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RESEARCH

Evaluation of Depression, Anxiety, and Sexual Function in Rectal Cancer Patients Before and After Neoadjuvant Chemoradiotherapy

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Abstract

Objective The association of treatment-related side effects and tumor characteristics with sexual function, depression, and anxiety were investigated in patients with locally advanced rectum cancer (LARC) receiving neoadjuvant chemoradiotherapy (CRT).

Material and Methods Thirty-two patients who received neoadjuvant CRT with LARC were included. The Arizona Sexual Experiences (ASEX) Scale was used to determine the sexual function status whereas the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) were used to evaluate the depression and anxiety status of the patient, respectively. The patients were asked to fill these scales before and at least 4 weeks after the neoadjuvant CRT. *T*-test and Mann–Whitney *U* test were used for the comparison of values.

Results Median age was 52.5 years (range: 33–76). Twenty-six patients were male, and 6 patients were female. At presentation, the tumor was located mostly in lower third rectum (72%), and 69% of the patients had T3 tumors. There was a statistically significant deterioration in the sexual functions of the patients ($p < 0.001$), a statistically significant decrease in their anxiety level after CRT (p: 0.037). Depression level was changed from mild to minimal during this process (p: 0.17). A significant deterioration in the ASEX scale was observed especially in patients with grade 2 and above gastrointestinal side effects (p: 0.01).

Conclusion This prospective study showed that the patient's anxiety and depression levels had decreased during the treatment process probably due to the decrease in the patient's symptoms. However, deterioration of the sexual function status which might be correlated to increased gastrointestinal side effects during CRT has been observed. So, clinical and psychiatric support including therapies for sexual dysfunctions is needed for LARC patients during and after the neoadjuvant CRT.

Keywords Radiotherapy · Rectum cancer · Neoadjuvant treatment · Beck Depression Anxiety Inventory · Arizona Sexual Experiences

Introduction

Colorectal cancer is the fourth most frequently diagnosed cancer. The new rectal cancer cases were 43,000 in 2018; furthermore, two-thirds of patients had local advanced rectal cancer [1]. Low anterior (LAR) or abdominoperineal resection (APR) with total mesorectal excision is the primary treatment for early-stage rectal cancer [1]. Neoadjuvant chemoradiotherapy (CRT) or short-course RT followed by total mesorectal excision is the standard of care for patients with locally advanced rectal adenocarcinomas (LARC) [2]. There is no compelling evidence favoring neoadjuvant CRT versus short-course RT in terms of oncologic outcomes [3]. However, neoadjuvant CRT provides greater tumor downstaging especially in cT4 tumors or tumors with mesorectal fascia involvement compared to short-course RT followed by immediate surgery [2].

The preoperative approach was associated with a significantly lower local recurrence rate and acute side effects compared with postoperative CRT [4]. However, both sexual and bowel function deteriorated significantly in more than 50% of patients after combined modality therapy [5]. The most

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common acute side effects are diarrhea, erythema, urinary frequency, urine incontinence, dryness of the vaginal, and impotence, respectively [6]. All these radiotherapy-induced toxicities affect the patients' quality of life (QL). Also, the diagnosis of cancer causes considerable anxiety and depression. In the literature, it has been reported that depression and anxiety are present in 30–39% of LARC patients [7].

Surgery is an important factor affecting the emotional status, especially the sexual function of the patients. Many studies demonstrated that surgery affects QOL, sexual dysfunction status, and anxiety [8–10]. However, there was a limited number of studies in the literature about the impact of neoadjuvant CRT on the quality of life, depression, and anxiety of patients with LARC [6, 11, 12]. The purpose of this prospective cohort study was to evaluate the effect of neoadjuvant CRT on patients' anxiety, depressive symptoms, and sexual problems.

Patients and Methods

All newly diagnosed LARC patients treated with neoadjuvant CRT in our clinic between 2016 and 2017 were included in this study. Exclusion criteria were (1) inoperable, (2) patient with a psychiatric history, and (3) non-completion of Beck Depression, Beck Anxiety, and Arizona scores.

In this study, age, sex, and education were obtained as general information whereas the tumor stage, location of the tumor, chemotherapy used during the radiotherapy, and acute side effects of gastrointestinal-genitourinary were assessed as clinical information. The education level of the patients was classified as low (primary school or not), intermediate (high school), or high (university degree).

Treatment

Patients were positioned in the supine position on a couch and immobilized with knee and foot supports. Planning computerized tomography scan (CT) of patients was taken from the level of the second lumbar vertebrae to the middle of the femurs on a GE Discovery RT scanner (General Electric Healthcare, Waukesha, WI). The clinical target volume (high and standard risk) was delineated according to the Radiation Therapy Oncology Group (RTOG) guidelines [13]. Planning target volume$_1$ (PTV) was generated by adding 7-mm margin around the CTVs. The standard risk PTV was prescribed with a dose of 45 Gy in 25 fractions, and high-risk PTV was prescribed with a dose of 50.4–54 Gy in 28–30 fractions [14]. IMRT plans were generated for each patient using the Eclipse version 15.6 treatment planning system by using 6 MV photon beams. Additionally, before the treatment, the patients were informed in detail about the radiotherapy process and the side effects of the CRT. All patients were treated using a Varian RapidARc linear accelerator. Patient positioning and isocenter verification were checked using kV-cone beam CT (CBCT) before radiotherapy. All patients received concurrent chemotherapy with capecitabine (825 mg/m2/twice daily) during radiotherapy per day except the weekend. All patients were evaluated weekly for acute toxicities, and CTCAE (Common Terminology Criteria for Adverse Events) v5.0 was used to grade acute gastrointestinal and genitourinary side effects. During radiotherapy, patients were followed by clinical examination every week, and nutritional solution support was provided.

Psychological Measures

All patients were asked to complete questionnaires for depression, anxiety, and sexual life of the patients prior to neoadjuvant CRT ("baseline") and at 6 weeks after the CRT before the surgery. The depression and anxiety levels of the patients were assessed by the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) questionnaires, respectively [15–17]. The validation of BDI and the BAI scale for the Turkish population was adapted by Aydemir et al. [18]. They constituted 21 items with a four-point response scale; a total score was obtained adding all items checked by the patient. The highest score was 63 points, and a higher score indicates more depression or anxiety. In this study, depression levels were stratified into the absence or minimum depression (0–9), mild (10–16), moderate (17–29), and severe depression (30–63) whereas anxiety levels were considered as minimum (0–7), mild (8–15), moderate (16–25), and severe (26–63). The Arizona Sexual Experiences (ASEX) Scale questionnaire includes five items, each scored 1 to 5 for evaluation of sexual life. The higher score indicates more sexual dysfunction. For the Turkish population, there were some values of receiver operating characteristics (ROC) for BDI and ASEX; they were 17 and 11, respectively [19].

Statistical Analysis

The changes in anxiety-depression and sexual function of the patients were evaluated. The Fisher exact test was used for quantitative variables while the Wilcoxon rank test was used for qualitative variables. In this study, we calculated mean scores for BDI, BAI, and ASEX and compared baseline data to after therapy data. The computer software SPSS version 21 for Windows (IBM Corp. Armonk, NY) was used for all statistical analyses, and $p < 0.05$ was considered for statistical significance.

For the purposes of our study, we performed a prospective analysis with appropriate Local Ethics Committee approval dated July 12, 2016, number A09. All participating patients gave written informed consent.

Results

The median age at diagnosis was 52.5 years (range: 33–76). Twenty-six patients were male, and 6 patients were female. At presentation, the tumor was located mostly in lower third rectum (72%), and 69% of the patients had T3 tumors. All patients' Karnofsky performance scale (KPS) was over 80 and completed planned radiotherapy. The dose reduction of the concomitant chemotherapy was required in two patients due to hematologic toxicity. Acute grade 2–3 gastrointestinal side effects were observed in 34% of the patients whereas acute grade 1 genitourinary side effect was observed in 45% of the patients. Acute grade 2–3 genitourinary side effects were not observed. The patients' tumors and the treatment characteristics are listed in Table 1.

Before the neoadjuvant CRT, the mean score of ASEX, BDI, and BAI was 14.2 (SD: ± 4.7), 9.4 (SD: ± 8.5), and 9.8 (SD: ± 9.2), respectively. The mean score of ASEX, BDI, and BAI after the neoadjuvant CRT was 17.7 (SD: ± 5.9), 7.6 (SD: ± 6), and 6.5 (SD: ± 6.2), respectively. The scores are shown in Table 2 and Fig. 1.

The BDI and BAI scores after the CRT were decreased compared to scores before the treatment. Although the depression level was changed from mild to minimal during this process, this difference was not statistically significant (p: 0.17). However, the scores of anxiety were significantly improved after the CRT compared to baseline (p: 0.037). We did not find any relationship between age, gender, tumor stage, and education with anxiety-depression scores.

The score of ASEX was increased after the CRT. The scores of all items for sexual functions were significantly higher at 6 weeks after the CRT compared to baseline evaluation (p: 0.001). The mean ASEX score before CRT was 12; however, the mean ASEX score increased to 15 after the CRT in patients with grade 2 and above gastrointestinal side effects. There was a positive correlation between deterioration of sexual function and grade 2–3 gastrointestinal toxicities ($p = 0.08$) (Fig. 2).

When we evaluated ROC of ASEX and BDI, the Turkish cut-off score of ASEX was 11 [19]. Before CRT, one patient's score was under 11 points in a female group whereas after CRT, all female patients' scores were above 11 points. However, in the male group, there were no differences in scores before and after CRT. Turkish cut-off score of BDI was considered to be 17. There were no differences in scores female and male groups for the Turkish cut-off score of BDI. According to the Turkey cut-off scores on the scale of ASEX and BDI, there was no statistical significance in the male and female groups.

Table 1 Patients' characteristics

Median age	52.5 (range: 33–76)
Sex	***n* (%)**
Male	26 (81%)
Female	6 (19%)
T stage	
T2	1 (3%)
T3	22 (69%)
T4	9 (28%)
N stage	
N0	3 (9%)
N1	19 (59%)
N2	10 (32%)
Location	
Superior 1/3	5 (16%)
Medium 1/3	4 (12%)
Lower 1/3	23 (72%)
Education	
Low	19 (60%)
Intermediate	7 (21%)
High	6 (19%)
Comorbidities	
Hypertension	4 (12%)
Diabetes mellitus	2 (6%)
Coronary artery disease	1 (3%)
Benign prostate hyperplasia	2 (6%)

Discussion

Our study assessed depression, anxiety status, and sexual function in patients with LARC before and after neoadjuvant CRT. This study showed the deterioration of sexual functions with CRT. Although moderate levels of cancer-related anxiety were detected in our patients before treatment, anxiety levels were decreased with CRT. This might be due to tumor regression and the reduction of tumor-related pain and symptoms.

Table 2 The questionnaire's score (ASEX-BAI-BDI) before and after RT was listed

	Before RT		**After RT**		
	Score (mean)	**SS**	**Score (mean)**	**SS**	***p***
ASEX	14.22	4.70	17.75	5.99	0.001
BAI	9.88	9.28	6.50	6.27	0.037
BDI	9.41	8.59	7.66	6.00	0.17

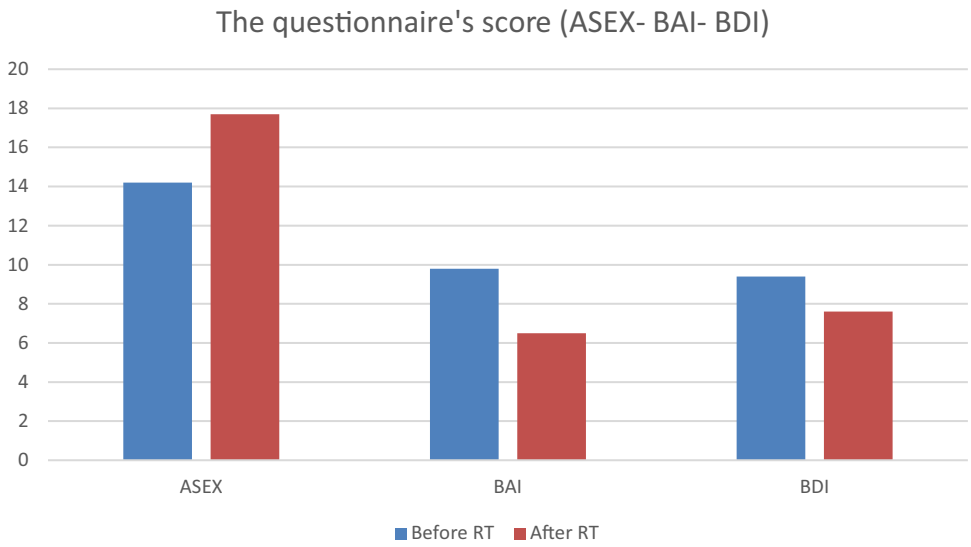


Fig. 1 The questionnaire's score (ASEX-BAI-BDI) before and after RT was listed

According to the guidelines for rectal cancer, neoadjuvant treatment is administered as first-line therapy for locally advanced rectal cancer [20]. The diagnosis of cancer is life-changing and caused considerable anxiety and depression. On the other hand, side effects of treatment may increase the level of anxiety and depression. The improvement in depressive and anxiety symptoms after treatment varied depending on the patient's symptoms and side effects [12]. The depression level was changed from mild to minimal during this process whereas the scores of anxiety were significantly improved after the CRT compared to the baseline in our study.

Surgery is an important factor affecting the QOL, especially the sexual function of the patients [21–24]. The primary tumor location and stage in rectum cancer change the surgical technique. Patients who underwent APR had higher incidence of urinary and sexual dysfunction. Preservation of the pelvic autonomic nerves decreased the incidence of urinary and sexual dysfunction. Santos et al. evaluated the quality of life, pain, anxiety, and depression in 41 patients treated with surgery (APR or TME). Fifty-two percent of the patients presented pain, and depression was observed in 47% and anxiety in 39%. They demonstrated a positive correlation between anxiety with gastrointestinal problems and sexual problems [12]. Attaallah and colleagues reported sexual dysfunction levels after radical surgery [21]. This study found 84 patients with rectal cancer rate of sexual dysfunction (90.5%). Female patients had rate of sexual dysfunction of (93%) whereas male patients had sexual dysfunction (67%) [21]. Costa et al.'s study, which included all male patients, evaluated sexual dysfunction before and after surgery [22]. Increased age, surgical technique (APR), and the presence of a stoma were decisive, of sexual dysfunction

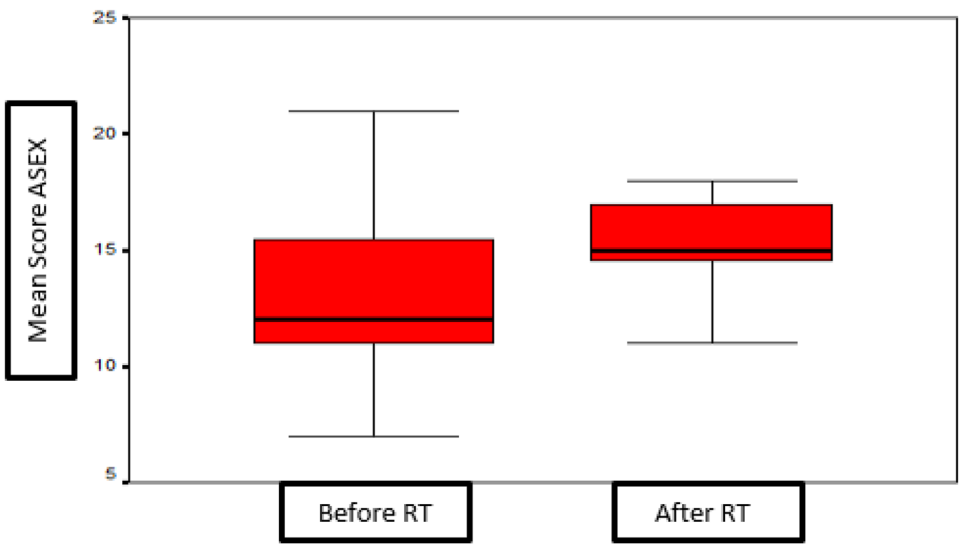


Fig. 2 The positive correlation between the deterioration of sexual function and gastrointestinal problems was determined. The first scale determined the mean score of the ASEX before RT, and the second scale determined the mean score of the ASEX after RTs

after surgery [22]. In the light of these results, surgery is an important factor in sexual dysfunction for rectal cancer survivors. Therefore, we decided to evaluate the effect of only the neoadjuvant CRT on patients' anxiety, depressive symptoms, and sexual activity.

Quality of life includes disease symptoms and treatment side-effects, functional status, psychological distress, social interaction, sexuality and body image, and satisfaction with medical treatment [25, 26]. Abdulkerim et al. investigated the quality of life of patients with rectal cancer treated with preoperative radiotherapy (RT) in the prospective study that compared with pre-RT and at 1 year after treatment scores about the various functions and symptoms scales. They found statistically significant improvement in their emotional state and their global QOL with a decrease in GI symptoms. However, they stated that the sexual dysfunction score increased significantly, particularly in men [27].

Health-related quality of life (HRQOL), fecal continence, and bowel function were evaluated in rectal cancer patients who underwent preoperative chemoradiotherapy. Clinically poor results in terms of constipation and diarrhea were shown [28]. Schag et al. stated some problems like changes in bowel habits, micturition, and sexual problems in rectal cancer patients [29]. Defecation frequency, usage of pads, and rectal blood loss were more commonly seen in patients with rectal cancer who had received preoperative RT; furthermore, these side effects affected the quality of life [30]. Other studies have shown that quality of life was adversely affected after neoadjuvant RT. Physical function, gastrointestinal, and urınary adverse effects returned to near baseline levels after therapy. But sexual function remained to deteriorate permanently after therapy [31, 32]. In addition to anxiety and depression, physical change could also cause sexual dysfunction. In particularly rectal cancer patients, changing body image factors might lead to psychological distrust affecting sexual performance [29]. In our study, we found deterioration of sexual function in our patients who had above grade 2 gastrointestinal side effects, which was comparable to other studies.

Psychological distress adheres to several factors, like poor performance status, malnutrition, and physiological dysfunction in cancer patients [33, 34]. Our patients had more than 80% KPS at the start of radiation. The performance status did not affect the psychological distress. In our opinion, patients with family support may decrease their level of depression and anxiety. In addition, relief in symptoms with tumor regression after treatment may affect patients' quality of life. However, Tavoli et al. showed increased levels of anxiety and depression during radiotherapy in patients who were aware of their cancer diagnosis [35].

Demographic factors and education level were evaluated in light of the literature. Tsunoda et al. investigated emotional function (EF), QLQ-C30, and Hospital Anxiety and Depression Scale (HADS) in a group of outpatients with colorectal cancer who had survived for at least 1 year after surgical treatment. Some factors such as age, sex, location of the tumor, tumor stage, and education have been evaluated in this study [36]. They stated that none of these factors affected the level of anxiety and depression. In Pucciarelli et al.'s study, no significant association was found between the EORTC and HRQOL scales and age, sex, early and late major complications, and time from surgery [28]. Similarly, Tavoli et al. found no statistically significant correlation of these factors with depression and anxiety [35]. We investigated the relationship between age, gender, tumor stage, and education with anxiety and depression levels and found no relation as stated in the literature.

In our study, there were relatively some limitations such as a small sample size, the lack of control measurement group healthy volunteers, and the lack of psychiatric examination of the patients. However, this study has homogeneous patient characteristics such as clinical stage, tumor location, neoadjuvant treatment, and surgery.

The present study prospectively evaluated the effect of CRT on patient psychology and quality of life with recorded outcome measures. This study found decreased anxiety and depression status of the patients but increased level of sexual dysfunction in rectal cancer patients with preoperative CRT. The family support, psychiatric consultation, and palliations in symptoms after the treatment might have important role in the patients' quality of life. So, both clinical and psychiatric support including therapies for sexual dysfunctions are needed for locally advanced rectal cancer patients during and after the neoadjuvant CRT.

Author Contributions M.D,T.K.Ç, Ö.F.D, D.Ç.Ö wrote the main manuscript. G.C prepared Fig. 1. All authors reviewed the manuscript.

Data Availability The data is available and accessible for the author of this study.

Declarations

Ethics Approval For purposes of our study, we performed a prospective analysis with appropriate Local Ethics Committee approval dated July 12, 2016, number A09.

Conflict of Interest The authors declare no competing interests.

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