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Anorectal Function and Quality of Life in Patients with Early Stage Rectal Cancer Treated with Chemoradiation and Local Excision

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Abstract

Background—Little is known about anorectal function and quality of life after chemoradiation followed by local excision, which is an alternative to total mesorectal excision for selected early rectal cancer patients.

Objective—Prospectively assess anorectal function and health-related quality of life of T2N0 rectal cancer patients treated with an alternative approach

Design—Prospective phase II trial

Settings—Multicentric study (ACOSOG trial Z6041)

Interventions—Patients with stage cT2N0 rectal adenocarcinomas were treated with an oxaliplatin/capecitabine-based chemoradiation regimen followed by local excision.

Main Outcome Measure—Anorectal function and quality of life were assessed at enrollment and 1 year postoperatively with the Fecal Incontinence Severity Index, Fecal Incontinence Quality of Life scale and Functional Assessment of Cancer Therapy-Colorectal questionnaire. Results were compared, and multivariable analysis was performed to identify predictors of outcome.

Results—Seventy-one (98%) patients were evaluated at enrollment and 66 (92%) at 1 year. Compared to baseline, no significant differences were found on Fecal Incontinence Severity Index scores at 1 year. Fecal Incontinence Quality of Life results were significantly worse in the lifestyle ($p<0.001$), coping/behavior ($p<0.001$) and embarrassment ($p=0.002$) domains. There were no

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PBL: conception and design, drafting the article, final approval

LAR: conception and design, acquisition of data, drafting the article, final approval

XWC: conception and design, acquisition of data, drafting the article, final approval

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differences in the Functional Assessment of Cancer Therapy overall score, but the physical well-being subscale was significantly worse and emotional well-being was improved after surgery. Treatment with the original chemoradiation regimen predicted worse depression/self-perception and embarrassment scores in the Fecal Incontinence Quality of Life, and male sex was predictive of worse scores in the Functional Assessment of Cancer Therapy overall score and trial outcome index.

Limitations—Small sample size, relatively short follow-up and absence of information before cancer diagnosis.

Conclusion—Chemoradiation followed by local excision had minimal impact on anorectal function 1 year after surgery. Overall quality of life remained stable, with mixed effects on different subscales. This information should be used to counsel patients about expected outcomes.

Keywords

rectal cancer; quality of life; chemoradiation; anorectal function; local excision

Introduction

Radical surgery with total mesorectal excision (TME), the standard of care for patients with early rectal cancer,¹ is associated with significant morbidity and anorectal functional impairment that may significantly reduce health-related quality of life (HRQOL).^{2–4} Functional impairment is especially common among patients with distal rectal tumors who undergo either an abdomino-perineal resection with a permanent colostomy or a low colorectal or coloanal anastomosis. Such low anastomoses are often associated with particularly distressing symptoms, including defecatory urgency, clustering of bowel movements, stool fragmentation, and fecal incontinence.⁵

In patients with early stage rectal cancers limited to the bowel wall, organ-preserving management approaches such as chemoradiation (CRT) and local excision (LE) are potentially both curative and effective in avoiding the sequelae and morbidity of TME.^{6, 7} Local excision has a limited impact on AF,⁸ but CRT administered after TME has been shown to impair AF compared with TME alone.⁹ By extrapolation, there is a possibility that CRT may also affect AF in patients who undergo LE. Currently, prospective high quality data on AF and HRQOL in patients treated with preoperative CRT followed by LE are lacking.

The ACOSOG Z6041 phase II trial investigated the outcomes of neoadjuvant CRT with a capecitabine/oxaliplatin regimen followed by LE in patients with stage cT2N0 rectal cancer. The results of the study's primary end-point of 3-year disease-free survival have been recently published. Oncologic outcomes were comparable to those of patients in previously published series who had tumors of a similar stage that were treated with TME.¹⁰ Whereas our previous report included only a summary of HRQOL and AF results, here we report the full HRQOL and AF data from patients included in this trial, with comparison of results at baseline to the data obtained from postoperative assessment at 1 year.¹⁰

Methods

The study design, inclusion criteria and treatment interventions, as well as pathological, surgical and oncological outcomes of the Z6041 Trial have been reported previously.^{10,11} In summary, the study enrolled patients with rectal adenocarcinoma, staged as cT2N0 via endorectal ultrasound (ERUS) or endorectal-coil MRI, and with tumors that were located within 8 cm of the anal verge, were less than 4 cm in maximal diameter, and occupied less than 40% of the rectal circumference. Initially, eligible patients underwent neoadjuvant CRT with a total radiation dose of 50.4 Gy or 54 Gy and chemotherapy consisting of capecitabine and oxaliplatin (original dose group). Because of an unfavorable toxicity profile, neoadjuvant treatment was adjusted during the study; the revised dose group received a reduced dose of external beam radiotherapy (from 54 Gy to 50.4 Gy) and capecitabine (from 825 mg/m² on days 1–14 and 22–35 to 725 mg/m² twice a day, 5 days a week, for 5 weeks). Patients were scheduled to undergo either conventional transanal excision (TAE) or transanal endoscopic microsurgery (TEM), at the surgeon's discretion, within 4 to 8 weeks after CRT completion. Adverse events (AEs) related to CRT or surgery were recorded and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.¹² After surgery, tumors were staged according to American Joint Committee on Cancer criteria.¹³ Patients with ypT0–T2 N0 tumors and negative margins were followed. Patients with ypT3 tumors, positive nodes, or positive margins were treated at the discretion of the supervising physician, and alternative surgical options, including TME, were considered. Patients were clinically evaluated every 4 months for 3 years, and subsequently every 6 months for the following 2 years. Proctoscopy and ERUS were performed at the physician's discretion. Colonoscopy was performed 3 years after initial surgery.

AF and HRQOL were evaluated before treatment at the time of enrollment (baseline) and at 12 months after surgery. AF was assessed using the Fecal Incontinence Severity Index (FISI), a validated instrument that addresses the frequency of leakage of gas, mucus, liquid, or solid stool, with higher scores indicating worse anorectal function.¹⁴ HRQOL was evaluated using two instruments. The first was the Functional Assessment of Cancer Therapy-Colorectal (FACT-C), a validated questionnaire that contains 34 items related to 5 subscales: physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), functional well-being (FWB; 7 items), and the colorectal cancer subscale (CCS; 7 items). A higher score reflects better HRQOL and overall function. PWB, SWB and CCS were used to calculate the Trial Outcome Index (TOI), which better reflects the true impact of the treatment intervention.¹⁵ The second HRQOL-validated instrument was the Fecal Incontinence Quality of Life Scale (FIQL), which is composed of 29 items evaluating four subscales: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items). Scores for each item range from 0 (worst) to 4 (optimal). Scores are calculated as the mean numeric response to all items within each scale, with a maximum possible overall score of 4.¹⁶

Descriptive summary statistics of HRQOL and AF at baseline and at 12 months following surgery were compared using Wilcoxon signed-rank tests. Minimally important differences in FACT-C scores were calculated according to previously reported methods. Differences of

2–3 points in the CCS, 4–6 in TOI, and 5–8 in the overall FACT-C score were considered clinically relevant.¹⁷ Multivariate logistic regression analyses were performed using variables considered relevant to outcome, adjusting for baseline scores. The variables considered were age, sex, pathologic complete response status (ypT0), treatment dose (original vs. revised), surgical approach (TAE vs. TEM), tumor distance from the anal verge, and adverse events during CRT or postoperatively. All statistical analyses was performed with SAS software (version 9.2; SAS Institute Inc., Cary, NC); p values <0.05 were considered statistically significant.

Results

Seventy-nine eligible patients were accrued for the trial and started treatment. The patient disposition and trial profile has already been published.¹⁰ Seven of 79 patients did not have local excision (n=2) or ultimately underwent TME for high-risk pathologic findings (n=5). The remaining 72 patients were treated with CRT and local excision and comprise the eligible study cohort.

Of the 72 eligible patients, 71 completed a baseline evaluation of anorectal function and HRQOL and 66 (92%) completed evaluations at 12 months after surgery. Of the 6 patients who did not complete the 12-month postoperative evaluation of AF and HRQOL, 1 patient died (8 months after surgery), 1 refused to complete the evaluation forms, and 4 missed the follow-up appointment and did not reschedule. The median age of those who completed both baseline and 12-month postoperative assessments was 63 years (range, 30–83); 47 patients (66%) were male. Forty-nine patients (69%) were treated with the original treatment dose and 22 (31%) received the revised dose. Thirty-four patients (47%) were found to have no residual tumor cells on pathological exam (ypT0). Forty-six patients (65%) underwent conventional TAE, and 25 (35%) underwent TEM. Overall, 38 patients had at least one grade 3 or higher AE; 34 patients (48%) had at least one grade 3 or higher AE during chemoradiation and 9 patients (13%) had at least one grade 3 or higher in the perioperative period (Table 1). AEs have been described in detail previously.¹¹

At the 12-month postoperative evaluation, no significant change was observed in the overall FIS score and its subdomains compared to baseline scores (Table 2). A waterfall plot analysis shows that the proportion of patients who experienced a deterioration in anorectal function and the proportion of patients who experienced an improvement were similar (Figure 1).

The FIQL showed significantly worse outcomes in the lifestyle, coping/behavior and embarrassment scales. Of note, the depression scale values did not change significantly. A waterfall plot analysis for the four categories of the FIQL questionnaire is shown in Figure 2.

Finally, overall FACT-C scores 1 year after surgery were not significantly different from baseline (p=0.75). While the overall score did not change for the entire group, waterfall plot analyses indicate that half of the patients experienced an improvement and the other half a deterioration (Figure 3). The SWB, FWB and CCS subdomains also showed no significant

difference. There was a statistically significant deterioration in the PWB subdomain (25.2 vs. 23.8, $p=0.03$), while there was a significant improvement in the EWB sub-domain (18.6 vs. 20.1, $p=0.02$). According to previously established minimally important differences, 19 patients (32%) presented a clinically significant decrease in the overall FACT-C score, 23 (38%) in the CCS score of the same questionnaire and 22 (37%) in the TOI. On the other hand, 20 (33%) had clinically significant improvement in the overall FACT-C score, 17 (28%) in the TOI score, and 17 (28%) in the CCS score.

None of the variables analyzed were predictors of a deterioration of the overall FISI score. In both univariate and multivariate analyses, treatment with the original CRT regimen was associated with worse outcomes in the depression/self perception and embarrassment domains of the FIQL questionnaire. Male sex was the only variable associated with worse overall FACT-C score in the univariate and multivariate analyses (Table 3).

Discussion

This study shows that the whole cohort of cT2N0 rectal cancer patients treated with CRT and LE did not experience a significant deterioration in AF as assessed by the FISI score 1 year after surgery compared to baseline. This is explained by the fact that the proportion of patients who experienced a deterioration on this score was similar to the proportion of patients who had better results. In contrast, patients reported deterioration in all domains of the FIQL questionnaire, except for the depression/self perception domain. Finally, the whole cohort did not report a deterioration in HRQOL measured with the overall FACT-C score; on the basis of this score, the numbers of patients improving and deteriorating were similar. While patients reported deterioration in the PWB subdomain of the FACT-C questionnaire, they also had better scores in the EWB subdomain.

Our findings also indicate that HRQOL may be affected more by the neoadjuvant regimen than by the LE method. A surprising finding of this study was the lack of correlation between the deterioration in the FIQL scores 1 year after CRT and LE without a significant change in the FISI score. This discrepancy may be attributable to differences in the sensitivity of the tools used to assess fecal incontinence.

Anorectal function and HRQOL are important outcomes in all patients treated for rectal cancer. These outcomes are particularly important in patients with early stage tumors who are willing to trade the high cure rates associated with a TME for the better AF and HRQOL that one would expect with organ-preservation approaches. While many studies have reported on AF and HRQOL in patients treated with LE alone, the number of studies investigating these outcomes after CRT and LE is limited.

In our study, mean scores for all domains of the FIQL questionnaire were worse than those reported for patients with early rectal cancers or with benign conditions treated with TEM alone.¹⁸ These differences are to some degree expected, as the combination of radiation and surgery is associated with greater deterioration in bowel function compared to surgery alone in patients with locally advanced rectal cancer treated with sphincter-saving TME.¹⁹ In a 2013 study from Italy, investigators evaluated functional outcomes 1 year after surgery in 23

patients with stage II or III rectal cancer treated with CRT and LE because they were unfit for surgery or achieved a clinical complete response. The investigators reported excellent results, with near-optimal continence and evacuative scores. However, baseline anorectal function was not collected, and the instruments used had not been previously validated.²⁰ In contrast, a more recent study from Poland reported significantly worse AF among 44 patients who underwent preoperative radiation and local excision. In that study, anorectal dysfunction symptoms experienced by patients included incontinence to flatus (51%), clustering of bowel movements (49%), incontinence to loose stools (46%), and urgency (49%). In all, 21% of patients experienced anorectal dysfunction classified as severe. As in the Italian study, anorectal function was assessed using a non-validated questionnaire, and therefore, the results could not be compared to other series. Of note, patients in the Polish study were treated with short-course radiation (SCRT) (25 Gy in 5 fractions over 1 week, followed by a 4 Gy boost in a single fraction). It is possible that the differences in the radiation protocol may explain the differences in outcomes between studies.²¹ A recent phase 1b-II trial investigating the efficacy of SCRT and LE for patients with stage I rectal cancer was closed before completing accrual due to unexpected high-grade short-term toxicity.²² It is possible that the higher-grade short-term toxicity associated with SCRT may result in higher rates of long-term anorectal dysfunction.

A number of studies have investigated AF and HRQOL in rectal cancer patients treated with neoadjuvant therapy and TME, but only a few have used the same validated instruments as those used in the Z6041 study protocol, limiting possibilities for comparisons between studies. In a multinational, prospective study, Fazio et al. assessed bowel function using the FISI questionnaire in patients with low rectal cancer who had a coloanal anastomosis with or without colonic reservoir. FISI scores at 12 months in all arms of Fazio's trial ranged from 35 to 50 and were significantly higher than the score reported by our patients (average of 28).²³ These data suggest that the impact of CRT and LE in fecal continence is less than that of sphincter-saving TME independent of the type of colorectal anastomosis. The FIQL results observed among our patients compare favorably to those of rectal cancer patients treated with CRT and TME, regardless of whether they experienced surgical complications.²⁴ These findings suggest that rectal cancer patients treated with CRT and LE experience a lesser deterioration in AF and HRQOL, as assessed by the FISI and the FIQL scores, than patients treated with TME. A recently published report of patient-reported outcomes from the NSABP R04 trial showed no significant differences in FACT-C at 1 year compared to baseline after neoadjuvant CRT and TME.²⁵ Surprisingly, mean scores in the enrolled patient population did not change significantly from baseline to 1 year after surgery, regardless of whether an abdomino-perineal resection or a sphincter-saving surgery had been performed. NSABP R04 patient scores were also similar to those of the Z6041 patients who were treated with an organ-sparing procedure. This similarity in baseline and 1-year post-treatment scores in both the NSABP and ACOSOG studies suggests that the FACT-C score may lack the sensitivity required to detect differences in rectal cancer patients treated with different procedures.

Our study also revealed that the more toxic original neoadjuvant treatment regimen was independently associated with a worse score in the embarrassment domain in the FIQL. As the dose of oxaliplatin was equivalent in the two regimens, this observation suggests that the

intensity of the neoadjuvant therapy independent of the dose of oxaliplatin may impact QoL both permanently and independently. On the other hand, we can only speculate about the cause of gender differences in the overall score and the TOI of the FACT-C questionnaire. Because of associated toxicities without a significant survival benefit, subsequent trials have abandoned the use of oxaliplatin in the neoadjuvant setting.

The strengths of our study are the prospective data collection before and after treatment, the use of validated questionnaires, and the high rate of questionnaire completion by the patients. However, there are also limitations. First, the number of patients is relatively small. Second, our 1-year follow-up period is relatively short. However, other studies have shown that AF and HRQOL seem to stabilize 1 to 2 years after treatment and deteriorate slowly thereafter.²⁶ Third, baseline scores were obtained when the patients already had a tumor in the rectum. The impact of the tumor on anorectal function and some domains of HRQOL is unknown. This might explain why some patients got better functional and HRQOL outcomes after treatment. Fourth, no objective measurement of bowel function such as anorectal manometry was performed. Although manometric findings often do not correlate with clinical outcomes, such an evaluation may have provided a more accurate assessment of the impact of this treatment modality in anal sphincter function. Finally, AF and HRQL were secondary outcomes of the ACOSOG Z6041 trial. As the information available about ARF and HRQOL for patients with early stage rectal cancer treated with CRT and LE at the time of the study design was limited, no power calculation was performed for these outcomes.

Despite these limitations, the results of this trial should be used to inform presurgical patient discussions regarding expected AF and HRQOL outcomes of this treatment strategy. These findings may also be applied to future trial design for studies comparing outcomes of neoadjuvant CRT and LE with other treatment modalities.

In conclusion, in our cohort of patients with cT2N0 low rectal cancer treated with LE after CRT, the proportion of patients with worse AF according to the FISFI score 1 year after surgery was similar to the proportion of patients with better results. However, during the same postoperative period, patients reported a slight decrease in HRQOL in some domains of the FIQL and FACT-C scoring systems. On the FACT-C questionnaire, two-thirds of the patients undergoing CRT and LE reported the same or better HRQOL 1 year after surgery. Male sex and more aggressive neoadjuvant therapy may have an impact on final HRQOL outcome.

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Figure 1. Waterfall plot of Fecal Incontinence Severity Index (FISI) scores. Absolute change from baseline at 1 year after surgery for every available patient.

Fecal Incontinence Quality of Life: Lifestyle

Fecal Incontinence Quality of Life: Coping/Behavior

Fecal Incontinence Quality of Life: Embarrassment

Fecal Incontinence Quality of Life: Depression/Self-perception

Figure 2.

Waterfall plot of Fecal Incontinence Quality of Life (FIQL) scores. Absolute change from baseline at 1 year after surgery for every available patient. A, FIQL Lifestyle; B, FIQL Coping/Behavior; C, FIQL Embarrassment; D, FIQL Depression/Self-Perception.

FACT-C: Overall

Figure 3.

Waterfall plot of overall Functional Assessment of Cancer Therapy-Colorectal (FACT-C) scores. Absolute change from baseline at 1 year after surgery for every available patient.

Table 1

Demographics, Tumor Characteristics, and Treatment (N=71)

Demographics	
Median Age, in years (range)	63 (30–83)
Sex, n (%)	
Male	47 (66)
Female	24 (34)
Race, n (%)	
White	64 (90.1)
Black	2 (2.8)
Native Hawaiian/Pacific Islander	1 (1.4)
Asian	2 (2.8)
American Indian or Alaska Native	1 (1.4)
Unknown/Not reported	1 (1.4)
ECOG PS, n (%)	
0	63 (88.7)
1	7 (9.9)
2	1 (1.4)
Tumor size, mean (SD)	2.77 (0.76)
Distance from anal verge, mean (SD)	4.83 (1.92)
Treatment	
Original Dose/Revised Dose	49/22
Adverse Events (>= Grade 3)	
CRT Related, n (%)	34 (47.9)
Surgery Related, n (%)	9 (12.7)

CRT: Chemoradiation Therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; SD: Standard Deviation.

Table 2

Baseline and 1-year AF and HRQOL Scores

	Baseline (n=71)	1 Year FU (n=66)	Absolute difference	<i>P-value</i>
FISI, mean (SD)				
Overall	25.9 (16.7)	27.8 (17.1)	1.5 (19.4)	0.67
Gas	7.8 (5.0)	7.9 (4.5)	−0.4 (5.4)	0.80
Mucus	3.1 (4.1)	3.3 (4.1)	0.1 (5.0)	0.63
Liquid Stool	6.1 (6.9)	7.2 (6.4)	1.2 (6.9)	0.33
Solid Stool	9.4 (7.9)	9.8 (7.5)	0.6 (9.9)	0.66
FIQL, mean (SD)				
Lifestyle	3.8 (0.3)	3.4 (0.7)	−0.4 (0.7)	<0.0001
Coping/Behavior	3.7 (0.4)	2.8 (0.8)	−0.8 (0.8)	<0.0001
Depression/Self perception	3.5 (0.5)	3.4 (0.7)	−0.2 (0.6)	0.11
Embarrassment	3.7 (0.4)	3.2 (0.9)	−0.5 (0.9)	0.0002
FACT-C, mean (SD)				
Overall	112.1 (13.5)	109.3 (18.9)	−2.1 (16.0)	0.75
Physical WB	25.2 (3.8)	23.8 (4.7)	−1.2 (3.2)	0.03
Social/Family WB	25.2 (3.5)	23.8 (5.1)	−1.5 (5.4)	0.11
Emotional WB	18.6 (3.9)	20.1 (3.5)	1.7 (3.7)	0.02
Functional WB	22.5 (4.7)	22.3 (5.8)	−0.1 (5.4)	0.79
Colorectal Concerns	20.7 (3.1)	19.6 (3.8)	−0.7 (4.2)	0.11
TOI (PWB +FWB + CCS)	68.3 (9.1)	65.5 (12.4)	−2.2 (9.9)	0.23

CCS: Colorectal Concerns; FACT-C: The Functional Assessment of Cancer Therapy–Colorectal; FIQL: Fecal Incontinence Quality of Life Index; FISI: Fecal Incontinence Severity Index; FWB: Functional Well-Being; PWB: Physical Well-Being; SD: Standard Deviation; TOI: Trial Outcome Index; WB: Well-Being.

Table 3

Predictive factors associated with AF and HRQOL. Univariate and multivariate logistic regression for absolute difference adjusted for baseline scores.

	Univariate adjusted for baseline score		Multivariate adjusted for baseline score	
	β (se)	P-Value	β (se)	P-Value
FISI				
Age $\geq$ 65	6.0784 (4.1017)	0.14	6.4205 (4.6218)	0.17
Sex (Male)	-3.211 (4.2489)	0.45	-5.485 (5.0433)	0.28
Pathologic Complete Response	-1.277 (4.1093)	0.76	-0.866 (4.4662)	0.85
Dose (Original vs. Modified)	1.3715 (4.6568)	0.77	-0.448 (5.1624)	0.93
Surgical approach (TEM vs TAE)	-1.346 (4.3036)	0.75	-0.927 (4.7275)	0.84
Distance from the anal verge	0.3158 (1.1499)	0.78	1.3092 (1.4203)	0.36
Adverse Events	-4.678 (4.1116)	0.26	-5.104 (4.4507)	0.26
FIQL Lifestyle				
Age $\geq$ 65	0.0316 (0.188)	0.87	0.092 (0.2091)	0.66
Sex (Male)	-0.114 (0.1908)	0.55	-0.119 (0.2268)	0.60
Pathologic Complete Response	0.1528 (0.1816)	0.40	0.1994 (0.1975)	0.32
Dose (Original vs. Modified)	-0.375 (0.2002)	0.066	-0.389 (0.2209)	0.08
Surgical approach (TEM vs TAE)	0.186 (0.1899)	0.33	0.1323 (0.21)	0.53
Distance from the anal verge	-0.011 (0.0507)	0.83	-0.018 (0.0621)	0.77
Adverse Events	-0.106 (0.1838)	0.57	-0.023 (0.1987)	0.90
FIQL Coping/Behavior				
Age $\geq$ 65	-0.224 (0.2094)	0.29	-0.14 (0.2381)	0.56
Sex (Male)	0.2024 (0.2142)	0.34	0.2459 (0.2569)	0.34
Pathologic Complete Response	0.1182 (0.2028)	0.56	0.0865 (0.2219)	0.70
Dose (Original vs. Modified)	-0.165 (0.2236)	0.46	-0.089 (0.2448)	0.72
Surgical approach (TEM vs TAE)	0.0972 (0.2109)	0.65	0.0299 (0.2342)	0.90
Distance from the anal verge	0.0222 (0.0551)	0.69	-0.021 (0.0695)	0.77
Adverse Events	-0.075 (0.2057)	0.71	0.0033 (0.2229)	0.99
FIQL Depression/Self perception				
Age $\geq$ 65	0.0626 (0.1588)	0.69	0.156 (0.1639)	0.34
Sex (Male)	-0.162 (0.1625)	0.32	-0.163 (0.1841)	0.38
Pathologic Complete Response	0.0121 (0.1557)	0.94	0.0273 (0.157)	0.86
Dose (Original vs. Modified)	-0.401 (0.1663)	0.019	-0.381 (0.1772)	0.036
Surgical approach (TEM vs TAE)	0.1797 (0.1601)	0.27	0.0992 (0.1677)	0.56
Distance from the anal verge	-0.024 (0.041)	0.57	-0.015 (0.0495)	0.76
Adverse Events	-0.171 (0.1562)	0.28	-0.129 (0.1581)	0.42
FIQL Embarrassment				
Age $\geq$ 65	-0.126 (0.2362)	0.60	-0.051 (0.2379)	0.83
Sex (Male)	0.0616 (0.2432)	0.80	0.123 (0.2763)	0.66

	Univariate adjusted for baseline score		Multivariate adjusted for baseline score	
	β (se)	P-Value	β (se)	P-Value
Pathologic Complete Response	-0.069 (0.2302)	0.76	-0.008 (0.2317)	0.97
Dose (Original vs. Modified)	-0.707 (0.2325)	0.0036	-0.587 (0.2519)	0.0241
Surgical approach (TEM vs TAE)	0.4827 (0.2272)	0.0382	0.3534 (0.2425)	0.15
Distance from the anal verge	-0.022 (0.0621)	0.72	-0.072 (0.074)	0.34
Adverse Events	-0.103 (0.2345)	0.66	-0.025 (0.2307)	0.92
FACT-C overall score				
Age $\geq$ 65	-1.938 (4.1354)	0.64	0.7375 (4.371)	0.87
Sex (Male)	-8.075 (4.1793)	0.06	-10.43 (4.9666)	0.0409
Pathologic Complete Response	-0.598 (4.1332)	0.89	-0.63 (4.2681)	0.88
Dose (Original vs. Modified)	-4.952 (4.6217)	0.29	-4.255 (4.855)	0.38
Surgical approach (TEM vs TAE)	0.7451 (4.291)	0.86	0.3124 (4.5792)	0.94
Distance from the anal verge	-0.556 (1.1008)	0.61	0.4414 (1.3392)	0.74
Adverse Events	-9.861 (3.9225)	0.0148	-7.788 (4.3167)	0.08
FACT-C CCS				
Age $\geq$ 65	0.3643 (1.0909)	0.74	-0.038 (1.2464)	0.98
Sex (Male)	-0.967 (1.1258)	0.39	-0.811 (1.4242)	0.57
Pathologic Complete Response	-0.915 (1.0876)	0.40	-0.892 (1.221)	0.47
Dose (Original vs. Modified)	1.3011 (1.22)	0.29	1.3385 (1.3783)	0.34
Surgical approach (TEM vs TAE)	-0.166 (1.141)	0.88	0.3071 (1.3109)	0.82
Distance from the anal verge	-0.153 (0.2978)	0.61	0.0064 (0.3852)	0.99
Adverse Events	-0.97 (1.0867)	0.37	0.0785 (1.2417)	0.95
FACT-C TOI				
Age $\geq$ 65	0.5792 (2.5902)	0.99	1.429 (2.7474)	0.61
Sex (Male)	-5.453 (2.6011)	0.0405	-6.538 (3.111)	0.0407
Pathologic Complete Response	-0.78 (2.5612)	0.76	-0.628 (2.6448)	0.81
Dose (Original vs. Modified)	-2.337 (2.9379)	0.43	-2.069 (3.0603)	0.50
Surgical approach (TEM vs TAE)	0.1677 (2.6824)	0.95	0.2996 (2.8577)	0.92
Distance from the anal verge	-0.522 (0.6833)	0.45	0.1585 (0.8295)	0.85
Adverse Events	-5.878 (2.4608)	0.0202	-4.739 (2.6884)	0.08

CCS: Colorectal Concerns; FACT-C: The Functional Assessment of Cancer Therapy–Colorectal; FIQL: Fecal Incontinence Quality of Life Index; FISI: Fecal Incontinence Severity Index; TAE: Transanal Excision; TEM: Transanal Endoscopic Microsurgery; TOI: Trial Outcome Index.