Quality of Life in Rectal Cancer Patients After Chemoradiation

ORIGINAL CONTRIBUTION

Quality of Life in Rectal Cancer Patients After Chemoradiation: Watch-and-Wait Policy Versus Standard Resection – A Matched-Controlled Study

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BACKGROUND: Fifteen to twenty percent of patients with locally advanced rectal cancer have a clinical complete response after chemoradiation therapy. These patients can be offered nonoperative organ-preserving treatment, the so-called watch-and-wait policy. The main goal of this watch-and-wait policy is an anticipated improved quality of life and functional outcome in comparison with a total mesorectal excision, while maintaining a good oncological outcome.

OBJECTIVE: The aim of this study was to compare the quality of life of watch-and-wait patients with a matched-controlled group of patients who underwent chemoradiation and surgery (total mesorectal excision group).

DESIGN: This was a matched controlled study.

SETTINGS: This study was conducted at multiple centers.

PATIENTS: The study population consisted of 2 groups: 41 patients after a watch-and-wait policy and 41 matched patients after chemoradiation and surgery. Patients were matched on sex, age, tumor stage, and tumor height. All patients were disease free at the moment of recruitment after a minimal follow-up of 2 years.

MAIN OUTCOME MEASURES: Quality of life was measured by validated questionnaires covering general quality of life (Short Form 36, European Organization for Research and Treatment of Cancer QLQ-C30), disease-specific total mesorectal excision (European Organization for Research and Treatment of Cancer QLQ-CR38), defecation problems (Vaizey and low anterior resection syndrome scores), sexual problems (International Index of Erectile Function and Female Sexual Function Index), and urinary dysfunction (International Prostate Symptom Score).

RESULTS: The watch-and-wait group showed better physical and cognitive function, better physical and emotional roles, and better global health status compared with the total mesorectal excision group. The watch-and-wait patients showed fewer problems with defecation and sexual and urinary tract function.

LIMITATIONS: This study only focused on watch-and-wait patients who achieved a sustained complete response for 2 years. In addition, this is a study with a limited number of patients and with quality-of-life measurements on nonpredefined and variable intervals after surgery.

CONCLUSIONS: After a successful watch-and-wait approach, the quality of life was better than after

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chemoradiation and surgery on several domains. However, chemoradiation therapy on its own is not without long-term side effects, because one-third of the watch-and-wait patients experienced major low anterior resection syndrome symptoms, compared with 66.7% of the patients in the total mesorectal excision group. See **Video Abstract** at http://links.lww.com/DCR/A395.

KEY WORDS: Quality of life; Radiation oncology; Rectal cancer; Rectal surgery; Surgical oncology; Watch-and-wait policy.

Patients with locally advanced rectal cancer are usually treated with neoadjuvant chemoradiation therapy (CRT) and surgery (total mesorectal excision (TME)). In approximately 15% to 20% of the patients, no residual tumor is reported after standard resection; this is called a pathologic complete response.[1] Based on this phenomenon, the watch-and-wait (W&W) policy has been developed.[2,3]

The W&W policy was meant to provide fewer functional problems in patients with rectal cancer. Previous studies have already shown promising oncological results for W&W patients with disease-free survival rates of 81% to 92% and overall survival rates of 97% to 100%.[2–5] Given this good oncological outcome, focus has shifted toward quality of life and functional outcome in studies that evaluate a W&W policy in patients with a complete response.

Total mesorectal excision has been shown to have a negative influence on the quality of life of patients with rectal cancer, with anorectal, sexual, and urinary dysfunction as common long-term sequelae.[6–8] Additional radiotherapy can increase the long-term risk for functional problems, probably because of fibrosis of the rectal wall, anal sphincter, and urogenital organs.[9]

It looks like patients who are treated in a W&W policy will have better functional outcomes and a better quality of life (QoL). However, the effect of radiotherapy alone is not clear yet.

The hypothesis of this study was that W&W patients with a sustained complete response after CRT have a better QoL and functional outcome than patients with rectal cancer who were treated by neoadjuvant CRT followed by TME.

PATIENTS AND METHODS

Patient Selection

The study was approved by the Committee on Medical Research Ethics and all patients provided written informed consent. This study population consisted of 2 groups: W&W patients (W&W group) with a sustained clinical complete response after CRT, and patients who underwent CRT followed by TME (TME group), without recurrences. The inclusion criteria for the W&W policy have been described in previous articles.[3,5] Patients were included in the W&W approach when they had a clinical complete response after CRT. A clinical complete response was described as no palpable tumor at digital rectal examination, no residual tumor and a white scar at endoscopy, negative biopsies from scar at histopathology (biopsy was not mandatory), and no residual tumor and no suspicious lymph nodes on MRI, including diffusion-weighted MRI. After 2 years, the late side effects of CRT were expected to have reached their plateau phase, which is why only patients with at least 2 years of follow-up were included.[10] All patients were disease free at the moment of recruitment. Patients were matched on sex, age, tumor stage, and tumor height, defined as distance from anorectal junction to the lower edge of the tumor on sagittal MRI.

Exclusion criteria were: preexistent functional problems of the pelvic floor, more extensive surgery than TME for locally advanced rectal cancer (eg, pelvic exenteration), Crohn's disease or ulcerative colitis, and pregnancy.

Questionnaires

Quality of life and pelvic functional outcome were assessed with the Short Form 36 (SF-36) health survey,[11] the European Organization for Research and Treatment of Cancer (EORTC) QLQ-30 questionnaire, version 3.0, Global Quality of Life Score,[12] the EORTC-QLQ-CR38,[13] the Vaizey score,[14] the low anterior resection syndrome (LARS) score,[15] the International Index of Erectile Function (IIEF),[16] the Female Sexual Function Index (FSFI),[17] and the International Prostate Symptom Score (IPSS).[18]

General Health

The SF-36,[11] is a generic QoL questionnaire (Dutch version of the Medical Outcomes Study Short-Form (SF-36)) consisting of 36 questions organized in 9 multi-item scales: physical functioning, physical role functioning, pain, general well-being, vitality, social functioning, emotional role functioning, mental functioning, and health change.

The EORTC-QLQ-C30[12] is a cancer-specific instrument to measure QoL. This questionnaire is subdivided into 5 functional levels (ie, physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and 1 global QoL scale. The scores are calculated into a score range from 0 to 100. A high score for a functional scale represents a high level of functioning. A high score in the symptom scale represents a high level of symptomatology and problems. A high score for the global health status and QoL represents a high QoL.

The EORTC-QLQ-CR38[13] is a colorectal-specific QoL questionnaire and consists of 38 questions. Validity and reliability have been described in Dutch patients with colorectal cancer. The questionnaire is subdivided into 4 functional scales (ie, body image, sexual functioning, sexual enjoyment, and future perspective) and 8 symptom scales (micturition problems, GI tract symptoms, chemotherapy side effects, defecation problems, stoma-related problems, male and female sexual problems, and weight loss). Half of the questions are completed by all patients, whereas the remaining 19 questions are divided into groups of questions relevant for subsamples of patients only (ie, male or female, patient with or without a stoma). These scores are also calculated into a score range from 0 to 100.

Defecation Problems

The Vaizey score[14] is a score to assess fecal incontinence. In this questionnaire, patients are asked to evaluate their defecation pattern of the previous 4 weeks, including questions regarding consistency of stool lost, frequency, and effect on lifestyle. Patients with high scores have more incontinence problems.

The LARS score[15] is a relatively new score evaluating bowel dysfunction after low anterior resection for rectal cancer. The questionnaire consists of 5 questions, including questions about incontinence for flatus and liquid stool, frequency, clustering, and urgency. The range of this score is 0 to 42 and is divided into no LARS (0–20 points), minor LARS (21–29 points), and major LARS (30–42 points).

Sexual Dysfunction

The IIEF and FSFI were used to indicate sexual problems. The IIEF[16] was used to assess male sexual function. In this questionnaire, 15 items are assessed. The questionnaire is subdivided into 5 response domains (erectile function, orgasmic function, intercourse satisfaction, sexual desire, and overall satisfaction). The domain scores are calculated by cumulating the scores of individual items in each domain. Complete erectile dysfunction is defined as an erectile function domain score <10, and partial erectile dysfunction as a score between 10 and 17.

The FSFI[17] is a questionnaire consisting of 19 items and has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions of sexual function in women. A higher score is related to more sexual problems.

Urinary Dysfunction

The IPSS[18] is a validated questionnaire to assess problems of the urinary tract. Officially, this score is used for patients with benign prostate hypertrophy to assess bladder function, but because of the lack of an alternative, this questionnaire seems the best option. The IPSS is subdivided into 7 items, which include incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Quality of life is also evaluated in this questionnaire. The range of this score is 0 to 35 and is divided into mild symptoms (0–7 points), moderate symptoms (8–19 points), and severe symptoms (20–35 points).

According to all questionnaire manuals, the missing values were dealt with as follows: if there was a missing value, the scale was considered missing.

Statistical Analysis

Baseline characteristics for all groups were calculated and compared by use of descriptive analysis. Independent sample *t* tests were used for continuous variables; the χ^2 test was used for categorical variables.

Differences in QoL between the 2 groups were analyzed with the Mann-Whitney *U* tests. We considered *p* values of <0.05 as statistically significant. Data were analyzed in SPSS for windows (version 22.0, SPSS, Chicago, IL).

RESULTS

Study Population

Of the 56 eligible W&W patients, 41 signed a written informed consent. This resulted in a response rate of 73.2% (see Fig. 1). These 41 W&W patients were matched with 41 patients who underwent CRT and TME (TME group). Patient characteristics are shown in Table 1.

General Health

Questions of the SF-36 were completed for all items in 93% of the responders. The W&W group reported better physical function (W&W: 46.6 vs TME: 34.13, $p = 0.02$), physical role (W&W: 47.4 vs TME: 34.5, $p = 0.01$), and emotional role (W&W: 45.3 vs TME: 36.6, $p = 0.004$) compared with the TME group. However, the TME group reported significantly better general health (W&W: 34.9 vs TME: 46.9, $p = 0.02$) compared with the W&W group, according to the SF-36 questionnaire. All results are shown in Figure 2.

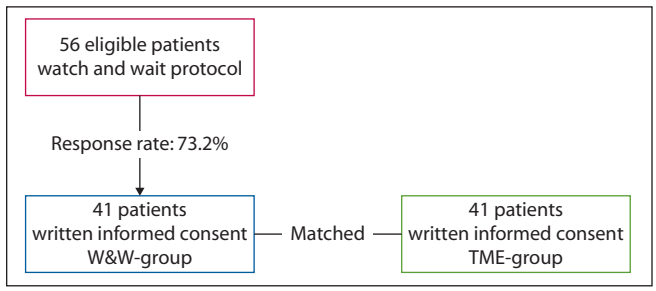

FIGURE 1. Study population. TME = total mesorectal excision; W&W = watch and wait.

TABLE 1. Patient characteristics

Variable	*CRT + TME (n = 41)*	*CRT + W&W (n = 41)*
Sex, n (%)		
Male	28 (68.3)	29 (70.7)
Female	13 (31.7)	12 (29.3)
Mean age, y (SD)	63.8 (20.2)	64.1 (11.8)
Mean tumor height, cm (SD)	3.6 (3.4)	3.5 (3.1)
T stage, n (%)		
cT2	7 (17.1)	8 (19.5)
cT3	33 (80.5)	32 (78.0)
cT4	1 (2.4)	1 (2.4)
Type of surgery, n (%)		
LAR	35 (85.4)	
APR	6 (14.6)	

CRT = chemoradiation therapy; TME = total mesorectal excision; W&W = watch and wait; LAR = low anterior resection (type of TME); APR = abdominal peritoneal resection (type of TME).

Questions of the EORTC-QLQ-C30 were completed for all items in 95% of the responders. The W&W group showed better physical functioning (W&W: 46.3 vs TME: 35.8, $p = 0.04$), role functioning (W&W: 46.4 vs TME: 35.7, $p = 0.04$), and cognitive function (W&W: 47.5 vs TME: 35.5, $p = 0.02$) compared with the TME group according to the EORTC-QLQ-C30 questionnaire. Also, the W&W group had significantly fewer financial difficulties (W&W: 34.7 vs TME: 48.6, $p = 0.001$) and a better global health status (W&W: 45.9 vs TME: 35.9, $p = 0.05$). The W&W group had a lower pain score than the TME group (36.8 vs 44.2 points, $p = 0.08$).

Questions of the EORTC-QLQ-CR38 were completed for all items in 92% of the responders. On the EORTC-QLQ-CR38, the W&W group showed a significantly better body image (W&W: 36.0 vs TME: 46.1, $p = 0.05$) compared with the TME group. The W&W group had a better QoL in the last week (W&W: 45.8 vs TME: 36.1, $p = 0.05$) compared with the TME group. All results are shown in Figures 3 and 4.

Defecation Problems

The Vaizey and LARS scores were completed for all items in 81% and 70% of the responders. Patients treated with an abdominal perineal resection were not able to fill in these questionnaires. The TME group reported significantly more fecal incontinence according to the Vaizey score (W&W: 28.8 vs TME: 39.8, $p = 0.02$) and LARS score (W&W: 26.0 vs TME: 35.5, $p = 0.04$). All results are shown in Figure 5. In both groups, there are patients with major LARS symptoms (W&W: 35.9% vs TME: 66.7%).

Based on the EORTC-QLQ-CR38, the W&W group had significantly fewer defecation problems (W&W: 16.1 vs TME: 25.8, $p = 0.01$).

Sexual Dysfunction

The FSFI and IIEF were completed for all items in 40% and 97% of the responders. There were no significant differences between the W&W and TME groups regarding sexual function in both male and female patients based on the IIEF and FSFI.

The EORTC-QLQ-CR38 showed a better sexual function in W&W patients (W&W: 44.0 vs TME: 33.9, $p = 0.04$) compared with the TME group.

Urinary Tract Dysfunction

The IPSS questionnaires were completed for all items in 98% of the responders. The W&W group reported fewer intermittency problems (W&W: 22.7 vs TME: 34.8, $p = 0.002$) and had a better QoL (W&W: 22.1 vs TME:

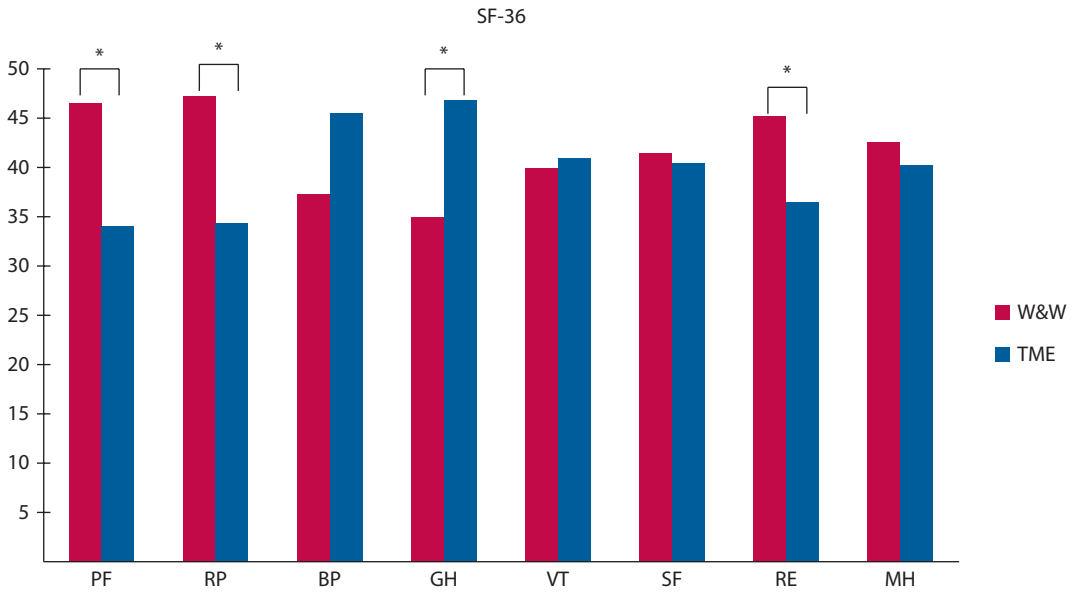

FIGURE 2. SF-36. *Significant result. PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health; SF-36 = Short Form 36; TME = total mesorectal excision; W&W = watch and wait.

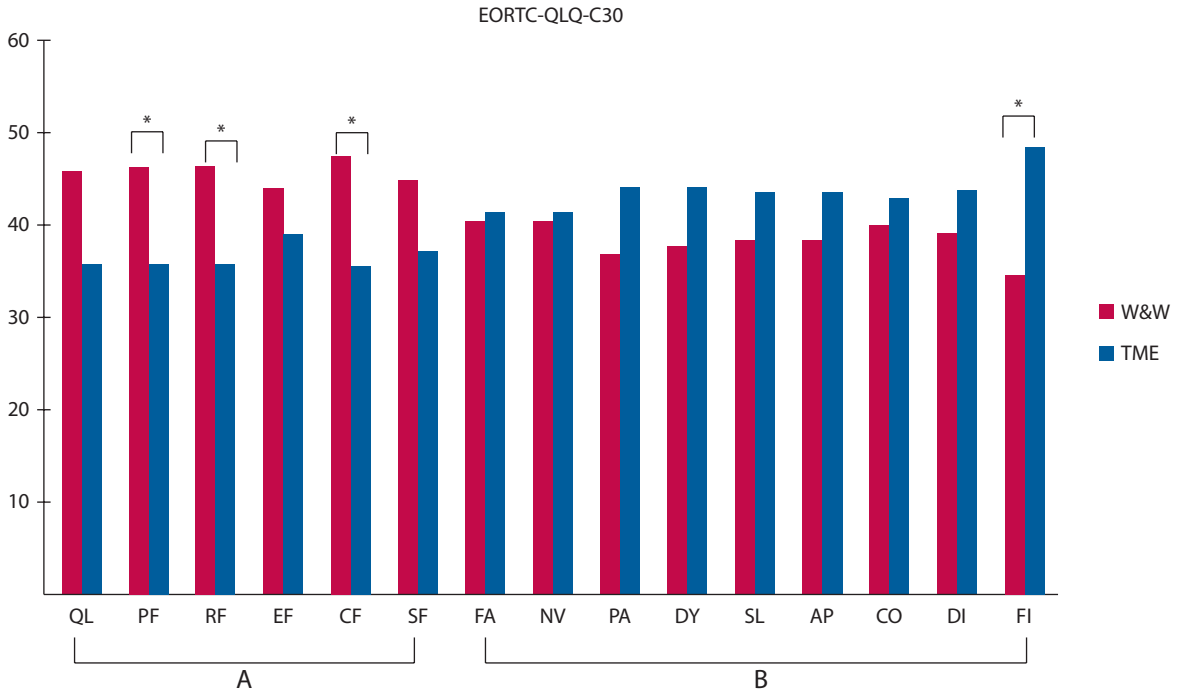

FIGURE 3. EORTC-QLQ-C30. *Significant result. A = functional scales, higher scores mean better results; B = symptom scales, lower scores mean better results; QL = global health status; PF = physical functioning; RF = role functioning; EF = emotional functioning; CF = cognitive functioning; SF = social functioning; FA = fatigue; NV = nausea and vomiting; PA = pain; DY = dyspnea; SL = insomnia; AP = appetite loss; CO = constipation; DI = diarrhea; FI = financial difficulties; EORTC = European Organization for Research and Treatment of Cancer; TME = total mesorectal excision; W&W = watch and wait.

34.1, $p = 0.003$). A trend was seen in 2 subgroups of the IPSS questionnaire. Patients in the TME group had more reports of a weak stream (W&W: 24.9 vs TME: 32.4, $p = 0.07$) and strain (W&W: 25.2 vs TME: 32.0, $p = 0.06$). Patients in the W&W group had mild symptoms (mean: 5.8); the TME group had moderate symptoms (mean: 10.6). All results are shown in Figure 6.

DISCUSSION

This matched controlled study showed that W&W patients with a sustained clinical response after chemoradiation had a better QoL than patients who underwent CRT and TME. Watch-and-wait patients had better scores regarding physical function, general health, cognitive function, and their financial situation. Additionally, the W&W group reported a better body image score, fewer defecation problems, and fewer urinary tract problems than the TME group.

Regarding general QoL, W&W patients scored better in almost every subgroup, with the exception of general health according to the SF-36 questionnaire. A possible explanation is that patients in the W&W group might feel more insecure because the rectum has not been resected. As a result, these patients might still experience a regrowth, a fact of which they are reminded at the more frequent and intensive follow-up visits and examinations compared with the less frequent follow-up of TME patients.

Until now, there have been limited studies are regarding QoL in W& W patients.[1,3,5,19] In the study of Habr-Gama, W&W patients were compared with patients treated with CRT followed by local excision.[19] On manometric assessment, W&W patients had better resting pressure and maximal squeeze pressure than patients who underwent local excision. On all domains of the questionnaires, there were fewer defecation problems in the W&W group than in the local excision group. To our knowledge, there are no studies comparing QoL between patients in a W&W policy and "standard treatment" with CRT and TME.

In the present study, W&W patients had fewer defecation problems than TME patients. Of the patients in the TME group, 66.7% had major LARS symptoms. This finding is in line with the literature showing a relatively high incidence of defecation problems after neoadjuvant CRT followed by TME, compared with TME only.[9,20–23] Although they did not undergo a resection, one-third of the patients in the W&W group still reported major LARS problems. This result can be explained by the fact that pelvic radiotherapy may induce long-term GI morbidity. Studies have shown that up to half of all patients undergoing pelvic radiotherapy for various tumors will develop late radiation-induced GI changes that impair their QoL.[24] Because some symptoms overlap, either caused by TME or pelvic radiation,[25] high LARS scores may be due in part to radiation-induced changes.

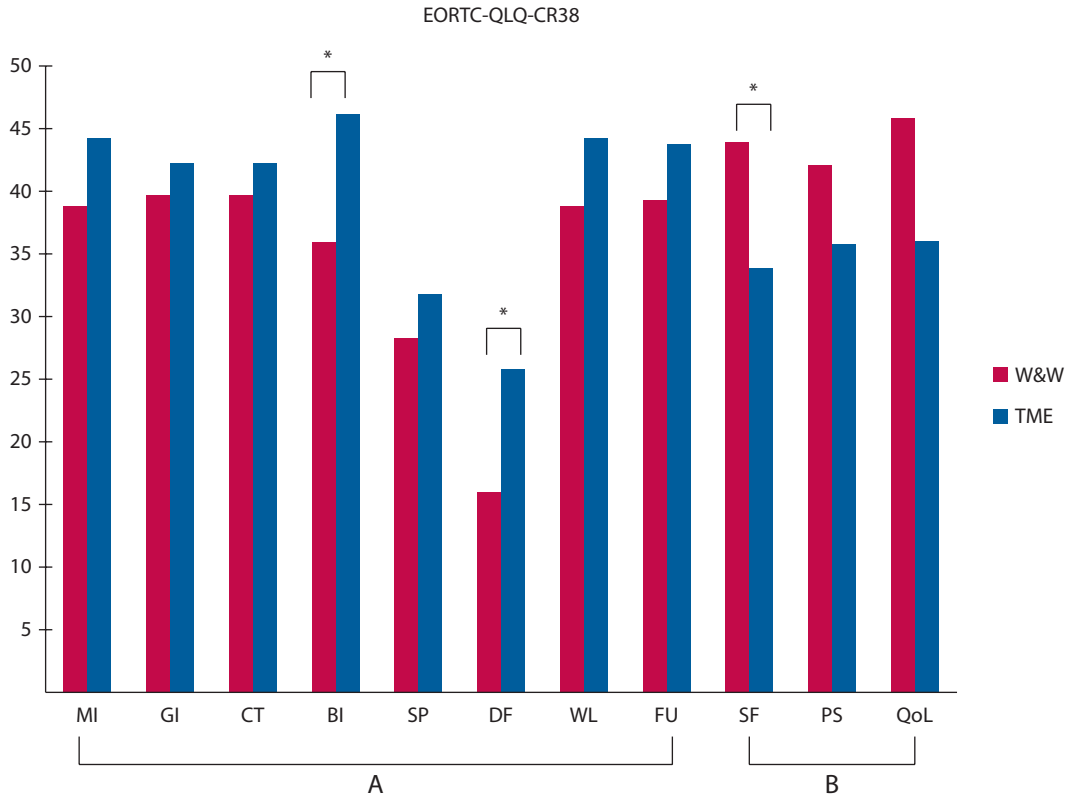

FIGURE 4. EORTC-QLQ-CR38. *Significant result. A = functional scales, lower scores mean better results; B = symptom scales, higher scores mean better results; MI = micturition problems; GI = GI problems; CT = chemotherapy side effects; BI = body image; SP = sexual problems; DF = defecation problems; WL = weight loss; FU = future; SF = sexual function; PS = pleasure in sex; QoL = quality of life in last month; EORTC = European Organization for Research and Treatment of Cancer; TME = total mesorectal excision; W&W = watch and wait.

Sexual dysfunction is a common problem after rectal cancer surgery.[8,26] Our study showed no significant differences between the 2 groups regarding sexual function in both male and female patients based on the IIEF and FSFI. In male patients, a trend of fewer erectile function problems is seen in the W&W group. No differences were seen in female patients. Because of the low response rate on both questionnaires, no meaningful conclusions regarding sexual function after W&W can be drawn yet. The low response rate of female patients is in accordance with previous studies that reported on sexual function after rectal cancer treatment, and is thought to be due to the fact that women are less likely to volunteer information to their physician regarding sexual problems because of anxiety.[27–30]

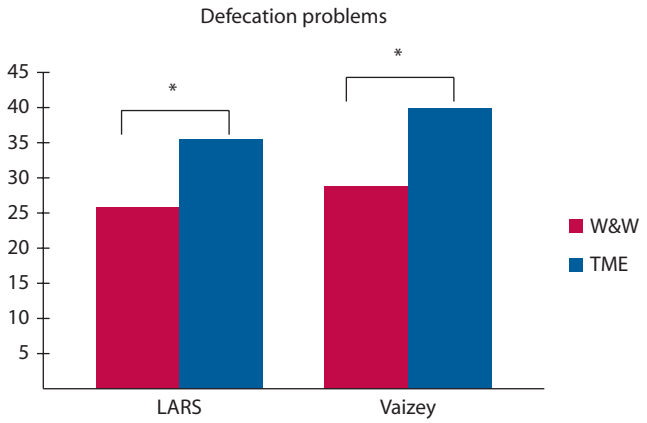

FIGURE 5. Defecation problems. *Significant result. LARS = low anterior resection syndrome; TME = total mesorectal excision; W&W = watch and wait.

Regarding urinary dysfunction, patients in the W&W group reported mild symptoms, whereas patients in the TME group had moderate symptoms. Rectal cancer surgery is associated with long-term urinary dysfunction, such as incontinence and difficulty in bladder emptying.[26,28,31] Known risk factors are perioperative blood loss, autonomic nerve damage, low rectal cancer, lymph node involvement, and preoperative urinary dysfunction.[31,32]

One of the mechanisms for functional problems after surgery is damage to the autonomic nervous system. Even optimal autonomic nerve–preserving surgical techniques could lead to sexual dysfunction because of intraoperative stretching or neuropraxia rather than nerve transection.[33–35] The male sexual function requires intact sympathetic and parasympathetic nervous systems for both erection and ejaculation.[30] The female sexual function is much less well understood. Theoretically, both sympathetic and parasympathetic stimulations are

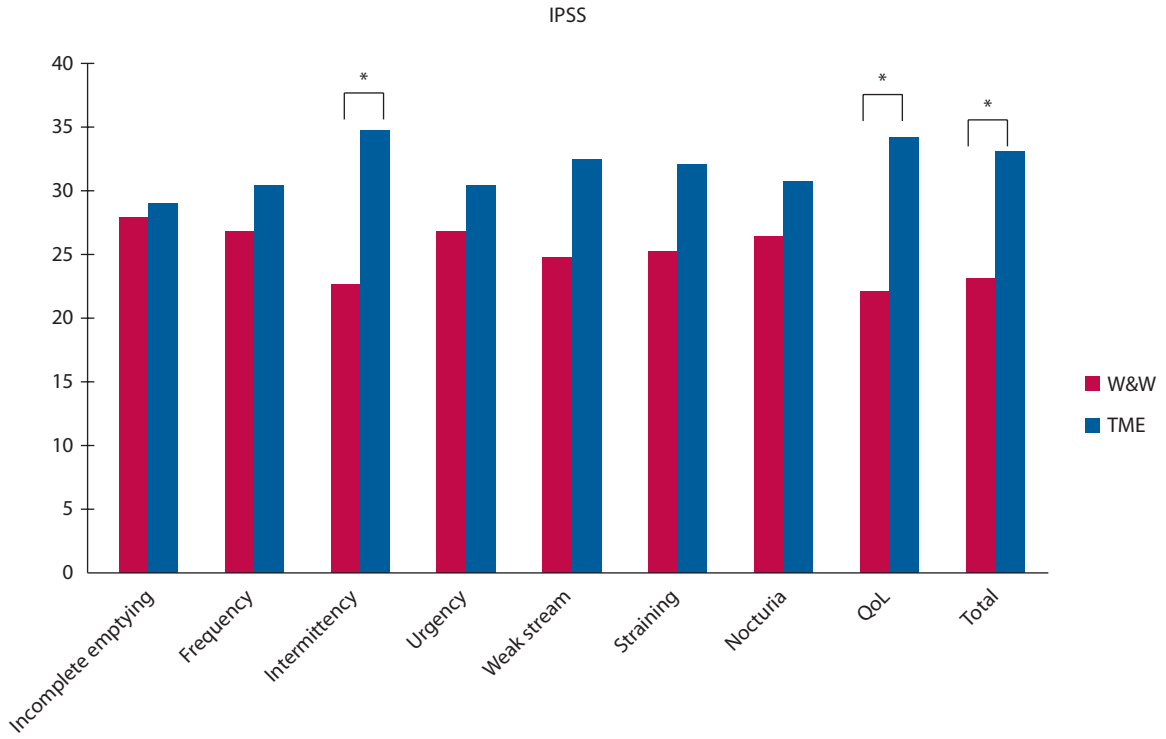

FIGURE 6. International Prostate Symptom Score (IPSS). *Significant result. QoL = quality of life in last month; TME = total mesorectal excision; W&W = watch and wait.

responsible for vascular engorgement, which results in vaginal and vulvar lubrication, but the exact mechanism is still unknown.[30] Regarding urinary function, damage to the superior hypogastric plexus and the hypogastric nerves may cause urge incontinence.[36] Adding CRT to surgery may increase the risk of genitourinary dysfunction compared with surgery alone.[28,37] Genitourinary toxicity is a well-known potential result of pelvic irradiation. Late radiation-induced genitourinary toxicity includes symptoms such as dysuria, urgency/frequency, incontinence, erectile dysfunction, infertility, and lubrication problems.[28] The exact mechanism behind radiation-induced genitourinary dysfunction remains unknown, but inflammation, fibrosis, and vascular changes all appear to be of importance.

Regarding cosmetics, the W&W group showed a better body image than the TME group based on the EORTC-QLQ-CR38. Age had no effect on these scores. However, these outcomes are to be expected, because all the patients in the TME group had a temporary or permanent stoma. Literature shows a lower QoL in patients with a stoma.[38,39] Moreover, the patients who had been operated on had to deal with abdominal scars.[40]

Limitations

There are some limitations to our study. The present study focuses on W&W patients who achieved a sustained complete response for 2 years, and therefore misses the 15% of patients in our entire cohort of W&W patients who require surgery for a regrowth. For a complete "intention to treat" understanding of the present QoL results, there should be a correction for the W&W group of approximately 15%. In addition, this is a study with a limited number of patients and with QoL measurements on non-predefined and variable intervals after surgery. Both these issues of "intention to treat" and possible selection bias are addressed in an ongoing prospective study in our center with predefined QoL evaluation intervals.

CONCLUSIONS

In conclusion, patients with a sustained clinical complete response after CRT for rectal cancer who are followed with a W&W policy have a significantly better QoL score on several domains in comparison with patients who undergo a TME after CRT. However, CRT on its own is not without long-term side effects, because one-third of the W&W patients experienced major LARS symptoms, compared with 66.7% of the TME patients. Together with the oncological data, it is important to discuss functional outcome with patients as well. This information may help patients to cope better with postoperative recovery after chemoradiation.

A prospective study with emphasis on functional outcome and QoL at several standard moments during follow-up has been started.

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