Patient-Reported Outcomes After Neoadjuvant Chemoradiotherapy for Rectal Cancer

A Multicenter Prospective Observational Study

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Objective: To prospectively describe patient-reported outcomes (PROs) after preoperative chemoradiotherapy (pCRT) for rectal cancer.

Background: Little evidence is available on PROs after pCRT for rectal cancer.

Patients and Methods: Patients with rectal cancer, candidates to receive pCRT, were enrolled in a multicenter prospective observational trial. Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and its colorectal cancer module (QLQ-CR38), and fecal incontinence and bowel function were evaluated using the fecal incontinence score questionnaire and a set of ad hoc questions. Questionnaires were filled out before CRT (t_0), 2 to 3 weeks after completion of CRT (t_1), and at 6 (t_2) and 12 months (t_3) after surgery. Primary analysis of selected scales included: global quality of life, physical functioning, social functioning, fatigue, body image, future prospective, and gender-related sexual problems.

Results: Of 149 eligible patients, questionnaires were completed in 100%, 95%, 88% and 77% of cases at t_0, t_1, t_2, and t_3, respectively. At t_3, 78% of patients reported stool fractionation and 72% sensation of incomplete defecation. Only 14% of patients had optimal continence. Physical/social functioning, fatigue, and body image showed a decrease just after pCRT and returned to baseline levels at 1 year after treatment. Global quality of life was stable over time. Male sexual problems were greatly impaired throughout the study period ($P < 0.001$) with major clinically meaningful changes between baseline and 1 year after treatment.

Conclusions: These findings add to the body of evidence available regarding pCRT and help clinicians to make more informed treatment decisions.

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Preoperative chemoradiotherapy (pCRT) or short course radiotherapy after total mesorectal excision are now considered standard care for locally advanced mid-low rectal cancer. With this approach, the rate of local recurrence at 5 years has been shown to range between 6% and 8%[1–3]; however, the related toxicity and surgical complications are greatly increased.[1–5] Previous work has shown that pCRT may have potential detrimental effects on rectal capacity, and sphincter and bowel function.[6,7] In addition, both treatment-related side effects and bowel dysfunction have been found to have a negative impact on patient-reported outcomes (PROs).[6,8–18] There is now evidence that PROs in surgical oncology can potentially provide valuable information to further support clinical decision-making by allowing clinicians and patients to make more informed treatment decisions.[19,20] Thus, understanding the patients' perspective in terms of health-related quality of life (HRQOL), symptom burden, and the possible functional limitations of adding pCRT to surgery might provide a more comprehensive picture of the overall treatment effectiveness.

Although studies have been published on PROs after surgery for rectal cancer, the majority of them included patients who did not receive neoadjuvant treatments or who only underwent preoperative radiotherapy.[11–13] The few published studies dealing with patients who received conventional pCRT included a small number of patients or used a retrospective design.[6,10,21]

The main objective of the current study was to prospectively describe key HRQOL issues including symptoms and functional aspects before starting pCRT and over a 1-year period from surgery in patients with mid-low rectal cancer undergoing pCRT after surgery with curative intent. Our research hypothesis was to observe a detrimental effect on various aspects of patient' HRQOL after neoadjuvant therapy and a recovery to baseline levels at the end of the study period.

PATIENTS AND METHODS

Patients and Treatment Modalities

The study was designed as a multicenter prospective observational study. Inclusion criteria were 18 years and older, primary histologically confirmed rectal adenocarcinoma located up to 11 cm from the anal verge, clinical tumor node metastasis stages II to III,[22] Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, no severe comorbidities and planned CRT after a surgery with curative intent. Exclusion criteria included metastatic disease, previous or synchronous colorectal or genitourinary neoplasia, previous surgery or trauma that could affect sphincter function, inflammatory bowel diseases, and previous pelvic irradiation. The pCRT included radiotherapy, delivered using a linear accelerator at a total dose of 45 Gy or more, with conventional fractionation (1.8 Gy/day, 5 sessions a week) and a 3-field or box technique concomitantly with 5-fluorouracil–based chemotherapy administered either by bolus or continuous venous infusion. For surgical treatment, a standard total mesorectal excision was suggested to be performed 4 to 8 weeks after

completion of CRT. The ethics committee approval was obtained from each participating center and all patients provided written informed consent.

Data Collection

At the time of enrolment, each patient received a booklet explaining background, aims, and characteristics of the study. Patients self-reported sociodemographic information, including patient's age and sex, education level, marital status, living arrangements, and employment status. Relevant clinical data were also prospectively collected and included ECOG performance status, type of neoadjuvant therapy and surgery, postoperative complications, pathologic tumor node metastasis stage, and stoma closure.

Patient-reported Outcomes

Fecal Incontinence and Bowel Function

Fecal incontinence was evaluated using the American Medical System (AMS) questionnaire for fecal incontinence,[23] which contains 5 items resulting in 1 fecal incontinence score (FIS), ranging from 0 (*perfect continence*) to 120 (*daily incontinence to solid feces severely compromising life style*). The responses provided data on the frequency of the patient's symptoms over the last 4 weeks, ranging from "never" to "several times daily". Bowel function was assessed with the following ad hoc questions, which included the presence of stool fractionation (never/rarely/always), daily frequency of bowel motions ($\leq 3/>3$), urgency (yes/no), use of pads (yes/no) and/or enema/laxative (yes/no), and/or antidiarrhea drugs (yes/no), and sensation of incomplete evacuation (yes/no). This approach has been previously used.[9,24]

Health-related Quality of Life

Two HRQOL measures were selected for this study, EORTC QLQ-C30 and the QLQ-CR38, which have robust psychometric properties resulting from their use in several international cancer clinical trials. The EORTC QLQ-C30 is a core measure designed to be supplemented with the disease-specific colorectal cancer module developed and validated specifically in patients with colorectal cancer.[25–27] Both instruments are available in Italian and have followed rigorous forward-backward translation procedures.[27]

The EORTC QLQ-C30 is a generic cancer HRQOL questionnaire consisting of 30 items and includes a scale measuring the global health status/HRQOL; 5 functioning scales: physical, role, emotional, cognitive, and social; 3 symptom scales: fatigue, nausea/vomiting, and pain; and 6 single-item scales: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact.

The QLQ-CR38 is a cancer disease–specific questionnaire consisting of 38 items. These are grouped into 4 functional scales (body image, sexual functioning and enjoyment, and future perspectives) and 8 symptom scales (micturition problems, symptoms in the area of the gastrointestinal tract, chemotherapy side effects, defecation problems, male and female sexual problems, weight loss, and stoma-related problems).

The items on both measures were scaled and scored using the recommended EORTC procedures.[28] Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. Provided at least half of the items in the scale were completed, the scale score was calculated using only those items for which values existed.

All questionnaires were self-completed with the following schedule: baseline assessment (within 2 weeks before the start of CRT) (t_0); between the second and third weeks after the completion of CRT and before surgery (t_1); 6 months (t_2) and 12 months after surgery (t_3). The assessments at 6 and 12 months after surgery were chosen because after 6 months the majority of patients requiring adjuvant chemotherapy have received their treatment and after 12 months the majority of patients with temporary stoma have their stoma reversed. In addition, because 6 and 12 months are time point assessments frequently used in the literature, it will render our findings more easily comparable with others studies.

Statistical Analysis

The study was designed as a longitudinal investigation requiring 150 patients, assuming a 0.050 significance level, an 80% power, and a between-level correlation of 0.2. The sample size was based on the ability to demonstrate a reduction of 5 points in the global health status/quality of life scale after neoadjuvant treatment (at t_1) and a recovery to the baseline value (t_0) 12 months after surgery (t_3). The considered baseline value was chosen from the metastatic colorectal local or locoregional cancer (mean, 73.1; SD, 19.3) reference data.[29]

The HRQOL and the fecal incontinence scales were analyzed as continuous variables, whereas bowel symptoms were analyzed as dichotomous variables (present or not). A repeated-measures linear regression model was performed for each of the HRQOL domains and the FIS, and a repeated-measures logistic regression model was applied for symptom assessment to take into account the longitudinal nature of the data through the correlation between assessment on the same patient. The analysis used a random patient intercept and time effect, and a compound symmetry covariance matrix. All available data at each assessment were included in the estimation of the mean effects and their significance.

To correct for multiple comparisons and to avoid type I error, the level of significance was set at $P = 0.01$ (2-sided). Primary analysis included the following scales selected a priori on the basis of clinical relevance*:* global health status/quality of life, physical and social functioning, body image, future perspective, fatigue, and male and female sexual problems. All other scales were analyzed on an exploratory basis. To further investigate the early impact of pCRT on patients' HRQOL, the proportion of patients who had a clinically meaningful deterioration between pre- and postneoadjuvant treatment (ie, t_0 vs t_1) was also evaluated in selected HRQOL scales. Differences of at least 10 points were classified as a *clinically meaningful* change;[30] that is, an increase by at least 10 or more points on a functional scale would mean a clinically meaningful improvement, whereas an increase by 10 or more points would be interpreted as worsening of a given symptom. Sensitivity analyses were also performed to investigate reasons for HRQOL missing data. The models used to check the mechanism of missing data included discrete time survival regressions. To identify the mechanism of covariate-dependent missing data, the probability of dropout at a given assessment was associated to selected covariates, such as age, gender, performance status, education, living arrangements, and institution. To verify the assumption of the observed data-dependent missingness, the probability of dropout at a given assessment was associated to the previously observed HRQOL scale value, conditional also on the clinical center. All analyses were performed using the SAS statistical package (SAS, release 9.1.3, Cary, NC).

RESULTS

Between February 2003 and June 2006, 149 eligible patients were enrolled from 12 centers in Italy. All patients provided a baseline assessment, and further compliance rates over the study period were 95% at t_1, 88% at t_2, and 77% at t_3. Details of the enrollment process are provided in Figure 1. Of 149 eligible patients at baseline, 95 completed questionnaires at all 4 time points, and 8 patients only completed a baseline assessment.

All patients received combined pCRT. The median (range) radiotherapy dose delivered was 50.4 (44–60) Gy with conventional

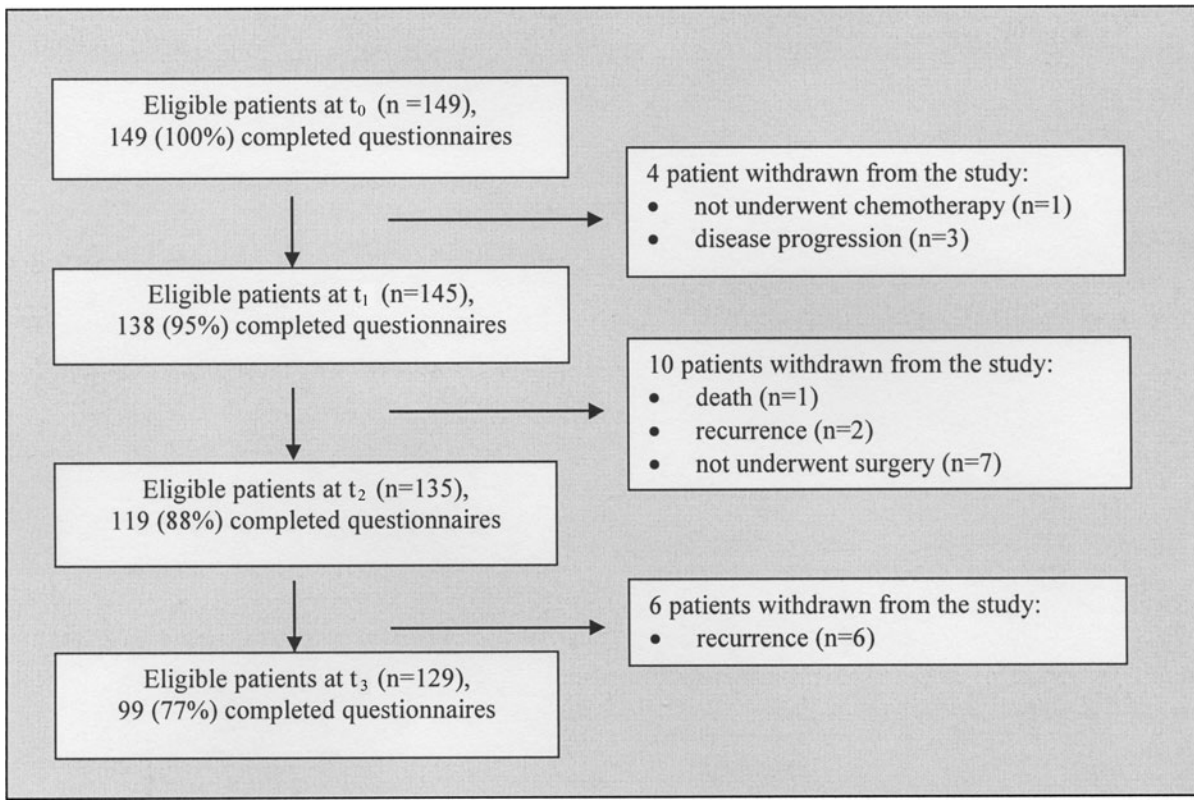

FIGURE 1. Summary of enrollment process and compliance rates over time.

(1.8 Gy per day) fractionation, and 5-fluorouracil–based chemotherapy; however, 7 patients did not undergo surgery. Details of patient characteristics are reported in Table 1. O 138 who underwent surgery, 120 had a radical (R_0) resection, 9 had a R_1-R_2 resection, in 3 cases the resection was considered undetermined and, in 4 cases no data were available. Of 116 patients who underwent a low anterior resection, 26 had a coloanal handsewn anastomosis and the remaining 90 had a stapled colorectal anastomosis. A temporary stoma was performed routinely (25 of 26) in patients who underwent a handsewn anastomosis. The intestinal continuity was reconstructed using a colonic J-pouch in 18 patients and a straight anastomosis in the remaining 98.

A stoma (either permanent or temporary stoma not reversed) was present in 31% and 19% of the evaluable patients at t_2 and t_3, respectively.

Fecal Incontinence and Bowel Function

Already at baseline, more than half of the patients had bowel function limitations mainly in terms of reporting a sensation of incomplete evacuation (67%). Although this percentage was significantly reduced just after pCRT (decreasing to 50%), at 6 months and 1 year after surgery, there were still a number of patients reporting this symptom, 78% and 72%, respectively. In all areas investigated, the percentage of patients reporting bowel function problems at 1 year after surgery was higher than that of baseline levels. Details are reported in Table 2.

A similar trend was observed for fecal incontinence problems (Fig. 2). A progressive worsening of the FIS was found during the study period with the FIS ranging from 33 at baseline to 63 at 6 months after surgery (overall time effect, $P < 0.001$). Although no statistically significant difference was found between pre- and post-CRT assessments, significantly worse scores were found at both postsurgery time points compared with the baseline levels. Only 14% of patients had no impairment in terms of fecal incontinence reporting a FIS score equal to 0 at the last time point assessment (data not shown).

Generic and Disease-specific Health-related Quality of Life Issues

Figure 3 shows the variations at each time point of the selected scales considered in the primary analysis. Given the poor compliance rate with the female sexual problem scale (ie, <30%), this was excluded from further analyses. The global health status/quality of life scores remained unchanged across the study period. Physical and social functioning, fatigue, and body image showed a trend toward a slight decrease just after pCRT and tended to return to baseline levels at 1 year after treatment; however, there were no clinically meaningful changes in these scales. Male sexual problems were highly impaired throughout the study period ($P < 0.001$) with major clinically meaningful changes (ie, 33 points) between baseline assessment and 1 year after treatment. Future perspective showed a clinically meaningful improvement (ie, 14 points) between baseline assessment and 1 year after treatment. Exploratory analyses conducted on the remaining functional and symptom scales did not show relevant changes during the study period. Emotional functioning showed a trend toward an improvement from baseline to the end of the study period, and micturition problems scale slightly decreased between the post-pCRT assessment and 1 year after treatment. Nevertheless, these changes were not clinically meaningful (data not shown).

Sensitivity analyses did not show any informative dropout pattern. Inspection of the HRQOL primary scales per dropout revealed

TABLE 1. Patient Characteristics

Characteristics	N (%)
Sex	
Male	92 (62)
Female	57 (38)
Age	
Median (range), yrs	64 (29–83)
Living arrangements	
Living alone	18 (12.1)
Living with others (spouse/partner, parents)	128 (85.9)
Missing	3 (2.0)
Education	
Elementary school–mid school	91 (61.1)
High school–university	37 (24.8)
Other	6 (4.0)
Missing	15 (10.1)
Employment status	
Retired	69 (46.3)
Employed	40 (26.8)
Housewife	15 (10.1)
Other	10 (6.7)
Missing	15 (10.1)
ECOG performance status	
0	44 (29.5)
1	83 (55.7)
2	15 (10.1)
≥3	2 (1.3)
Missing	5 (3.4)
Type of surgery*	
Low anterior resection	116 (81.7)
Abdominoperineal resection	14 (9.9)
Local excision	6 (4.2)
Other (Hartmann, colostomy)	3 (2.1)
Missing	3 (2.1)
Stoma*	
No stoma	47 (33.1)
Definitive stoma	14 (9.9)
Temporary stoma	78 (54.9)
Missing	3 (2.1)

* Patients (n = 7) who did not undergo surgery are not included.

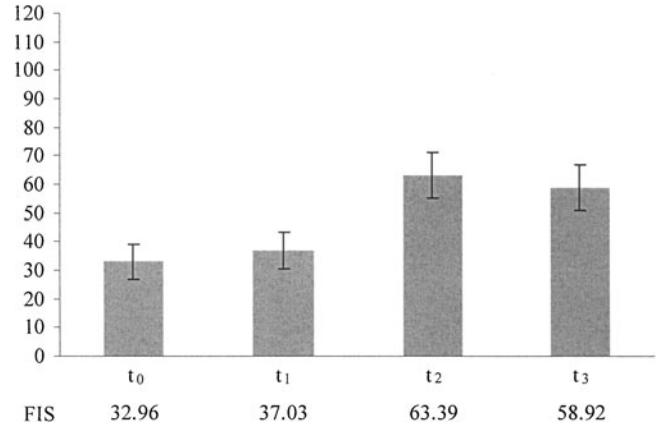

FIGURE 2. Fecal incontinence score over time (overall time-effect, $P < 0.001$). Values are expressed as mean (95% confidence interval).

similar score profiles, and no systematic increase or decrease before dropout could be identified (data not shown). The missing data mechanism was modeled with discrete time univariate survival regression, but this showed no trends for key baseline covariates, including age (≥70 years) ($P = 0.506$), performance status ($P = 0.664$), education ($P = 0.694$), or living arrangements ($P = 0.646$). However, an institutional effect was evident both in univariate and multiple analyses ($P = 0.011$) suggesting that some participating institutions were performing better at obtaining PRO data from their patients.

To evaluate the early impact of pCRT on patients' HRQOL, the proportion of patients with a clinically meaningful deterioration on selected scales was also calculated. Fatigue levels deteriorated in 49% of patients who reported a clinically meaningful deterioration (at least ≥10 point increase in the scale) between t_0 and t_1. A similar trend, showing a major impact of pCRT on patients' HRQOL outcomes was also evident in 47% of patients who reported a clinically meaningful impairment in the male sexual problem scale. Details are reported in Figure 4.

DISCUSSION

PROs are now well-established outcomes in oncology to better understand treatment effectiveness from the patient's perspective and to help making more informed treatment decisions.[31] One of the National Cancer Institute Strategic Objective is to ensure the best outcome for all, including improving the "quality of life for cancer patients, survivors and their families."[32]

TABLE 2. Bowel Function: Proportion of Patient Reporting Symptoms Each Time Point

Patient-reported Symptom Prevalence	t_0, n (%)	t_1, n (%)	t_2, n (%)	t_3, n (%)	*P* Time Effect
Presence of stool fractionation (yes)	69 (47)	71 (54)	61 (75)	60 (78)	<0.001
Urgency (yes)	51 (36)	66 (50)	40 (51)	28 (38)	0.017
Use of pad (yes)	32 (22)	30 (22)	44 (54)	39 (49)	<0.001
Use of enema/laxatives (yes)	22 (15)	13 (10)	15 (18)	13 (16)	0.220
Use of anti-diarrhea drugs (yes)	2 (1)	9 (7)	7 (9)	8 (10)	0.061
Daily frequency of bowel motions (>3)	53 (36)	30 (22)	39 (49)	28 (38)	<0.001
Sensation of incomplete evacuation (yes)	99 (67)	68 (50)	64 (78)	58 (72)	<0.001

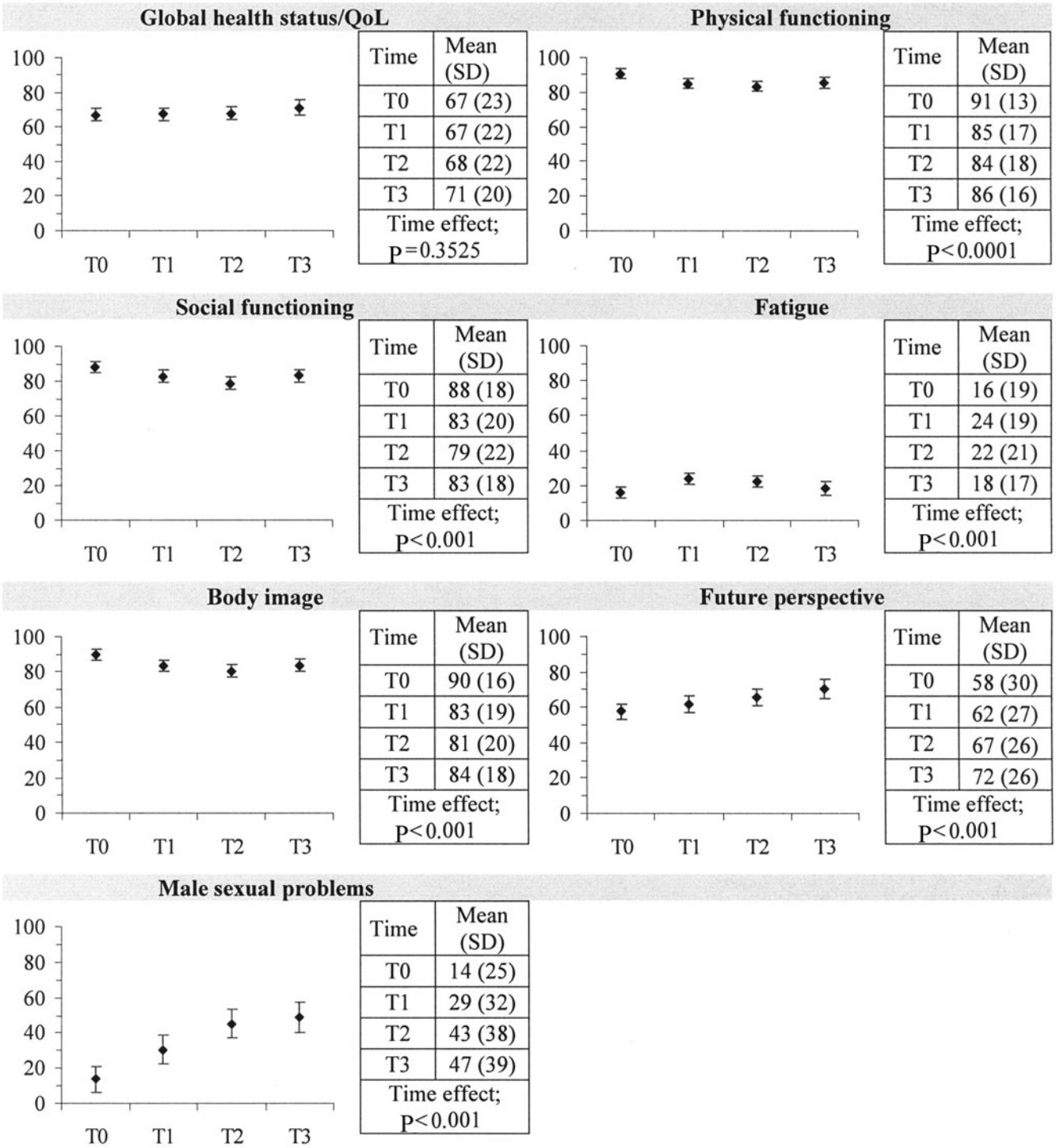

FIGURE 3. Selected health-related quality of life domains over time for the EORTC QLQ-C30 and the QLQ-C38 questionnaires. For "Future perspective," "Physical functioning," "Social functioning," and "Global health status/QoL" scales, a higher score represents a higher level of functioning and perception on that scale.

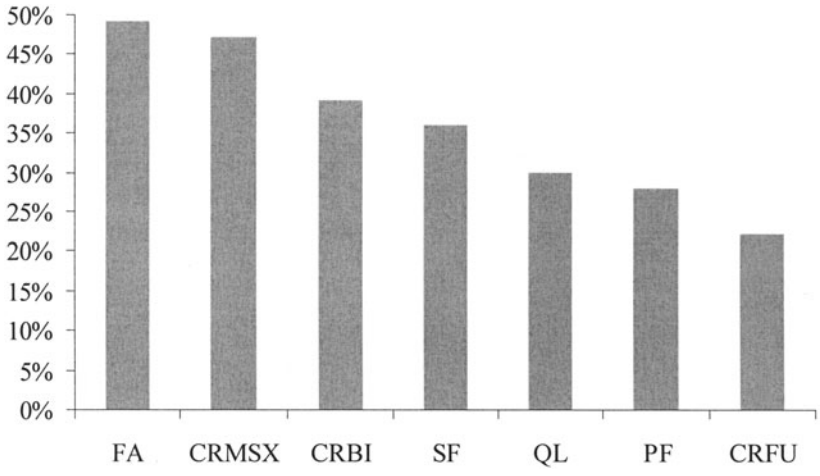

FIGURE 4. Proportion of patients with a clinically meaningful deterioration just after chemoradiotherapy (t_1) compared with baseline levels (t_0) in selected health-related quality-of-life scales. CRBI indicates body image; CRFU, future perspective; CRMSX, male sexual problems; FA, fatigue; PF, physical functioning; QL, global health status/quality of life; SF, social functioning.

Although the effects of pCRT in terms of HRQOL have been evaluated in patients undergoing surgery for other diseases such as esophageal cancer,[33] to the best of our knowledge, there are no prospective studies investigating PROs in rectal cancer patients undergoing surgery after pCRT. Therefore, the aim of this research was to understand the major health problems experienced by this population over the 1-year period from the start of treatment in terms of HRQOL, bowel function, and fecal incontinence. Although previous work has broadly shown a good level of HRQOL in disease-free survivors of rectal cancer patients, it also highlighted that these patients still report symptoms and functional limitations even years after the diagnosis.[1–8,17,18]

Likely related to the presence of tumor and in line with other reports,[24] we found that bowel function was quite poor already at baseline in one-third to two-thirds of patients (Table 2). The proportion of patients reporting bowel function–related problems was generally higher 1 year after treatment. This could possibly be due to the combined negative effects of both radiotherapy and surgery on bowel function.

Impairment in terms of fecal continence was noted throughout the study period and this was particularly evident at the 6th and 12th months after surgery compared with baseline levels. Considering that patients who are candidates to receive pCRT are usually in good general condition, with ECOG performance status from 0 to 1 and that older patients (>75 years old) are excluded from this approach, we could expect that in unselected series of patients with rectal cancer, bowel function and fecal incontinence could be even worse than that reported in the present study.

Seven key HRQOL scales were selected a priori to avoid *type I* errors. In general, we found that over time, physical and social functioning, fatigue, and patients' perception of body image tended to decrease but without showing a clinically meaningful impairment. No variation of scores over time was observed in the global quality-of-life scale. Patients reported the highest levels of fatigue just after pCRT and before undergoing surgery and then returned basically to baseline levels (Fig. 3). This is also confirmed by the fact that half of the patients (Fig. 4) had a clinically meaningful deterioration in terms of fatigue after pCRT, hence already presenting major limitations in this area at the time of surgery procedure. The male sexual problem scale was also highly affected during treatment with a major clinically meaningful deterioration at the 12th month after treatment. This finding was consistent with a previous report, using the same questionnaires on patients with rectal cancer treated with preoperative radiotherapy,[34] which reported major limitations on this scale. Marijnen et al[11] for example, also found a worse sexual function in male patients who received preoperative radiotherapy compared with those who underwent surgery without preoperative radiotherapy. Exploratory analyses conducted on additional HRQOL scales did not reveal any similar major limitations over time for other symptoms (data not shown).

It is noteworthy that patients' future perspective improved over time possibly reflecting decreased patient concerns regarding their own health status as treatment progressed. This could be confirmed by the score on the emotional functioning scale, which showed an increase from baseline to the 12th month after treatment. Again this finding was previously reported by Allal et al.[34]

This article has limitations. We were not able to investigate the female sexual problem scale due to low patient compliance, and we also used an ad hoc set of items to evaluate bowel function. However, there is a lack of standardized internationally validated tool to assess bowel function in rectal cancer patients,[18] and our goal was also to investigate this issue. In addition, this is not an international study, and a larger and culturally different sample could have yielded different results. It is also possible that changes in functional outcomes observed in this study were not exclusively stemming from pCRT approach and other factors, such as patients' general condition, surgical complications, level of the anastomosis, and shape of anastomosis (straight or J-pouch or side to end), not taken into consideration in this study, could have had a role.

In conclusion, this study suggests that the combination of pCRT and surgery might provide major limitations in terms of male sexual problems, fecal incontinence, and bowel function. In addition, pCRT might already provide significant symptom and functional limitations just before undergoing surgery. This information, along with what it is already known in terms of traditional clinical outcomes of pCRT after surgery in rectal cancer patients, may help clinicians understand the overall value of this approach and provide patients with more information regarding what to expect from this treatment.

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