

Effects of preoperative chemoradiotherapy on anal sphincter functions and quality of life in rectal cancer patients

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Abstract

Purpose Deterioration of anorectal function after long-course preoperative chemoradiotherapy combined with surgery for rectal cancer is poorly defined. We conducted a prospective study to evaluate the acute and long term effects of preoperative chemoradiotherapy on anorectal function and quality of life of the patients.

Methods There were 26 patients in surgery group and 31 patients in preoperative chemoradiotherapy group. Anorectal function and quality of life of the patients were assessed by anorectal manometry, incontinence score, quality of life questionnaire.

Results Significant lower resting pressures in both groups and lower maximal squeeze pressures in the preoperative chemoradiotherapy group were observed after postsurgical evaluations compared with the paired pretreatment ones. In the surgery group, both the Wexner continence score, FIQL score, and the rectoscopy score were comparable before and after surgery, whereas significant worsening in the Wexner score was observed in the preoperative chemoradiotherapy group postoperatively ($P < 0.01$). Significant reduction in

anal canal resting pressures and squeeze pressures, Wexner score, and FIQL score were observed immediately after the completion of preoperative chemoradiotherapy. Significant lower maximal squeeze pressures and worsening of the Wexner scores were observed in the preoperative chemoradiotherapy group compared to the surgery group during the postoperative assessments ($P < 0.05$ and $P < 0.01$, respectively).

Conclusions Both total mesorectal excision and preoperative chemoradiotherapy may adversely affect the anorectal function. Careful selection of the patients who will benefit from neoadjuvant therapy and identifying the patients with a high risk of developing functional problems may help to improve functional outcomes for the treatment of rectal cancer.

Keywords Rectal cancer · Preoperative chemoradiotherapy · Anorectal manometry · Quality of life

Introduction

Currently preoperative chemoradiotherapy (CRT) combined with total mesorectal excision (TME) is the standard procedure in sphincter-preserving therapy for stage II and III rectal cancer. Neoadjuvant CRT in patients with locally advanced rectal cancer has proven to show oncologic benefits on local control and long-term survival [1–3]. After preoperative CRT, downstaging or complete regression of the tumor may occur which may result in an increase in the number of sphincter-saving operations performed [1, 4, 5]. Both preoperative CRT and low anterior resection (LAR) may impair anorectal functions which has major negative implications on the quality of life (QoL) of the patient. The main effects of pelvic irradiation on deterioration of anorectal function are vascular toxicity and damage to the anal sphincter muscle and pudendal nerve [6, 7].

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The aim of this study was to evaluate the acute and long-term effects of pelvic irradiation as a neoadjuvant treatment for rectal cancer on anorectal function and QoL of the patients by using several different tools (anorectal manometry, incontinence score, QoL questionnaire, and rectoscopy).

Patients and methods

Between February 2002 and March 2006, 57 patients with localized rectal cancer were prospectively constituted the intent-to-treat population in the Colorectal Unit of Department of Surgery, Dokuz Eylul University Hospital, Izmir, Turkey.

Pretreatment evaluation included clinical history, general clinical examination, digital rectal examination, a complete blood workup, blood chemistry profile, carcinoembryonic antigen assessment, rigid proctosigmoidoscopy and/or colonoscopy, tumor biopsy, chest X-ray, computed tomography of the abdomen, pelvis, and thorax, and endorectal coil magnetic resonance imaging (ERMRI). In patients for whom it was impossible to pass the ERMRI probe through stenosing rectal tumors, surface MRI was utilized for local staging.

Patients who had undergone prior pelvic surgery or pelvic radiotherapy (RT), patients who had received postoperative pelvic RT and patients who had had a local excision or abdominoperineal resection (APR), and patients who had unresectable tumor were excluded from the study. The treatment regimen was assessed according to the patient's tumor location, stage, age, concomitant medical conditions, and World Health Organization performance status in a multidisciplinary team approach including colorectal surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, and gastroenterologists. The study was approved by the Ethics Committee of Dokuz Eylul University, School of Medicine.

Eligible patients were divided into two groups: surgery group, patients treated with only surgery ($n=26$) and preoperative CRT group, patients who underwent CRT before surgery ($n=31$). Tumor localization was subsequently subdivided into lower rectum (0 to 5 cm from anal verge), middle rectum (5.1 to 10 cm), and upper rectum (10.1 to 15 cm). Patients in the preoperative CRT group were further subdivided according to the tumor location as middle rectum ($n=12$) and lower rectum ($n=18$).

Assessment of continence

Wexner continence score: the Wexner continence score is a questionnaire, which scores the severity of fecal incontinence [8]. The scoring system is composed of five items which are focused on type and frequency of incontinence (solid, liquid, gas, and wearing of a pad) and lifestyle

alterations. Frequency is scored as follows: 0= never; 1= rarely (<1/month); 2= sometimes (<1/week, ≥ 1 /month); 3= usually (<1/day, ≥ 1 /week); 4= always (≥ 1 /day). Overall score is the sum of the scores of individual items and the lowest score 0 represents perfect continence and the highest score 20 represents worst incontinence.

Anorectal manometry: manometric evaluation of anal sphincter function was performed in our institution's Anorectal Physiology Laboratory. An eight-channel catheter with a water perfusion system was used for the investigation (Medical Measurement Systems, Enschede, The Netherlands) and digitized measurements were analyzed with a computer software. One surgeon (A.E.C.) routinely performed anorectal manometry. Each patient was instructed to empty the rectum before the examination. With the patient in the left lateral position and hips flexed at 90°, the catheter was introduced from the anus. Anal canal resting and squeeze pressures, the first sensation (FS) of rectal filling, maximal tolerable volume (MTV), and presence of rectoanal inhibitory reflex (RAIR) were measured.

Assessment of macroscopical changes

Macroscopical changes on anal canal and rectal mucosa were scored by rectoscopy according to the presence of mucosal pallor or atrophy, telangiectasia, contact bleeding, ulceration, and loss of compliance [9] (each item adds one point to the overall score).

Assessment of quality of life

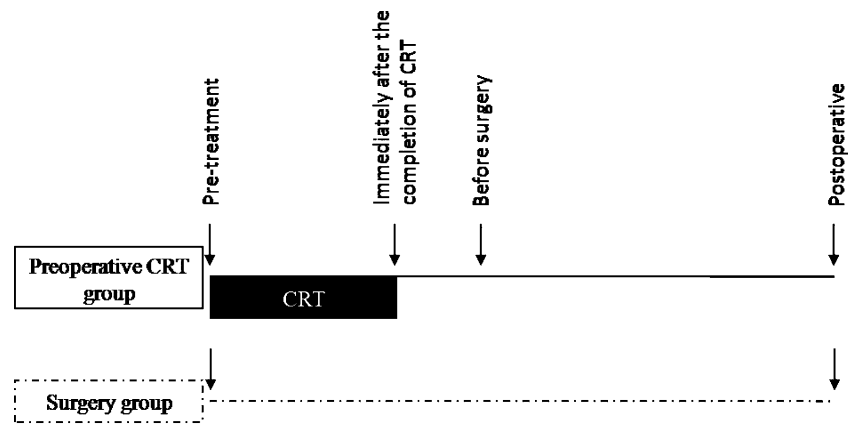
Quality of life was assessed by the fecal incontinence quality of life questionnaire [FIQL] [10] which is a specific questionnaire to measure health-related QoL in patients with fecal incontinence. In this questionnaire, there are 29 items which are further grouped into four functional subscales: life style (ten items), coping/behavior (nine items), depression/self perception (seven items), and embarrassment (three items). Scores for items are assigned a value from 1 (worst) to 4 (optimal). Scale scores are the mean response to all items in the scale.

Assessments for continence, macroscopical changes, and QoL were performed before surgery and postoperatively for patients in the surgery group and before and immediately after the completion of preoperative CRT, before surgery, and postoperatively for patients in the preoperative CRT group (Fig. 1).

Chemoradiation protocol

Patients with stage II or III rectal carcinoma in the middle or lower rectum were treated with 6-MV photons by a four-

Fig. 1 Timing of the evaluations in both surgery and preoperative CRT groups



field pelvis technique. The fields extended from L5/S1 level superiorly to the lower border of obturator foramina inferiorly, with a 1 to 1.5 cm margin on the bony pelvic inlet. Patients received RT 1.8 Gy/day, 5 days/week to give a total 25 fractions over a period of 5 weeks for a total of 4,500 cGy with concurrent chemotherapy (5-fluorouracil 225 mg/m²/day infusion for 5 days/week during a period of 5 weeks).

Surgery

The surgical technique included a mesorectal excision as described previously [11]. A total mesorectal excision was performed for tumors in the lower and middle rectum; for patients with upper rectal tumors, the mesorectum was divided 5 cm from the distal border of the tumor with high ligation of the inferior mesenteric artery. If the tumor was attached to adjacent parietes or viscera, en bloc excision was performed. A temporary diverting loop ileostomy was constructed in all patients who had preoperative CRT. In patients who had sphincter invasion and in whom 1 cm distal border was not achieved, APR was performed. In the preoperative CRT group, patients underwent surgery 8 weeks after the completion of CRT.

Statistical analysis

Quantitative data were expressed as mean \pm SD; scores were expressed as median and range. The Mann–Whitney *U* test and the *t* test were used to compare median scores and mean values, respectively. The Wilcoxon signed rank test was used for nonparametric comparison of dependent variables. Frequencies between different groups were calculated by means of the Fisher's exact test. The Paired samples *t* test was used to compare the values in the same patient during the treatment. Repeated measurement analyses were used for comparison of anorectal manometrical changes between the subgroups of preoperative CRT during the treatment; $P < 0.05$ was considered to be significant in all analyses.

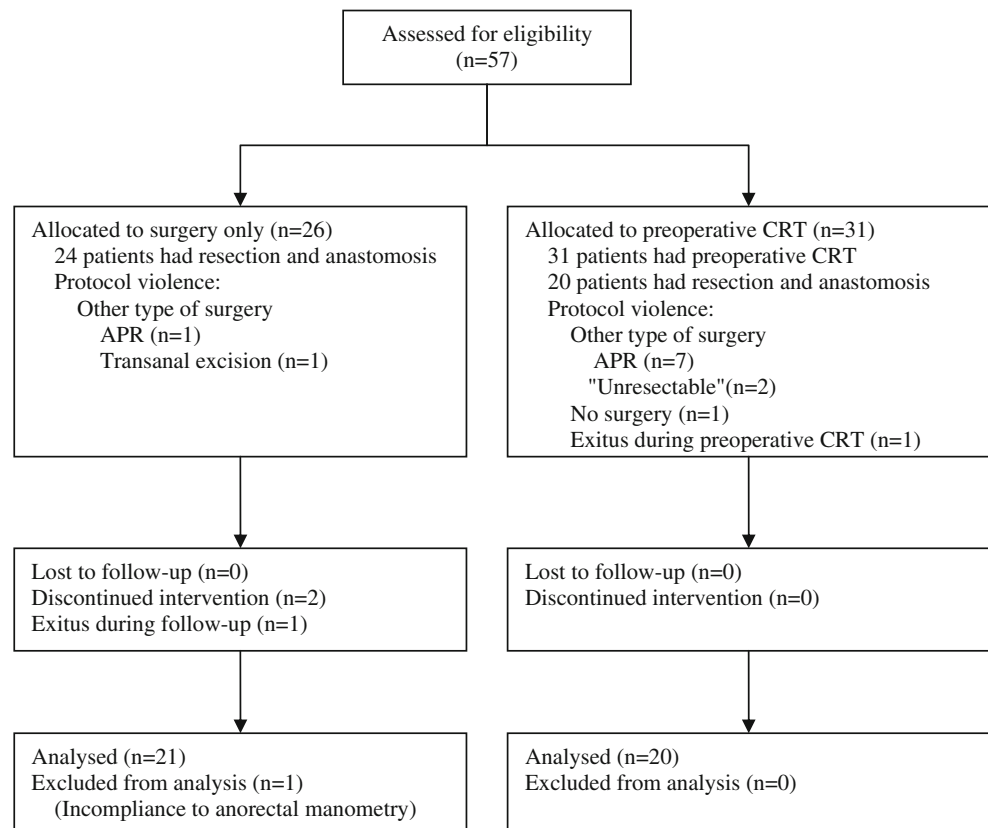
Results

Fifty-seven patients gave informed consent to participate in the study. The mean patient age was 61 years (range, 25–85 years) and male/female ratio was 1:8. Twenty-four patients underwent resection and anastomosis without preoperative CRT (surgery group), and 20 patients underwent resection and anastomosis after CRT (preoperative CRT group). In the surgery group, one patient underwent APR and one patient underwent transanal local excision. In the preoperative CRT group, three patients were considered as having unresectable tumors due to the diagnosis of frozen pelvis detected either by preoperative radiological imaging just before the surgery or at the laparotomy; seven patients underwent APR and one patient who had coronary vascular disease died due to acute coronary syndrome during preoperative CRT (Fig. 2).

No anastomotic leakage was observed in either group. Preoperative CRT did not result in significant morbidity. The most frequent adverse effect of preoperative CRT was grade 1–2 skin irritation which affected 47% of the patients; two patients had grade four intestinal adverse effects. Intermittent diarrhea was controlled with symptomatic therapy. Three patients (9.7%) showed histopathological complete response, and 16 patients (51.6%) showed ypT and/or ypN downstaging in the preoperative CRT group.

The demographic data of the study population, tumor characteristics, and pretreatment evaluations are presented in Table 1. No significant differences were observed in terms of age, sex, and pretreatment evaluations between the groups. Patients in the preoperative CRT group had more advanced and distally located tumors. Postoperative evaluations were repeated after a median of 417 days (range, 149–477 days). The pressures in the anal canal showed significant lower resting pressures (RP) in both groups and lower maximal squeeze pressures (SP) in the preoperative CRT group after surgery compared with paired pretreatment ones (Fig. 3). In the surgery group, both the Wexner continence score, FIQL score, and rectoscopy score were comparable before and after

Fig. 2 Flow diagram of the study progress through the phases



CRT = chemoradiotherapy; APR = abdominoperineal resection.

Table 1 Demographic characteristics and pretreatment evaluations of patients in surgery group and preoperative CRT group

	Surgery group (n=26)	Preoperative CRT group (n=31)
Age, mean (range), year	65 (41–85)	59 (38–76)
Sex, (male/female)	19/7	18/13
Stage		
I	14	0
II	6	8
III	6	23
Location of tumor		
Upper rectum	11	1
Middle rectum	6	12
Lower rectum	9	18
Anorectal manometry		
Mean RP, mean ± SD, mmHg	56.4±10.7	61.9±13.1
Maximum RP, mean ± SD, mmHg	77.9±13.3	84.8±15.4
Mean SP, mean ± SD, mmHg	115.9±27.3	117.1±26.4
Maximum SP, mean ± SD, mmHg	169.8±28.7	171.0±26.5
Rectal first sensation (ml)	38 (24–55)	41 (27–53)
Maximum tolerable volume (ml)	141 (92–178)	136 (105–167)
RAIR (positive/negative)	26/0	30/1
Rectoscopy score, median (range)	0 (0–2)	0 (0–2)
Wexner score, median (range)	0 (0–13)	0 (0–3)
FIQL score, mean (range)	3.8 (2.9–4)	3.7 (3.4–4)

CRT chemoradiotherapy, RP resting pressure, SP squeeze pressure, RAIR rectoanal inhibitory reflex, FIQL fecal incontinence quality of life scale

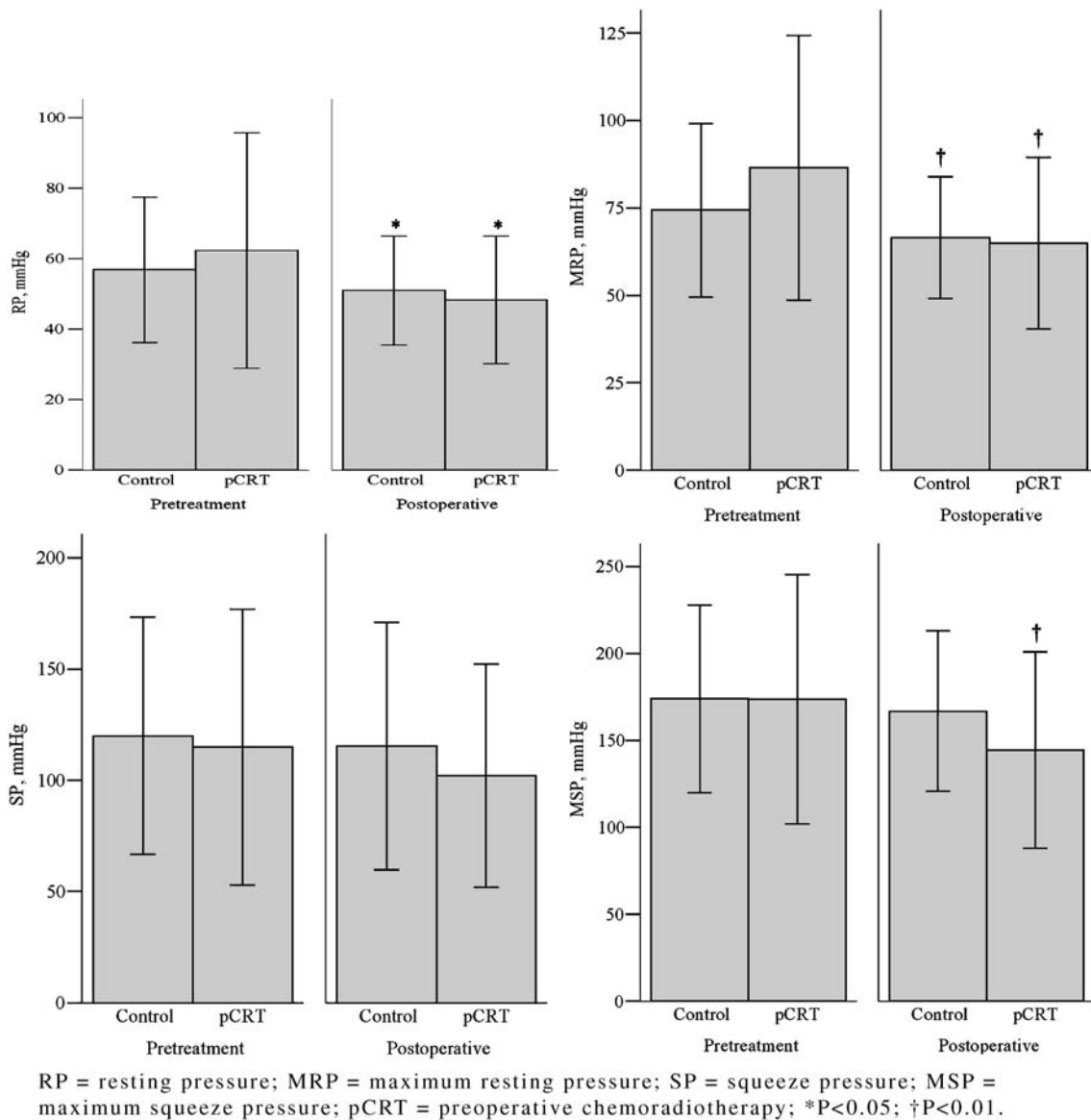


Fig. 3 Comparison of pretreatment vs. postoperative evaluations of anal sphincter pressures in both groups

surgery where as significant worsening in the Wexner score observed in the preoperative CRT group postoperatively compared with the pretreatment ones (3 vs. 0; $P<0.01$). Table 2 presents the comparison of postoperative evaluations of the groups. Patients in the preoperative CRT group had significantly lower maximal SP (144.4 ± 28.2 mmHg vs. 166.8 ± 23.1 mmHg) and had a significant worsening of the median Wexner continence scores (3 vs. 0) compared with the patients treated with only surgery ($P<0.05$ and $P<0.01$, respectively) during the postoperative assessments.

In the preoperative CRT group, resting and squeeze anal canal pressures were significantly reduced by CRT, and the Wexner continence score and FIQL (both subscales) were adversely affected during CRT (Table 3). Demographical

characteristics and pretreatment evaluations were comparable for patients in the preoperative CRT group according to the tumor localization which was subdivided into the middle and lower rectum. The only significant difference was observed in the maximal RP (MRP), which was adversely affected in patients with middle rectal tumors during the treatment ($P<0.015$).

The threshold for first sensation and maximum tolerable volume measurements and disappearance of RAIR were not significantly different between the groups or during the different periods of the study.

Macroscopical changes assessed and scored by rectoscopy revealed no significant difference between the groups or during the different periods of the study.

Table 2 Postoperative evaluations of anorectal function and QoL

	Surgery group (<i>n</i> =20)	Preoperative CRT group (<i>n</i> =20)	<i>P</i> value
Anorectal manometry			
Mean RP, mean ± SD, mmHg	50.9±7.7	48.3±9.0	0.337
Maximum RP, mean ± SD, mmHg	66.5±8.7	64.9±12.2	0.678
Mean SP, mean ± SD, mmHg	115.4±27.8	102.0±25.1	0.171
Maximum SP, mean ± SD, mmHg	166.8±23.1	144.4±28.2	0.018
Rectal first sensation (ml)	36 (22–50)	39 (23–55)	0.317
Maximum tolerable volume (ml)	147 (83–180)	136 (90–175)	0.614
RAIR (positive/negative)	18/3	16/4	0.696
Rectoscopy score, median (range)	0 (0–1)	0 (0–2)	0.434
Wexner score, median (range)	0 (0–13)	3 (0–7)	0.006
FIQL score, mean (range)			
Lifestyle	3,6 (3.0–4.0)	3.5 (2.9–4.0)	0.102
Coping/behavior	3,7 (2.7–4.0)	3.5 (2.8–4.0)	0.160
Depression/self perception	3.7 (3.6–3.8)	3.6 (3.3–3.8)	0.102
Embarrassment	3,6 (3.1–4.0)	3.5 (2.6–4.0)	0.142

CRT chemoradiotherapy, RP resting pressure, SP squeeze pressure, RAIR rectoanal inhibitory reflex, FIQL fecal incontinence quality of life scale

Discussion

Efforts to improve outcomes for the treatment of rectal cancer continued with adjuvant and neoadjuvant CRT after the introduction of TME. Randomized trials have demonstrated improved oncological outcomes and lower toxicity of preoperative CRT [1, 12]. Administration of preoperative CRT may also lead to an increase in the number of sphincter-saving procedures performed because the tumor size is reduced before surgery [1, 13, 14]. Both preoperative CRT and surgery can impair anorectal functions and may adversely affect the patient's QoL especially for deep-sated

tumors. Health-related QoL is an important consideration when evaluating the efficacy of treatment. In our study, we aimed to assess the effects of preoperative CRT on anorectal functions and patients QoL.

The main pathogenesis for impairment of anorectal functions with pelvic RT is the irradiation of the anal canal. Irradiation may damage the myenteric plexus and inhibit the impulse conduction, or it may directly damage the anal sphincter muscles and cause fibrosis [9, 15–17]. The long-term effects of postoperative RT on anorectal functions have been studied in a randomized study where patients with resectable rectal cancer were randomized to surgery

Table 3 Immediate effects of preoperative CRT on anorectal functions and QoL

	Before CRT	Immediately after CRT	<i>P</i> value
Anorectal manometry			
Mean RP, mean ± SD, mmHg	60±7	53±9	0.002
Maximum RP, mean ± SD, mmHg	82±14	73±15	0.000
Mean SP, mean ± SD, mmHg	115±23	104±27	0.000
Maximum SP, mean ± SD, mmHg	169±28	146±32	0.000
Rectal first sensation (ml)	41 (27–53)	39 (23–50)	0.094
Maximum tolerable volume (ml)	136 (105–167)	128 (100–170)	0.073
RAIR (positive/negative)	30/1	28/2	0.487
Rectoscopy score, median (range)	0	1	0.083
Wexner score, median (range)	0	5	0.004
FIQL score, mean (range)			
Lifestyle	3.9	3.3	0.015
Coping/behavior	3.9	3.2	0.011
Depression/self perception	3.8	3.7	0.008
Embarrassment	3.8	3.4	0.032

CRT chemoradiotherapy, RP resting pressure, SP squeeze pressure, RAIR rectoanal inhibitory reflex, FIQL fecal incontinence quality of life scale.

Table 4 Studies comparing the effects of preoperative long-course CRT on anorectal functions in patients underwent surgery with or without preoperative CRT

Author	Year	n	Groups	Evaluation		
				Anorectal manometry	Wexner score	F/U (months)
Gervaz et al. [22]	2001	42	Preoperative CRT (50.4 Gy): n=19; surgery: n=23	Postoperative RPs were lower in preoperative CRT group (between groups).	NA	2–3
Ammann et al. [16]	2003	50	Preoperative CRT (45 Gy): n=28; surgery: n=22	No significant difference in surgery group; MRP and MTV decreased significantly in preoperative CRT group (preoperative vs. postoperative)	NA	13
Pietsch et al. [23]	2007	39	Preoperative CRT (50.4 Gy): n=12; surgery: n=27	No significant difference between groups	No significant difference between groups	3–6

F/U follow-up, CRT chemoradiotherapy, RPs resting pressures, MRP mean resting pressure, NA not applicable

alone or surgery combined with postoperative RT [18]. They reported worse anorectal dysfunction, measured as stool frequency, fecal urgency, and fecal incontinence in patients who had postoperative RT than that of patients who had received no adjuvant therapy. Although this was a randomized study with a long observational period, in all cases, sphincters were irradiated which may lead to an overemphasis on the risk of anorectal dysfunction. Also the irradiation of the neorectum may contribute to the negative results in patients who received postoperative RT. The functional effects of irradiation on anorectal function are dose dependent [19]. The effects of a preoperative short-course RT administration on the risk of developing fecal incontinence in patients who underwent LAR have been studied in randomized and nonrandomized studies [15, 20, 21]. Pollack et al. [15] concluded that short-course RT, including the anal sphincters, impairs anorectal function. There were no significant differences in QoL scores between irradiated and nonirradiated patients in Swedish and Dutch trials [15, 20] whereas Murata et al. [21] reported worsened QoL in irradiated patients. Currently, the effects of preoperative long-course radiation on anorectal function have not been studied in a randomized trial. Results of three studies assessing the effects of preoperative long-course CRT on anorectal functions in patients who underwent surgery with or without preoperative CRT were summarized in Table 4 [16, 22, 23]. There are several other studies evaluating postoperative anorectal function and/or QoL in patients who underwent preoperative long-course CRT. Wagman et al. [24] and Lim et al. [6] reported worsened incontinence scores and Tjandra et al. [25] reported impaired QoL in patients who underwent preoperative long-course CRT. In our study, we observed an impairment of the Wexner score at the postoperative long-term evaluations in patients who underwent preoperative

CRT; which did not significantly impaired the patients QoL assessed by FIQL questionnaire.

Total mesorectal excision and anastomosis can lead to anterior resection syndrome which is characterized by urgency, frequent bowel movements, and some degree of fecal incontinence. Impairment of innervation by pelvic nerve injury and loss of rectal reservoir function after surgery may contribute to the alteration of continence and QoL. We demonstrated that only TME results in reduction of sphincter pressures without any significant change in the Wexner score and patients' QoL. Addition of preoperative CRT to TME results in reduction of both resting and squeeze anal canal pressures and Wexner continence score without any significant effect on patients QoL. As our two groups are not balanced for tumor localization and stage, those effects may not only due to preoperative CRT. We performed additional analysis excluding upper rectal tumors in surgery group. The only difference was between Wexner scores; there was no significant difference between groups.

The disappearance of RAIR and decrease in maximum-tolerated volume may result in increased stool frequency and may contribute to the negative effects of sphincter impairment on QoL in patients who underwent preoperative CRT. Our results showed lower MTVs and RAIR disappearance in the preoperative CRT group during postoperative evaluations, but the differences between the surgery and preoperative CRT groups were not significant.

Lim et al. and Ammann et al. investigated the relation between the tumor localization and effects of preoperative CRT on anorectal function, and Ammann et al. showed impairment of MRP, MTV, and FS in patients with middle rectal tumors. In our study, we only observed a significant impairment of MRP during preoperative CRT in patients with middle rectal cancer. These results may contribute to

the hypothesis of Varma et al. [9] proposing that the internal anal sphincter, because of its fixed anatomical position and small volume, is particularly susceptible to the effects of irradiation.

In conclusion, both TME and CRT may adversely affect the anorectal function to some degree. Selection of the patients who will benefit from neoadjuvant therapy, identifying the patients with a high risk of developing functional problems, avoiding unnecessary irradiation of the anal sphincters, and the acceptance of modern three-dimensional conformal RT techniques may all help to improve functional outcomes for the treatment of rectal cancer.

One goal of surgeons and oncologists who work with rectal cancer patients is to improve their health-related quality of life issues. Therefore, as new technological innovations in this field move toward even more advanced “state of the art” capabilities, weighing the possible oncological outcomes for patients along with the potential deleterious effects on functional results will continue to present a formidable challenge.

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