC survivors.

**Methods:** The medical records of 61 male survivors of CRC treated with surgery and/or chemotherapy ± RT were retrieved from the medical oncology outpatient clinics during routine follow-up visits in 2011–2012. Patients older than 55 years and those with ED history before diagnosis were excluded. International Index of Erectile Function (IIEF) questionnaire was filled in by the patients.

**Results:** The patient mean age was 47.6±6.7 years (range 18-55) at the time of filling in the questionnaire. According

to the International Index of Erectile Function (IIEF) score, 83.6% of the patients had some degree of ED. The risk factors of erectile dysfunction were advancing age ( $p=0.01$ ), tumor location ( $p=0.01$ ), type of surgery ( $p=0.02$ ), presence of stoma ( $p=0.003$ ) and RT ( $p=0.005$ ). Chemotherapy didn't impact ED ( $p=0.46$ ). Also, there was no significant correlation between smoking status, hypertension, diabetes mellitus, cardiovascular disease, stage of the tumor and ED. Also hormonal disturbances such as serum FSH, LH and testosterone levels did not affect the presence of ED.

**Conclusion:** Overall, 83.6% of the male CRC survivors had some degree of ED according to the IIEF. The risk factors of ED were advancing age, tumor location, type of operation, presence of stoma and RT. Clinicians should be aware of these risk factors to offer their patients adequate treatment options and also come up with new treatment strategies necessary to reduce further ED in CRC survivors.

**Key words:** chemotherapy, colorectal cancer, erectile dysfunction, radiotherapy, surgery

## Introduction

Among all malignancies CRC ranks fourth in incidence and second in cancer-related deaths in the United States [1]. Mortality from CRC has decreased year by year due to earlier diagnosis though screening programs and new better treatment alternatives [1,2]. With advances in treatment, CRC is being transformed from incurable disease to an illness that is increasingly curable. As a result of therapeutic improvements, the importance of long-term follow-up has caught more attention and led to increased interest in the

unique problems, risks, needs, and concerns of survivors who have completed treatment. Long-term effects of treatment can persist and include fatigue, sleep difficulty, fear of recurrence, anxiety, depression, negative body image, sensory neuropathy, gastrointestinal problems, urinary incontinence and sexual dysfunction [3].

Researchers have also shown that, in terms of both physical and mental well being, the quality of life CRC survivors was inferior when compared with age-matched individuals without cancer [4,5]. Sexual function is considered to be an important determinant of the quality of life. ED is a

persistent inability to achieve and/or maintain an erection for satisfactory sexual activity. The prevalence of ED in healthy men varies according to diagnostic methods and countries. The IIEF score was developed by Rosen et al. and has proved to be a relatively standard way of defining and quantifying ED [6]. In a study of Ponholzer et al. a total of 2869 men were evaluated according to the IIEF score and some degree of ED was detected in 32.2% of subjects in all age groups. The prevalence of ED increased with advancing age and reached 37.5% between 51–60 years and 71.2% between 71–80 years [7].

In a recent study, higher prevalence of sexual dysfunction was reported in CRC survivors compared with normal population [8]. In this study, erectile problems were more often present in rectal cancer (54%) than in colon cancer survivors (25%) and normal population (27%). In the literature, sexual dysfunction ranges between 25–82% in CRC patients [8–12]. The associated risk factors of sexual dysfunction in CRC survivors can be due to the location of tumor, type of surgical treatment, RT and the presence of stoma [8–15]. The incidence of ED after surgery for rectal cancer has been reported to be 30–70% [13,16,17]. The injury of hypogastric and pelvic splanchnic nerves during rectal cancer resection is a well-known cause of ED [9]. These nerves can be accidentally damaged during the dissection of the mesorectum. Surgeon-related factors are also important in the treatment of rectal cancer, both for achieving local disease control and for preserving sexual function [18]. Conventional low anterior resection (LAR) and abdominoperineal resection (APR) for rectal cancer are associated with local recurrence and ED [19]. Total mesorectal excision (TME) with autonomic nerve preservation has proven to cause less ED compared to APR and LAR [17]. Pelvic RT alone can affect sexual function, however research-based knowledge about sexual problems after preoperative or postoperative RT is limited [20,21]. In a recent trial, Bruheim et al. reported that RT for rectal cancer is associated with significantly poorer erectile function (ER) in males [11].

Cancer is known to be associated with sexual dysfunction for a multitude of reasons. First of all, cancer is generally a disease of older people and therefore the risk of preexisting ED is substantial. Furthermore, the presence of cancer in the body may result in decreased sexual desire and may also interfere with sexual function through systemic effects, like pain and cachexia. The psychological trauma associated with cancer diagno-

sis may impede all sexual activity. Late effects of chemotherapy also include oligospermia or azoospermia and infertility [22]. However, data is lacking on the late effects of CRC treatment on the male sexual function, especially after cancer has been controlled, all treatments are discontinued and the patient is essentially relieved of the associated psychological stress. Improved long-term survival of CRC patients treated with surgery and/or chemotherapy and/or RT has led to increased awareness of long-term side effects, including affecting sexual life, which can ultimately affect the quality of life in these patients [23]. However, the absolute risk factors of ED have not been defined in CRC.

The aim of this prospective research was to identify the severity and the absolute risk factors of ED in male CRC survivors.

## Methods

The medical records of male patients who were diagnosed with CRC in our clinic between 2001 and 2010 were analysed.

### *Inclusion/exclusion criteria*

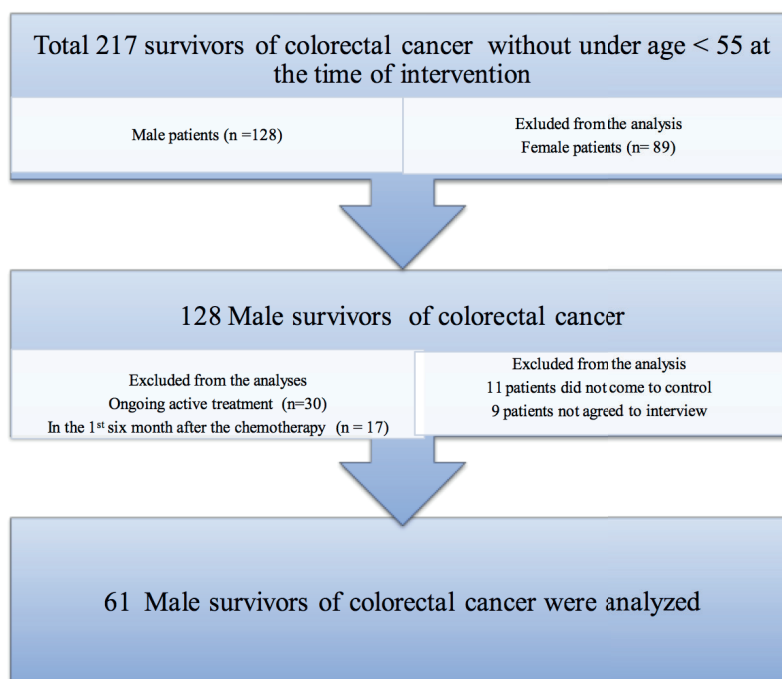
Patients aged over 55 years and patients with a history of ED before their diagnosis were excluded. Study patients had to be male, disease-free and off treatment for at least 6 months at the time of evaluation. Their treatment should include surgery and/or chemotherapy ± RT and relevant information was retrieved from the medical oncology outpatient clinics records during routine follow-up visits in 2011 and 2012. From a total 217 CRC patients, 61 met the criteria and entered the study (Figure 1).

### *Therapeutic modalities*

Concerning the type of operation, APR was performed in 12 (19.7%) patients, LAR in 20 (32.8%) and colon surgery (left or right hemicolectomy, sigmoid resection and transverse colectomy) in 29 (47.5%) patients. Surgery was performed by different surgeons. Neither TME nor nerve-sparing operation were performed. Twenty-seven (37.7%) rectal cancer patients were treated with postoperative chemoradiotherapy (with daily fluorouracil infusion). The total dose of RT was between 40–50Gy. No preoperative RT was delivered.

### *IIEF scoring*

Patients completed a survey questionnaire that was designed to obtain information about demographic characteristics, risk factors for ED, and the IIEF to assess their current level of sexual function. To measure ED, we used the IIEF which is a 15-item questionnaire



**Figure 1.** Diagram summarising the study population.

with good psychometric properties. IIEF is a simple and easy-to-fill in test with good sensitivity and specificity. IIEF has been translated and validated in several languages, including Turkish. It consists of 15 questions that assess male sexual function in 5 different domains including EF, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Responses are based on the patients' experiences within the previous 4 weeks and are scored with the Likert scale, with lower scores indicating the severity of sexual function. It has been shown that the ER domain, which includes 6 questions (maximum score of 30), provides a reliable measurement for classifying the severity of ED as mild, moderate, or severe. EF score of IIEF ranked in 4 levels: 1-10, severe ED; 11-16 moderate ED; 17-25, mild ED and 26-30, no ED.

Serum LH, FSH, and testosterone levels were also checked on the same day of the IIEF questionnaire. Blood samples for all hormone measurements were taken in the morning after an overnight fasting.

We analysed the impact of age, type of operation, tumor location, history of diabetes mellitus, cardiovascular disease, hypertension and hyperlipidemia, smoking status, chemotherapy, RT and the stage of disease on the severity of ED.

#### Statistics

All statistical analyses were performed by using SPSS for Windows version 18.0.(SPSS, Chicago, IL). Univariate statistical analyses were conducted to describe the demographic characteristics and medical treatment history of the patients in the study. Descriptive statistics, including frequencies, means, medians,

and standard deviations (SD), were calculated where appropriate. Student's t-test, Mann-Whitney U test, and chi-square test were conducted as appropriate to compare patients with ED and patients with normal EF. Bivariate analyses were conducted to examine the relation of measures of sexual outcome (the global score of the IIEF measuring a combination of function and satisfaction and the frequency of sex in the past month, measured by one item from the IIEF) with demographic, medical, and sexual factors. Two-sided p values of <0.05 were considered statistically significant.

#### Results

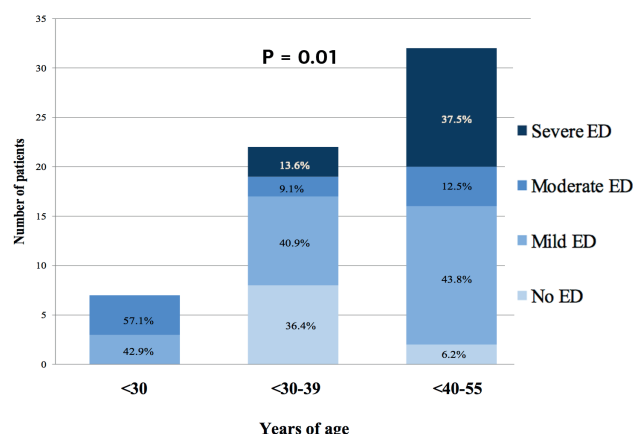
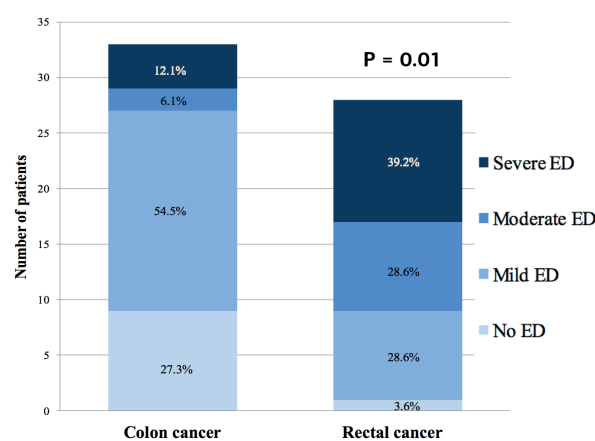
A total of 61 male CRC survivors were included in this study. The mean age of the study population was  $44.3 \pm 7.5$  and  $47.6 \pm 6.7$  years (range 18-55) at the time of diagnosis and intervention, respectively. The median follow-up of the study population was 36 months (range 14-102). The mean interval between the end of active treatment and study evaluation was 32 months (range 8-98). Thirty-three (54.1%) patients had colon cancer and 28 (45.9%) rectal cancer. Five (8.2%) patients had stage I disease, while 28 (45.9%), 21 (34.4%), and 7 (11.5%) patients had stage II, III and IV disease, respectively. All stage IV patients were tumor-free at the time of filling in the IIEF questionnaire (6 patients liver, 1 patient lung plus and liver treated with metastasectomy). Chemotherapy was administered to 82% of the patients, whereas 37.7% were treated with RT. The medi-

**Table 1.** Demographic and clinical characteristics of the participating male colorectal cancer survivors

Characteristics	N	%
Total	61	100
Age (years)		
<30	7	11.5
30-39	22	36.1
40-55	32	52.4
Marital status		
Married	60	98.4
Single	1	1.6
Level of education		
Low	41	67.2
Intermediate	17	27.9
High	3	4.9
Smoking status		
Never	14	23.0
Exsmoker	31	50.8
Current smoker	16	26.2
Hypertension		
No	54	88.5
Yes	7	11.5
Diabetes mellitus		
No	58	95.1
Yes	3	4.9
Hyperlipidemia		
No	54	88.5
Yes	7	11.5
Coronary heart disease		
No	60	98.4
Yes	1	1.6
Location of tumor		
Colon	33	54.1
Rectum	28	45.9
TNM stage		
I	5	8.2
II	28	45.9
III	21	34.4
IV	7	11.5
Type of operation		
APR	12	19.6
LAR	20	32.8
Other*	29	47.6
Presence of stoma		
No	46	75.4
Yes	15	24.6
Chemotherapy		
Never	11	18.0
Fluorouracil-based	22	36.1
Oxaliplatin-based	25	41.0
Irinotecan and other	3	4.9
Radiotherapy		
No	38	62.3
Yes	23	37.7

\*Other: left hemicolectomy, right hemicolectomy, transverse colectomy and sigmoidectomy. TNM: tumor-node-metastasis, APR: abdominoperineal resection, LAR: low anterior resection

an number of chemotherapy cycles was 6 (range 4-12) for both colon and rectal cancer. The baseline characteristics including comorbid diseases and demographic data are described in Table 1.

**Figure 2A.** Erectile dysfunction (ED) according to the IIEF score by age groups.**Figure 2B.** Erectile dysfunction (ED) according to the IIEF score by tumor location.

According to the IIEF score, 83.6% of the patients had some degree of ED. The severity of ED was as follows: 42.6% of patients had mild ED, whereas 16.4% and 24.6% had moderate and severe ED according to the IIEF score, respectively. In terms of age, moderate-severe ED was observed in 50.0% of the patients  $\geq 40$  years old, whereas 31.0% moderate-severe ED was observed in patients  $< 40$  years old (Figure 2A,  $p=0.01$ ). According to tumor location, moderate-severe ED was 67.8% and 18.2% in patients with rectal and colon cancer, respectively (Figure 2B,  $p=0.01$ ). Concerning the type of operation APR was performed in 12 (19.7%) patients, LAR was performed in 20 (32.8%) and colon surgery (left or right hemicolectomy, sigmoid resection and transverse colectomy) in 29 (47.5%) patients. In APR patients the moderate-severe ED was 66.7%, in LAR patients the moderate-severe ED was 60.0%, whereas 17.2% moderate-severe ED was observed

in non-APR, non-LAR patients (Figure 2C,  $p=0.02$ ).

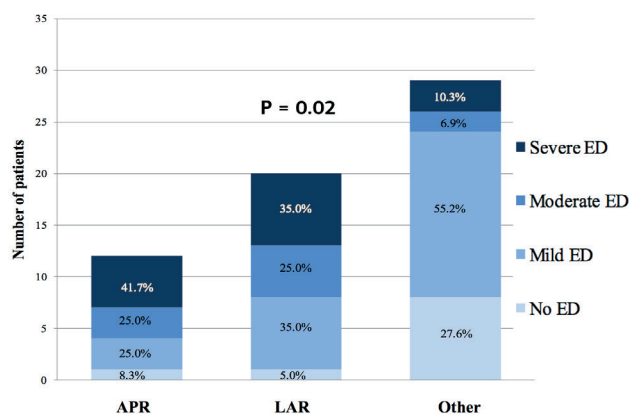
At the time of filling in the IIEF questionnaire, stoma was found in 15 (24.6%) of the patients. Moderately-severe ED was found in 80.0% of the patients with stoma whereas moderately-severe ED was found in only 28.2% of the patients without stoma (Figure 2D,  $p=0.003$ ). Of the survivors 37.7% were treated with pelvic RT; moderate and severe ED was observed in 69.6% of those patients, compared with 23.7% of the patients without RT (Figure 2E,  $p=0.005$ ). There was no effect of chemotherapy on ED ( $p=0.46$ ). Also there was no significant correlation between smoking status, hypertension, diabetes mellitus, cardiovascular disease, tumor stage and ED. All of the ED risk factors in male CRC survivors according to the IIEF score are described in Table 2.

Median serum FSH level of the patients was  $15.4 \pm 12.4$  mIU/ml (range 1.14–8.75), median serum LH level was  $6.3 \pm 3.2$  mIU/ml (range 1.7–8.6), and median serum testosterone level was  $9.4 \pm 3.3$  pg/ml (range 8.9–42.5). Thirty-one (50.8%) of the patients had elevated FSH, 14 (22.9%) had elevated LH, and 5 (8.2%) had decreased testosterone levels. These hormonal disturbances did not affect the presence of ED and its severity.

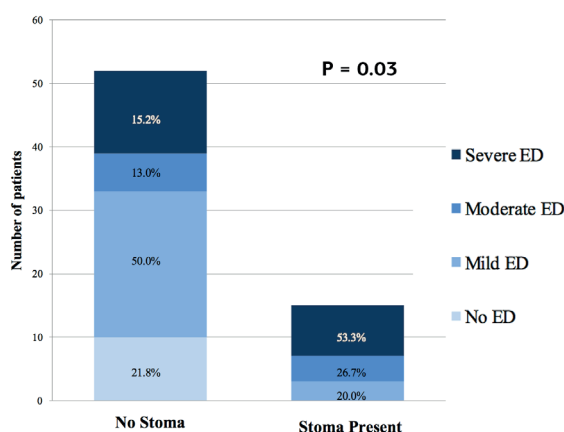
### Discussion

In this study we examined the effect of demographic and clinical risk factors on ED. According to the IIEF score, 83.6% of the patients had some degree of ED, 42.6% had mild ED, whereas 41.0% had moderate-severe ED. The results of the present study show that location of the tumor, the presence of stoma, treatment with RT, type of surgery and increasing age cause significantly higher risk of ED in male CRC survivors. No significant correlation between smoking status, hypertension, diabetes mellitus, cardiovascular disease, stage of the tumor and ED was noticed. To our knowledge the present study is the first to evaluate all the risk factors of ED in male CRC survivors under the age of 55.

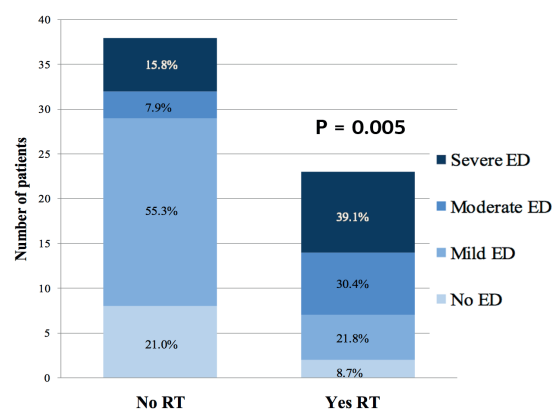
In a recent population-based trial, erectile problems in male survivors were significantly more common in rectal cancer (54%) compared to colon cancer (25%) and normal population (27%) according to the European Organisation for Research and Treatment of Cancer (EORTC) module Quality of Life Questionnaire-Colorectal 38 (QLQ-CR-38) [8]. In this study, male rectal cancer patients had significantly more ejaculation problems than colon cancer patients (68 vs 47%). Also, in the subgroup analyses, male CRC patients at



**Figure 2C.** Erectile dysfunction (ED) according to the IIEF score by type of operation. APR: abdominopereineal resection, LAR: low anterior resection, Other: left hemicolectomy, right hemicolectomy, transverse colectomy and sigmoidectomy.



**Figure 2D.** Erectile dysfunction (ED) according to the IIEF score by presence of stoma.



**Figure 2E.** Erectile dysfunction (ED) according to the IIEF score by radiotherapy (RT).

**Table 2.** Risk factors of erectile dysfunction in male colorectal cancer survivors according to the IIEF score

Characteristics	No ED	Mild ED	Moderate ED	Severe ED	p-value
	N (%)	N (%)	N (%)	N (%)	
Age (years)					
<30 (N=7)	0 (0)	3 (42.9)	4 (57.1)	0	0.01
30-39 (N=22)	8 (36.4)	9 (40.9)	2 (9.1)	3 (13.6)	
40-55 (N=32)	2 (6.3)	14 (43.2)	4 (12.5)	12 (37.5)	
Smoking status					
Never (N=14)	1 (7.2)	8 (57.1)	2 (14.3)	3 (21.4)	0.52
Exsmoker (N=31)	7 (22.6)	11 (35.5)	4 (12.9)	9 (29.0)	
Current smoker (N=16)	2 (12.5)	7 (43.8)	4 (25.0)	3 (18.7)	
Hypertension					
No (N=54)	8 (14.8)	24 (44.4)	10 (18.6)	12 (22.2)	0.32
Yes (N=7)	2 (28.6)	2 (28.6)	0 (0)	3 (42.8)	
Diabetes mellitus					
No (N=58)	9 (15.5)	24 (41.4)	10 (17.2)	15 (25.9)	0.51
Yes (N=3)	1 (33.3)	2 (66.7)	0 (0)	0 (0)	
Cardiovascular disease					
No (N=60)	10 (16.7)	26 (43.3)	10 (16.7)	14 (23.3)	0.32
Yes (N=1)	0 (0)	0 (0)	0 (0)	1 (100)	
Location of tumor					
Colon (N=33)	9 (27.3)	18 (54.5)	2 (6.1)	4 (12.1)	0.01
Rectum (N=28)	1 (3.6)	8 (28.6)	8 (28.6)	11 (39.2)	
TNM stage					
I (N=4)	0 (0)	1 (25.0)	1 (25.0)	2 (50.0)	0.77
II (N=28)	7 (25.0)	12 (42.8)	3 (10.8)	6 (21.4)	
III (N=21)	2 (9.5)	9 (42.9)	5 (23.8)	5 (23.8)	
IV (N=8)	1 (12.5)	4 (50.0)	1 (12.5)	2 (25.0)	
Type of operation					
APR (N=12)	1 (8.3)	3 (25.0)	3 (25.0)	5 (41.7)	0.02
LAR (N=20)	1 (5.0)	7 (35.0)	5 (25.0)	7 (35.0)	
Other* (N=29)	8 (27.6)	16 (55.2)	2 (6.9)	3 (10.3)	
Presence of stoma					
No (N=46)	10 (21.8)	23 (50.0)	6 (13.0)	7 (15.2)	0.003
Yes (N=15)	0	3 (20.0)	4 (26.7)	8 (53.3)	
Chemotherapy					
Never (N=11)	0 (0)	4 (36.4)	5 (45.4)	2 (18.2)	0.46
Fluorouracil-based (N=22)	2 (9.1)	9 (40.9)	6 (27.3)	5 (22.7)	
Oxaliplatin-based (N=25)	2 (8.0)	4 (16.0)	10 (40.0)	7 (28.0)	
Irinotecan and other (N=3)	0 (0)	2 (66.7)	0 (0)	1 (33.3)	
Radiotherapy					
No (N=38)	8 (21.0)	21 (55.3)	3 (7.9)	6 (15.8)	0.005
Yes (N=23)	2 (8.7)	5 (21.7)	7 (30.5)	9 (39.1)	
FSH (mIU/ml)					
Low-normal (N=30)	6 (20.0)	16 (53.3)	3 (10.0)	5 (16.7)	0.16
High (N=31)	4 (13.0)	10 (32.2)	7 (22.6)	10 (32.2)	
LH (mIU/ml)					
Low-normal (N=47)	10 (21.3)	20 (42.6)	6 (12.7)	11 (23.4)	0.19
High (N=14)	0 (0)	6 (42.8)	4 (28.6)	4 (28.6)	
Testosterone (pg/ml)					
Low (N=5)	1 (20.0)	2 (40.0)	0 (0)	2 (40.0)	0.46
Normal (N=56)	9 (16.1)	24 (42.8)	10 (17.9)	13 (23.2)	

\*Other: left hemicolectomy, right hemicolectomy, transverse colectomy and sigmoidectomy. FSH: follicle stimulating hormone, LH: luteinizing hormone, ED: erectile dysfunction, IIEF: International Index of Erectile Function. For other abbreviations, see footnote of Table 1

advanced age were significantly less sexually active compared to normal population. In our study, moderate-severe ED was significantly higher in rectal cancer (67.8%) survivors compared to colon cancer (18.2%) survivors, as mentioned in previous studies. In another recent trial, Milbury et al. reported that moderate-severe ED was observed in 65.5% of male CRC survivors. This study has shown that advanced age, type of surgery and poor social support were risk factors of sexual dysfunction according to the IIEF score [24].

ED is also one of the most negatively impacting complications of pelvic surgery. The most important and well-known surgical risk factor for ED is APR in male patients [25-27]. In our study, moderate-severe ED was observed in 66.7, 60.0 and 17.2% in APR, LAR, non-APR and non-LAR patients, respectively.

ED is due to the injury of hypogastric and pelvic splanchnic nerves during rectal surgery, with an incidence of 40-60%. With advances in surgical techniques, TME, a nerve-sparing approach, was introduced by Heald et al. [28]. Compared to the APR, TME offers a high prevalence of sexual function [17,25-27]. In the Dutch TME trial, Lange et al. investigated the risk factors of sexual dysfunction after TME with or without preoperative RT in rectal cancer patients [13]. In this study, sexual dysfunction scores were evaluated preoperatively and periodically in the postoperative period. It was reported that ED was observed in 79.8% of male patients after rectal cancer treatment compared to the preoperative period. In both male and female patients sexual functions deteriorated in the postoperative period and remained worse in male patients. Significant risk factors in multivariate analysis for ED were anastomotic leakage and excessive blood loss perioperatively [13]. Preservation of sexual function in males is more difficult and depends on the complete pelvic autonomic nerve preservation (PANP). Urinary functions can improve with complete PANP but sexual function can still deteriorate [29]. In a recent trial, Sartori et al. reported that with laparoscopic TME, urinary functions were improved but sexual impairment remained as an important problem in approximately 50% of male rectal cancer patients [9]. Jayne et al. from UK Medical Research Council, reported that EF and overall sexual function tended to be worse following TME compared to conventional open surgical technique [30].

Pelvic RT also can affect EF alone [20]. Radiotherapy can induce ED by creating fibrosis and by increasing the endocrine hypogonadism [31,32].

In a literature review of late adverse effects of RT on rectal cancer Birgisson et al. reported that in males the sexual activities of those who were still active preoperatively decreased to 67% in irradiated patients and 76% in non-irradiated patients [33]. In a case-control study, male patients with rectal cancer were treated with surgery alone or with preoperative RT up to 40-50 Gy plus surgery [34]. In this study, sexual dysfunction in the RT arm was significantly higher than in the surgery-alone arm. As a result of this study, RT impacted adversely the sexual function, reaching its climax at 8 months postoperatively [34].

In a study of late effects of RT on ED in males with rectal cancer Bruheim et al. reported that the prevalence of moderate-severe ED was 86 and 55% in the RT and non-RT arms, respectively [11]. Although more than half of the patients were additionally treated with chemotherapy, there were no significant differences of ED with additional chemotherapy in the subgroup analyses. In a study evaluating ED in male patients treated with preoperative RT followed by surgery or surgery alone according to the 5-item version of IIEF (IIEF-5) score, the total IIEF-5 score decreased significantly in the RT plus surgery group compared to the surgery-alone group [10].

In the study of Lange et al. the presence of a temporary or definitive stoma was associated with sexual problems, probably indicating its psychological role in the development of sexual dysfunction, due to decrease in arousal with the presence of stoma [13]. The effect of age on ED after cancer surgery was not defined definitively. In one study of 26 male patients, Danzi et al. reported that the age of patients was the most important factor in sexual dysfunction [35].

In the treatment of ED in male CRC survivors sildenafil can be an effective treatment approach. In a randomized, double-blind, placebo-controlled study of sildenafil in rectal cancer, this agent completely reversed or satisfactorily improved post-proctectomy ED in 79% of patients with mild and well tolerated side effects [36].

Our study differs from other studies in that only young male CRC survivors were investigated. Chemotherapy did not affect ED in our study, similar to the results of previous studies [31,34,37,38]. Diabetes, smoking and hypertension represent the most common risk factors of vasculogenic sexual dysfunction [39]. The incidence of diabetes, hypertension and atherosclerotic diseases increases with aging; however, because the upper age limit of our study was 55, the effect of vasculogenic fac-

tors on ED can not be arisen.

Our study presents some limitations because of its cross sectional design. Psychological factors and genitourinary functions were not evaluated, thus both could effect IIEF score. The small number of the study population due to the upper age limit and studying only male patients is another limitation.

ED after CRC treatment is multifactorial and several risk factors have been defined in its development. Due to the complexity of the pathophysiology of ED in CRC, future prospective studies should be done and ED risk scales should be made

to increase awareness.

In conclusion, 83.6% of the male CRC survivors had some degree of ED according to the IIEF. The significant risk factors of ED were older age, tumor location, type of operation, presence of stoma and RT. Clinicians should be aware of these risk factors to offer their patients adequate treatment options, while new treatment strategies are necessary to further reduce ED in CRC survivors.

## Acknowledgements

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