

## RESEARCH ARTICLE

# Impact of Adjuvant Chemoradiotherapy for Rectal Cancer on the Long-Term Quality of Life and Late Side Effects: A Multicentric Clinical Evaluation by the Turkish Oncology Group

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### Abstract

**Aim:** Although preoperative chemoradiotherapy (CRT) has proven its benefits in terms of decreased toxicity, there is still a considerable amount of cases that do not receive postoperative CRT. Oncologists at different geographic locations still need to know the long-term effects of this treatment in order to manage patients successfully. The current paper reports on long-term quality of life (QOL) and late side effects after adjuvant CRT in rectal cancer patients from 5 centers in Anatolia. **Methods:** Rectal cancer patients treated with postoperative CRT with minimum 1-year follow-up and were in complete remission, were evaluated according to RTOG and LENT-SOMA scales. They were also asked to complete Turkish version of EORTC QLQ-C30 questionnaire and the CR-38 module. Each center participated with the required clinical data. **Results:** Two hundred and thirty patients with median age of 55 years participated and completed the study. Median follow-up time was 5 years. All patients received RT concomitant with chemotherapy. Common parameters that both increased functional health scales and yielded better symptom scores were long term interval after treatment and sphincter-saving surgery. In addition, surgery type and follow-up time were determined to be predictors of QOL scores and late toxicity grade. **Conclusion:** Postoperative CRT was found to have a great impact on the long term QOL and side effects in rectal cancer survivors. The factors that adversely affect these are abdominoperineal resection and shorter interval. The findings may encourage life-long follow-up and cooperation with patients, which should be mentioned during the initial counseling.

**Keywords:** Rectal cancer - chemoradiotherapy - quality of life - Anatolia

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### Introduction

The benefits of chemoradiotherapy (CRT) in addition to surgery in patients with rectal cancer have been well documented. Improvements in surgical technique, RT facilities and new chemotherapeutic agents have led to the development of current successful therapeutic interventions. These improvements have resulted in better survival for patients with rectal cancer. With better survival, therefore, the increased length of follow-up, attention has been directed to late adverse effects of the treatments.

Health is currently understood as a complete state of physical, mental and social well-being dubbed as the "Quality of Life" (QOL), rather than merely an absence of disease (Goker et al., 2011). It is an important outcome

measure of cancer treatment and has been found to be a prognostic variable in survival of rectal cancer patients (Ezat et al., 2012). QOL represents an individual's capacity to undertake daily activities, combined with satisfaction with one's state of health and balance between disease control and treatment-related adverse effects (Matrah et al., 2012). The literature from Western countries offers some information about rectal cancer survivors' adjustment years after adjuvant CRT for rectal cancer (Bruheim et al., 2010; Kasperek et al., 2012). It is not always possible to adopt the findings of these studies to other countries with a different sociocultural background which may have an important impact on the QOL.

The purpose of this study was to evaluate QOL and late side effects of postoperative CRT using validated instruments in rectal cancer survivors living in Anatolia.

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## Materials and Methods

This study was approved by the Ethics Review Board at Gazi University Faculty of Medicine (Ankara, Turkey). Informed signed consent in accordance with the Declaration of Helsinki was obtained from all study participants.

### Study Design

Patients who had undergone postoperative adjuvant CRT for locally advanced rectal cancer at 5 Turkish Oncology Group (TOG) member centers were identified. The patients were considered eligible for the study if the follow-up since the completion of all of the treatments was more than one year and were still free of disease. Patients with any recurrence, who suffered from another malignancy and sustaining major comorbidities that would render QOL assessment impossible were excluded. All patients received a phone call inviting them to come to the hospital to fill-out QOL questionnaire.

### Questionnaires

**EORTC QLQ-C30:** It is a cancer-specific, self-report questionnaire validated in several studies and comprises 30 questions. It consists of 5 functional scales, 3 symptom scales, a global health/ quality of life scale, and 6 single items (Aronson et al., 1993). The current standard Turkish version of the QLQ-C30 and the original scoring manual were used (Fayers et al., 2001).

**EORTC QLQ-CR38 colorectal cancer module:** This is also a patient self-rating questionnaire that comprises 38 questions (Sprangers et al., 1999). The general structure comprises four multi-item/ single-function scales, and one single symptom item.

### Toxicity scales

Radiation Therapy Oncology Group (RTOG) "Late Radiation Morbidity Scoring Schema" for lower gastrointestinal and genitourinary were used to grade the severity of radiotherapy related side effects (Cox et al., 1995). Late toxicity was dichotomized in the statistical models.

A late effect of normal tissue-subjective objective management analytic (LENT-SOMA) table for the small intestine/colon and bladder was used to grade the severity of radiation-induced complications (Overgaard and Bartelink, 1995). The scores of the parameters were summed as it was originally recommended, but were not divided by the number of elements as this was not advocated previously (Denekamp et al., 1996). The toxicity was graded according to the summed LENT-SOMA score as it was previously reported (Kilic et al., 2000; 2001).

### Statistics

Data analysis was carried out with SPSS 15.0 for Windows program package (SPSS Inc, Chicago, and Illionis, USA). The quality of life scores were expressed as mean and median. The differences between variables with categorical data were examined using the chi-square test. Kruskal-Wallis test was used for variables with more than

2 categories and the Mann-Whitney U-test for pairwise comparisons that accounted for the nonparametric distribution of the QOL scores. Correlations between QOL and toxicity variables were carried out using the Pearson bivariate correlation. QOL and toxicity data were entered into MANCOVA multivariate variance analysis to ascertain independent prognostic factors. A 5% level of statistical significance was used for clinical variables ( $p < 0.05$ ), and a 2% level of statistical significance was chosen for quality of life variables ( $p < 0.02$ ) to reduce the risk of type I errors arising from multiple testing.

## Results

Two hundred and thirty patients with a median age of 55 years (range, 18-80 years) participated in this study. Patient characteristics are presented in Table 1. Median follow-up time was 5 years (range, 1.1-14.6 years). All patients received external beam pelvic radiotherapy with megavoltage energies ( $>10$  MV) and mostly four-field (box) technique. Radiotherapy dose was 50.4 Gy in all but 45 Gy in 5 patients and 54 Gy (including boost to the primary site) in 8 patients with a conventional fractionation. All of the patients received concomitant chemotherapy including 5-fluorouracil (5FU). Radiotherapy was initiated with the first cycles in 85% of patients, and with 2<sup>nd</sup> or 3<sup>rd</sup> cycle for the remaining. After the completion of chemoradiotherapy, chemotherapy was completed to 6 cycles. During most of the period the RT treatment planning was based on 2-dimensional simulation, usually with three standard fields. Approximately after the year of 2005 all of the centers included had begun to use 3-dimensional planning according to the guidelines of International Commission of Radiation Units and Measurements (ICRU) and RTOG.

Except for the 14 illiterate patients whose questionnaires were completed by their caregivers, all patients completed the questionnaire themselves in 20-35 minutes. Calculated scores for the QLQ-C30 and the CR-38 module are shown in Table 2 and 3, respectively. Factors that yielded better functional scores were long-term interval after treatment

**Table 1. Patient Characteristics**

Variable	n (%)	
Gender	Female	104 (45)
	Male	126 (55)
Age	<60 year	143 (62)
	≥60 year	87 (38)
Surgery	Abdominoperineal resection	86 (37)
	Low anterior resection	144 (63)
Total mesorectal excision	Negative	58 (25)
	Positive	172 (75)
Education status	Illiteracy	33 (14)
	<High school	115 (50)
	High school	36 (16)
Social life	University	46 (20)
	With the family	210 (91)
	With friends	5 (2)
Follow-up time	Alone	15 (7)
	<5 year	68 (25)
	≥5 year	162 (75)

(≥5 years) (6 scores: physical, role, emotional and social functioning, body image and future perspective), LAR (5 scores: role, emotional and social functioning, body image and future perspective), male gender (3 scores: emotional and sexual functioning and future perspective), and ≥60 years or older age (2 scores: emotional functioning, future perspective). Factors that yielded better symptom scores were long interval after treatment (≥5 years) (5 scores: nausea/vomiting, dyspnea, appetite loss, financial problems and CT side effects), operation with LAR (5 scores: nausea/ vomiting, pain, appetite loss, CT side effects and sexual problems), presence of TME (4 scores: fatigue, CT side effects, defecation problems, weight loss), less than 60 years old age (2 scores: sexual problems and appetite loss), male gender (1 score: defecation or stoma-related problems) (p<0.02 for each).

Patients were grouped according to age (<60 vs. ≥60 years), gender (male vs. female), surgery type (APR vs. LAR), and follow up time (<5 vs. ≥5 years). Emotional and social functioning were the worst in female patients younger than 60 years, operated with APR and less than 5 years follow up (n=20) (58.24 and 73.79, respectively) whereas the best in male patients older than 60 years, operated with LAR and more than 5 years follow up (n=25) (90.06 and 94.58, respectively) (p=0.003 for each). Statistically significant differences were found for body image and future perspective in favor of male patients, older than 60 years, operated with APR and with more than 5 years follow up when compared to the female subjects with the same features (p<0.0001 and 0.004, respectively). Symptom scores of nausea/vomiting, pain and appetite loss were highest in female patients older than 60 years older whatever the follow up time is (p<0.02 for each). Sexual functioning and sexual enjoyment were found to be higher in male patients than the female ones (p=0.002 for each). Patients were grouped according to gender, age and surgery type. The worst sexual functioning and sexual enjoyment were determined in male patients operated with APR (7.13 for each) whatever the age and follow up time are. It is the best in younger male patients operated with LAR whatever the follow up time is (37.48 for sexual

functioning and 37.47 for sexual enjoyment, respectively) (p=0.002 and 0.003, respectively).

According to the late rectal and urinary toxicities, no significant difference was observed in patients operated with APR or LAR according to both of the toxicity scales. Both the rectal and urinary toxicities were more common in patients operated with APR and with a longer follow-up time than the remaining (p=0.02 and 0.035, respectively). There were no differences in global health status when patients were compared with rectal toxicity (RTOG scale, all grades, n=54) to the remaining without any rectal toxicity (n=176). The patients with rectal toxicity (RTOG scale) had significantly lower scores than the ones without toxicity for several scales: Physical functioning (68.5 vs. 77.7, p<0.001), role functioning (78.5 vs. 87.2, p<0.001), social functioning (79.7 vs. 94.5, p=0.003). When rectal toxicity was evaluated with LENT-SOMA scale, statistically significant differences were observed between the patients with (n=80) and without any toxicity for the following scales; global health status (69.4 vs. 74.7, p=0.002), physical functioning (68.5 vs. 83.5, p<0.0001), role functioning (78.5 vs. 93.5, p<0.0001) and social functioning (79.7 vs. 94.5, p=0.003).

Significant correlations were observed between RTOG rectal toxicity grade and the scores of the following QOL symptom scales; gastrointestinal symptoms (r=0.272, p<0.0001), weight loss (r=0.145, p=0.028) and defecation problems (r=0.160, p=0.015). When the LENT-SOMA scale was used, significant correlations were determined between the rectal toxicity grade and gastrointestinal symptoms (r=0.277, p<0.0001), defecation problems (r=0.195, p=0.003), fatigue (r=0.158, p=0.016), nausea/vomiting (r=0.140, p=0.034), and diarrhea (r=0.230, p<0.0001).

There were no differences in global QOL or any functioning scales when the patients with any RTOG urinary toxicity (n=33) were compared with the subjects without any toxicity (n=197). However, the small group of patients with grade 2 or more RTOG urinary toxicity (n=11, all were operated with APR) had significantly lower scores for global QOL and social function than the remaining patients (70 vs. 75.9, p=0.001 and 63.3 vs. 76.9, p<0.0001; respectively). In addition to this, it is found that there is a statistically significant correlation between the LENT-SOMA urinary toxicity grade and the scores

**Table 2. Calculated Scores for QLQ-C30 v3.0**

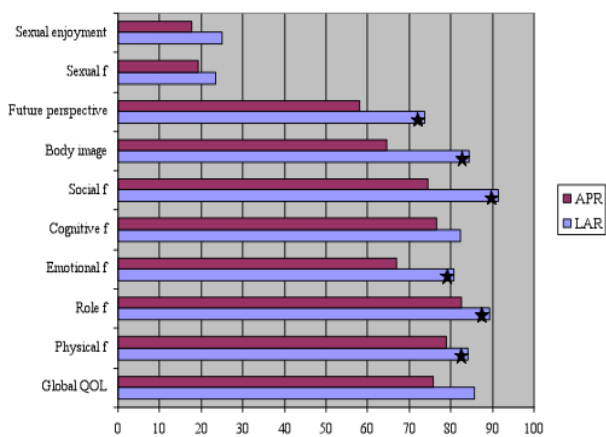
Variable	Mean score	Median score	IQR	Range
<b>Functional scale</b>				
Physical function	82.2	86.7	79.9-84.3	11-100
Role function	86.8	100.0	83.6-89.9	0-100
Emotional function	75.5	83.3	72.3-78.8	0-100
Cognitive function	80.1	83.3	77.3-82.9	10-100
Social function	85.0	100.0	81.9-88.1	0-100
Global health	80.0	75.0	71.6-76.6	0-100
<b>Symptom scale</b>				
Fatigue	27.8	22.2	24.7-30.9	0-100
Nausea-vomiting	7.4	0	4.9-9.8	0-100
Pain	16	0	13.0-19.0	0-100
Dyspnea	9.2	0	6.6-11.7	0-100
Insomnia	19.6	0	15.7-23.4	0-100
Appetite loss	9.9	0	7.1-12.6	0-100
Constipation	16.7	0	13.2-20.2	0-100
Diarrhea	20.4	0	1.5-24.1	0-100
Financial problems	20.1	0	15.9-24.0	0-100

\*IQR- Interquartile range

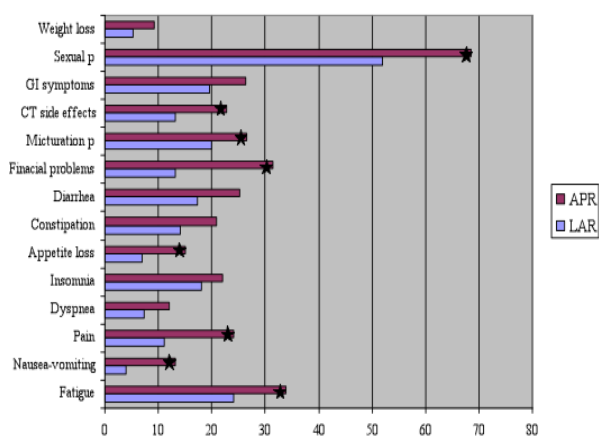
**Table 3. Calculated Scores for QLQ-CR 38**

Variable	Mean score	Median score	IQR	Range
<b>Functional scale</b>				
Body image	76.9	88.8	73.4-80.4	0.0-100.0
Future perspective	67.9	66.7	63.2-71.9	0.0-100.0
Sexual function	21.9	16.6	18.4-25.2	0.0-100.0
Sexual enjoyment	22.3	0.0	18.6-25.9	0.0-100.0
<b>Symptom scale</b>				
Micturation problems	22.4	22.2	19.5-25.2	0.0-88.8
CT side effects	16.8	11.1	14.4-19.3	0.0-77.7
GI symptoms	22.1	20.0	19.4-24.7	0.0-100.0
Sexual problems	58.2	66.7	53.2-63.2	0.0-100.0
Defecation problems	16.8	14.2	14.2-19.5	0.0-66.7
Stoma-related problems	40.5	40.4	35.0-45.9	0.0-90
Weight loss	6.8	0.0	4.4-9.2	0.0-100.0

\*IQR- Interquartile range, CT -chemotherapy, GI- gastrointestinal



**Figure 1. Median Global Health Status and Functional Scales by Surgery Type.** QOL- Quality of life, f.-function, LAR- Low anterior resection, APR- Abdominoperineal resection



**Figure 2. Median Symptom Scores by Surgery Type.** GI- gastrointestinal, CT- Chemotherapy , LAR- Low anterior resection, APR- Abdominoperineal resection

of sexual problems ( $r=0.503$ ,  $p<0.0001$ ). According to the findings from the study using multivariate variance analysis, surgery type (APR or LAR) and follow-up time ( $<5$  vs.  $\geq 5$  years) were determined to be the predictors of quality of life scores and late toxicity grade ( $p=0.01$  for each).

## Discussion

Although local recurrence and survival are important outcomes after rectal cancer treatment, bowel function and quality of life are also important outcomes. In this study validated questionnaires and personal interviews were used to assess the effect of adjuvant CRT on QOL and toxicity in rectal cancer patients. The present study demonstrates that postoperative adjuvant CRT for rectal cancer is associated with considerable impairments of QOL, especially in patients with APR and patients with a longer follow-up period.

Radiation has proven itself valuable in the treatment of rectal cancer, but part of it is not without serious morbidity. Postoperative RT treatment volumes for rectal cancer generally include several critical structures that may cause toxicity such as the small intestine, part of the large bowel, anal canal, sometimes, sphincters,

bladder, genital organs and the residual rectal volume. A previous toxicity and QOL study in rectal cancer patients performed by Bruheim et al. (2010) showed that patients treated with postoperative RT had significant long-term toxicity including fecal incontinence and increased bowel frequency comparing with the non-irradiated ones.

In our study, EORTC QLQ C30 was used with the CR38 module. These questionnaires are comprehensive and had been validated in different cultural populations (Bruheim et al., 2010; Mrak et al., 2011; Theodoropoulos et al., 2012). Besides the generally used RTOG toxicity scale, LENT-SOMA scoring system which might have been the best and semi-objective was used for the first time in a QOL study. The differences in the rate of specific radiation toxicities in the previously published reports and the current study may also be a result of different toxicity scoring systems.

Sociocultural factors are in relation with the incidence of late effects, but especially with QOL of patient. Because of its strategic location at the intersection of Asia and Europe, Anatolia has been the center of several civilizations since prehistoric times. The culture of this region combines a largely diverse and heterogeneous set of elements that are derived from the Ottoman, European, Middle Eastern and Central Asian traditions. During the last century with the development of industrial cities in Anatolia, rapid and profound sociocultural changes have been observed not only in urban areas but also in rural settlements. There are many differences in culture, community identity, community participation and ownership between communities in Western and Asian countries. Anatolia has a unique sociocultural environment with its mixed cultural and ethnic background, therefore it is difficult to adopt the results of QOL studies from the Western and Eastern countries. Our results showed that patients with longer follow-up time and sphincter-preserving surgery (LAR) had better QOL. Although younger age and female gender did not have any effect on symptoms, they caused significantly worse scores in some functional scales. There have been conflicting QOL results concerning patients operated with sphincter-saving procedure or APR in the literature (How et al., 2012). The literature data from US do not provide evidence to support the thesis that the QOL after LAR/ AR is superior to that after APR (de Compos-Labota et al., 2011; Neuman et al., 2012). Living with a permanent stoma significantly changes the life style, not only the physical and social aspects but the psychological ones as well. Survivors may experience many things, including adapting to the new anatomy, managing the stoma, and living in the same sociocultural era with the problems of stoma. Moreover, they always remind the threat of cancer recurrence every time they care for the stoma. Therefore, some survivors may exclude themselves not only from the society but from their families as well. In addition; the gender, sociocultural background and age have a great impact on the perception of QOL. Younger patients may be more active and therefore experience the limitations resulting from the cancer to a greater extent, whereas older people may have more unwillingness to express unmet needs or problems with which they believe they should be able to

cope (Milbury et al., 2012). Numerous studies concerning QOL in groups with different pathologies have reported better results for men versus women. Several explanations have been suggested for this. One is that women have a greater life expectancy and physical problems, therefore, resulting in a poorer QOL after cancer and related treatments. Another suggestion is that, it is generally easier for women to communicate with personal information. It is also socially acceptable for women to express their feelings and problems, whereas men tend to adopt a role of strength, tolerating all sorts of problems. In Anatolia, there is a social disadvantage for women that the sociocultural background is male-oriented and the lower overall status of women may result in lower QOL perception.

Several limitations need to be kept in mind when interpreting our data. This study included only the rectal cancer survivors who were able to come to hospital and agreed to be included. Like most of the previous studies reflecting QOL of patients, exclusion of those subjects with recurrent disease may cause a picture that is somewhat imbalanced. However, the main purpose of the study was just to determine the problems experienced by the survivors. On the other side, we are unable to comment on the influence of treatments in the QOL and life standards, as preoperative data were not collected. A prospective, longitudinal study evaluating the toxicity and QOL parameters should be undertaken in order to give an answer for this. A selection of survivors with locally advanced rectal cancer who show no evidence tumor recurrence throughout a period of 12 months after the completion of all adjuvant treatments might exemplify a subgroup of patients determined to fight with their cancer. The patients with a fighting attitude may survive longer than patients who stoically accept their fate. This attitude has been dubbed by the experts the "Fighting Spirit" (Alcalar et al., 2012). The perception of the treatment-related (including surgery) adverse effects and their impact on QOL might have been affected by this spiritual attitude.

Although preoperative long term CRT followed by surgery has been accepted as the standard treatment modality and the number of patients undergoing postoperative CRT has been progressively decreasing, there has still been a population of rectal cancer survivors irradiated postoperatively who need to be evaluated according to the late effects of the treatment and QOL (Kilic et al., 2006). In summary, the data observed in the present analysis suggests that resection extent and the follow-up period have great impact on the prognosis of rectal cancer patients who had undergone postoperative CRT. This finding may be enough just to support preoperative multimodality treatments even the survival outcomes might be similar. Supportive care protocols regarding colostomy problems should be supported especially in patients irradiated after APR. The results also mention the importance of life-long follow-up and cooperation with the patient and the caregiver. These findings should be addressed in the patient counseling at the diagnosis both in order to give help to both the subjects to prepare themselves for the long-term consequences in order to develop an important tolerance of toxicity, and the politicians to develop national health care services

to supply the appropriate supportive prophylactic or symptomatic care when needed.

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