Long-Term Health-Related Quality of Life in Patients With Rectal Cancer After Preoperative Short-Course and Long-Course (Chemo) Radiotherapy

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Abstract

Long-term health-related quality of life is compared between patients with rectal cancer preoperatively treated with long-course chemo radiotherapy (CRT) or with short-course radiotherapy. Apart from less satisfaction with urinary function reported by patients who had CRT, no clinically relevant differences in health-related quality of life and patient-reported symptoms between patients who had CRT and short-course radiotherapy were found at 5 years after rectal cancer treatment.

Background: Both preoperative short-course radiotherapy (SC-PRT) and preoperative long-course chemo radiotherapy (CRT) have shown to reduce local recurrence rates after total mesorectal excision (TME), but neither resulted in improved survival. This study compared the long-term health-related quality of life (HRQL) and symptoms between CRT and SC-PRT. **Methods:** Patients who were preoperatively treated with a total dose of 50.0 to 50.4 Gy for locally advanced rectal cancers were identified from 2 hospital registries. Starting from 2011, all patients who were disease-free in the study population (n = 105) were sent a HRQL-questionnaire composed of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and questions on bowel and urinary function. Patients who underwent SC-PRT in the TME trial were used as a reference group. **Results:** HRQL results from 85 patients receiving CRT (81.0%), with a median follow-up time of 58 months, were compared with the results of patients who underwent SC-PRT (n = 306). Apart from more nausea and vomiting reported by patients receiving CRT (mean score for CRT 5.9 vs. 1.3 for SC-PRT; $P < .01$; not clinically relevant) and less satisfaction with urinary function indicated by patients who received CRT (mean score for CRT 71.2 vs. 81.2 for SC-PRT; $P < .01$), no significant differences were found in HRQL and symptoms between patients who received CRT and SC-PRT. **Conclusions:** This analysis of HRQL in patients who received CRT shows no clinically relevant differences in long-term HRQL and symptoms between patients who received CRT and SC-PRT, apart from less satisfaction with urinary function reported by patients who received CRT. These results indicate that both approaches have a comparable impact on long-term HRQL.

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Introduction

The surgical treatment for resectable rectal cancer consists of a total mesorectal excision (TME). Depending on the tumor location, infiltration depth of the tumor, and lymph node involvement, treatment is combined with preoperative short-course radiotherapy (SC-PRT) or preoperative long-course chemo radiotherapy (CRT). There is no international consensus on the use of these treatment schedules or the most appropriate patient selection for these schedules. Both SC-PRT and CRT have shown to reduce local recurrence rates.[1-6] However, none of these neoadjuvant therapies resulted in an improved overall survival,[2-6] which emphasizes the importance of knowledge of health-related quality of life (HRQL) after these different treatment schedules. A randomized Polish trial compared the HRQL after SC-PRT (5 × 5 Gy) and CRT (28 × 1.8 Gy, 5-fluorouracil and leucovorin) followed by TME. After a median follow-up time of 12 months, no difference in HRQL was found between these groups.[7] However, since SC-PRT uses a higher dose per fraction in a short overall treatment time, there may be a risk for more late radiation-related toxicity compared with CRT. Long-term reported HRQL outcomes can provide additional information, which can be used to inform patients and healthcare providers and support evidence-based shared decision-making. Therefore, the aim of this study is to compare patient-reported symptoms and HRQL of patients treated with CRT to patients treated with SC-PRT for rectal cancer with a long follow-up time.

Patients and Methods

Study Population and Treatment

For this retrospective study, patients with locally advanced rectal cancer treated with long-course (chemo) radiotherapy between January 2003 and October 2010 were identified in the registries of the Leiden University Medical Center (LUMC) and Radiotherapy Center West (RCW). Locally advanced rectal cancer was defined as a tumor with growth into an adjacent organ, in close proximity to the mesorectal fascia, or any tumor accompanied by N2-status. Exclusion criteria were prior malignancies, local recurrences, metastatic disease at presentation, a higher received dose than 50.4 Gy, and prior pelvic radiotherapy.

Patients were treated with chemotherapy (capecitabine alone, capecitabine and oxaliplatin, 5-fluorouracil and leucovorin, or capacetibine and bevacizumab) and a total radiation dose of 50 to 50.4 Gy in daily fractions of 1.8 to 2.0 Gy delivered by a 4-field technique. The primary tumor and the mesentery containing the perirectal and presacral nodes, as well as the internal iliac nodes up to the S1/S2 junction, were included in the clinical target volume, as well as the perineum if an abdominoperineal resection (APR) was planned. Otherwise, the lower border was at least 3 cm caudally to the primary tumor. Five to 8 weeks after the last radiation treatment, patients underwent surgery according to the TME principles.

Patients treated with SC-PRT in the Dutch TME trial were used as a reference group. These patients had a clinically resectable adenocarcinoma without evidence of distant metastases and an inferior margin of the tumor located below the level of S1/S2 and within 15 cm of the anal verge. Patients who received SC-PRT were treated with 25 Gy in 5 fractions delivered with a 3 or 4-field technique. Within 10 days of the start of radiotherapy, patients underwent surgery according to the TME principles. More details on the TME trial design are reported in previous studies.[8-11] The local ethics committee approved this retrospective study, and informed consent for the questionnaire was obtained from all patients.

Measurements

Starting from June 2011, HRQL questionnaires were sent to patients who were disease-free. Patients who did not respond received 2 reminders. Patients were asked to complete the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC QLQ-C30) and an additional questionnaire on bowel and urinary function. The EORTC QLQ-C30 is a general cancer HRQL-questionnaire composed of 30 items. It includes a global health status scale, 5 functional scales (physical, role, emotional, cognitive, social), 3 symptom scales (fatigue, pain, nausea and vomiting), and 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[12] The additional questionnaire on bowel and urinary function was previously used in the Dutch TME trial.[9] All items of this questionnaire are reported in the Appendix. Scores of the additional questionnaire on urinary and bowel function were compared between the study group and the patients of the TME trial who received SC-PRT (n = 306) after a median follow-up of 5 years.[9] However, since the QLQ-C30 was not included in the HRQL questionnaire sent to patients in the TME trial at 5 years, but was included in the questionnaire sent at 14 years, the 14-year QLQ-C30 scores of the SC-PRT were used. This is based on a previous longitudinal study of the TME trial, which reported that the QLQ-C30 scores between 5 and 14 years after treatment were mostly only influenced by age.[13] This is also supported by population-based studies.[14-17] Likert-type scales were used for all questions, except for 3 dichotomous questions. All single-item and subscale responses were linearly converted to 0 to 100 scales. A higher score for functioning reflects better functioning, whereas a higher score for symptoms represents a higher level of symptoms and decreased HRQL.

Statistics

Analyses were performed with IBM SPSS Statistics, version 20.0. The Reverse Kaplan-Meier methodology was used to compute the median follow-up time. Mean scores were calculated, and missing values were handled according to the guidelines provided by the EORTC Quality of Life Group.[18] To prevent against false-positive results owing to multiple testing, a 2-sided P value of .01 was regarded statistically significant. Differences in mean scores were considered clinically relevant if the differences were larger than 5 points on a scale of 100 points.[19]

Matching of the reference data was based on previous analysis in the Dutch TME trial (data not shown). This analysis showed that the T status, N status, the positive or negative circumferential resection margin, tumor height, type of operation, and presence of a stoma did not influence HRQL and urinary symptoms. However, HRQL was associated with gender and age. Therefore, the reference data of the TME trial were matched for age and gender with the CRT group. Linear regression and logistic regression models were used to compare the HRQL and symptoms between the groups that received CRT and SC-PRT.

Table 1 Patient and Clinical Characteristics for the HRQL Responders

Characteristics	CRT (n = 85)		SC-PRT (n = 306)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	69		68	
Range	26-89		40-91	
Gender				
Male	55	64.7	199	65.0
Female	30	35.3	107	35.0
TNM stage				
0	0	0	8	2.6
I	1	1.2	140	45.8
II	14	16.5	84	27.5
III	64	75.3	74	24.2
IV	0	0	0	0
Unknown	6	7.1	0	0
Distance to anal verge, cm				
0-5	32	37.6	86	28.1
5-10	30	35.3	123	40.2
10-20	16	18.8	96	31.4
Unknown	7	8.2	1	0.3
Operation type				
LAR	20	23.5	200	65.4
APR	47	55.3	91	29.7
Hartmann	17	20.0	15	4.9
No resection	1	1.2	0	0
Stoma present				
Yes	67	78.8	129	42.2
No	18	21.2	177	57.8

To compare HRQL, data of the SC-PRT patients were matched for age and gender with the CRT patients.
Abbreviations: APR = Abdominoperineal resection; CRT = preoperative long-course chemo radiotherapy; HRQL = health-related quality of life; LAR = low anterior resection; SC-PRT = preoperative short-course radiotherapy.

Results

Study Population and Compliance

In total, 247 patients with locally advanced rectal cancer were treated between January 2003 and October 2010. Of these, 189 patients (123 LUMC; 66 RCW) met the inclusion criteria. In June 2011, 105 of the 189 study patients were disease-free. These patients were sent a HRQL questionnaire, and 85 patients responded (response rate, 81.0%). Except for 13 patients (15.3%), all responders received chemotherapy during long-course radiotherapy. For most patients (70.6%), concurrent chemotherapy consisted of twice-daily oral capecitabine (825 mg/m^2), 6 patients (7.1%) received capecitabine and oxaliplatin, 1 patient (1.2%) received 5-fluorouracil and leucovorin, and 5 patients (5.9%) received capecetibine and bevacizumab. The median follow-up time since diagnosis was 58 months (range, 15-98 months).

Questions of the QLQ-C30 were completed for all items in 92.9% of the responders. With regard to the questions on bowel function, patients without a stoma completed all items in 72.2% and patients with stoma in 77.6%. When up to 2 missing items were allowed, these rates were 88.9% and 92.6%, respectively. Patient characteristics of the patients who received CRT and SC-PRT are listed in Table 1. As expected, patients who received CRT had more advanced TNM stages compared with patients who received SC-PRT, and 75.3% of the patients who received CRT underwent an APR or Hartmann operation compared with 34.6% of those who received SC-PRT. As described in the methods section, these differences in patient characteristics did not influence HRQL or urinary symptoms.

Bowel and Urinary Symptoms

No significant differences in bowel or urinary function were found between patients who received CRT and SC-PRT, matched for age and gender (Table 2). However, for bowel symptoms, trends were observed towards increased anal mucus loss and more limitation in work or household activities caused by bowel function in the patients who received CRT. For urinary symptoms, patients who received CRT showed a trend towards more urine-retention after miction and a trend towards more difficulty to start miction. Furthermore, patients who received CRT were significantly less satisfied with their urinary function.

Table 2 Bowel and Urinary Function

	Mean Scores CRT	Mean Scores SC-PRT	*P*
Bowel function			
Fecal incontinence	42.2	34.6	.34
Fecal incontinence at night	22.9	13.4	.15
Ability to delay bowel emptying	65.6	66.5	.86
Anal blood loss	6.3	4.8	.78
Anal mucus loss	22.9	11.2	.07
Peristomal skin irritation	18.2	16.8	.54
Stoma smell	16.4	21.1	.27
Stoma bleeding	11.5	14.1	.47
Stoma leakage	10.6	12.0	.70
Painful stoma	7.0	6.3	.65
Noisy stoma	26.6	25	.65
Blood loss from stump	8.0	7.1	.60
Mucus loss from stump	14.6	17.9	.40
Impact of bowel dysfunction on			
Work or household activities	22.5	15.5	.03
Activities outside the house like shopping	24.8	22.2	.41
Social activities like theater or cinema visiting	23.8	24.8	.89
Urinary function			
Urinary frequency during the day	6.3	6.3	.77
Frequency urinary incontinence	57.1	54.2	.86
Use of pads for urinary incontinence	41.2	29.3	.18
Urine retention after miction	24.2	18.0	.08
Need to urinate again within 2 hours	26.2	25.9	.85
Stream hesitation	23.1	18.9	.24
Difficulty postponing miction	28.2	24.7	.35
Weak urinary stream	31.2	26.2	.16
Difficult to start miction	15.8	10.3	.06
Satisfaction			
Bowel function[a]	83.1	76.3	.11
Urinary function[a]	71.2	81.2	<.01

A higher score for functioning ([a]) reflects better functioning, whereas a higher score for symptoms represents a higher level of symptoms and decreased health-related quality of life. Abbreviations: CRT = Preoperative long-course (chemo) radiotherapy; SC-PRT = preoperative short-course radiotherapy.

EORTC QLQ-C30

Patients who received CRT and SC-PRT reported no differences in global health status and patient functioning (Table 3; Figure 1). Although patients who received CRT reported significantly more nausea and vomiting compared with those who received SC-PRT (mean score for CRT 5.9 vs. 1.3 for SC-PRT; $P < .01$), this difference is below a clinically relevant level. Moreover, patients who received SC-PRT reported a trend towards more diarrhea than those who received CRT (Table 3).

Discussion

This analysis of HRQL in patients who received CRT after a median follow-up time of 58 months shows no clinically relevant differences in long-term HRQL and patient-reported symptoms between CRT and SC-PRT, apart from less satisfaction with urinary function reported by patients who received CRT. These results are in line with the short-term HRQL of the Polish trial at 12 months after treatment.[7] Also, in a study comparing 10 × 2.9 Gy followed by immediate surgery (n = 108) versus 28 × 1.8 Gy with concomitant chemotherapy and delayed surgery (n = 117), no differences in HRQL were found after 67 months, except for a better score for physical functioning in the group that received CRT (mean scores 77 vs. 82, respectively; $P = .04$).[20] These results support our findings that long-term patient-reported HRQL is similar in patients who received SC-PRT and CRT. In addition, a randomized trial comparing 25 × 2 Gy with or without 5-fluorouracil and leucovorin, which included 78 patients with locally advanced rectal cancer, revealed no differences in HRQL, evaluated with the EORTC QLQ-C30 several years after treatment.[21] Thus, chemotherapy does not seem to aggravate long-term HRQL either when added to these radiotherapy schedules. However, a study by Tiv et al, which included 1011 patients randomized between PRT, CRT, PRT and postoperative chemotherapy, and CRT and postoperative chemotherapy, found a decrease in some long-term HRQL variables and an increase in diarrhea after adding chemotherapy.[22] In this study, 73% of the patients underwent sphincter-sparing surgery, which can lead to the Low Anterior Resection Syndrome. This syndrome is associated with a decrease of HRQL.[23]

In addition to the long-term HRQL, analysis of the physician-reported toxicity at 4 years in the Polish trial also demonstrated no significant difference in the crude overall incidence of late toxicity (28.3% and 27.0%, respectively; $P = .81$).[24] Taken together, these results show that long-term patient-reported HRQL and physician-observed toxicity do not differ between SC-PRT and

Table 3 Scores of EORTC QLQ-C30

	Mean Scores CRT	Mean Scores SC-PRT	P[a]
Global health status	79.6	78.9	.90
Functional scales			
Physical functioning	84.5	82.6	.56
Role functioning	82.5	83.3	.73
Emotional functioning	86.9	86.3	.85
Cognitive functioning	84.0	84.1	.90
Social functioning	84.6	87.7	.27
Symptom items			
Fatigue	23.8	22.5	.59
Nausea and vomiting	5.9	1.3	<.01
Pain symptoms	11.2	11.1	.92
Dyspnoea	11.8	11.6	.89
Insomnia	15.4	18.5	.42
Appetite loss	8.5	4.6	.12
Constipation	8.6	10.8	.51
Diarrhea	5.8	10.6	.09
Financial difficulties	9.5	6.8	.27

A higher score for functioning reflects better functioning, whereas a higher score for symptoms represents a higher level of symptoms and decreased health-related quality of life.
Abbreviations: CRT = Preoperative long-course (chemo) radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; SC-PRT = preoperative short-course radiotherapy.
[a]Difference between CRT and SC-PRT.

CRT. This is in contrast with the thought that the higher dose per fraction and short overall treatment time of SC-PRT would increase the risk for late radiation-related toxicity compared with the lower doses per fraction within CRT.

Acute toxicity after CRT and SC-PRT is reported in several studies. The Polish trial found more early radiation toxicity after CRT compared with SC-PRT (18.2% vs. 3.2%, respectively; $P < .001$).[24] This was also found in the randomized trial comparing 25 × 2 Gy with or without 5-fluorouracil and leucovorin: grade 3 and grade 4 acute toxicity was seen in 29% of the patients after CRT and in 6% of the patients after RT alone.[25] However, as described above, none of these studies reported a difference in the long-term toxicity or HRQL between the treatment groups. Furthermore, in the Stockholm III trial, in which patients were randomly allocated to either SC-PRT followed by surgery within 1 week, SC-PRT and surgery after 4 to 8 weeks, or long-course radiotherapy (25 × 2 Gy) followed by surgery after 4 to 8 weeks, no differences in the incidence of severe acute radiation toxicity were found.[26] Long-term toxicity and HRQL of this trial should still be awaited.

For locally advanced tumors, down-staging is required to facilitate surgical resection with negative resection margins. The previously described Polish trial found more down-staging after CRT (16%) compared with SC-PRT (1%).[25] This difference in down-staging did not result in a difference in local recurrence rate, disease-free survival, or overall survival between the treatment groups.[24] Moreover, the Trans-Tasman Radiation Oncology Group study, in which 326 rectal cancer patients were randomized between 5 × 5 Gy followed by early surgery and 6 courses of adjuvant chemotherapy versus 28 × 1.8 Gy and continuous fluorouracil followed by surgery in 4 to 6 weeks and 4 courses of adjuvant chemotherapy, more down-staging was also found after CRT (45%) compared with SC-PRT (28%). However, no significant difference in local recurrence rate, relapse-free survival, and overall survival were found as well.[27] Thus, while these trials reported more downsizing and down-staging effects after CRT, this did not result in differences in overall survival.

An alternative strategy is SC-PRT with delayed surgery to allow for tumor regression. The interim results of the Stockholm III trial showed pathologic complete responses of 0.8% after SC-PRT followed by surgery within 1 week, 12.5% after SC-PRT and surgery after 4 to 8 weeks, and 5% after long-course radiotherapy followed by surgery after 4 to 8 weeks, indicating that there is more tumor regression with SC-PRT and delayed surgery.[26] At present, new initiatives like the RAPIDO (Radiotherapy And Preoperative Induction therapy followed by Dedicated Operation) trial, which compares CRT with SC-PRT followed by chemotherapy and delayed surgery, are accruing patients.[28] Long-term oncological outcomes have to be awaited before an evidence-based decision about the optimal patient selection and treatment can be made, since no benefit of CRT over SC-PRT is found based on local control, survival, acute toxicity, and long-term HRQL, according to the studies described above.

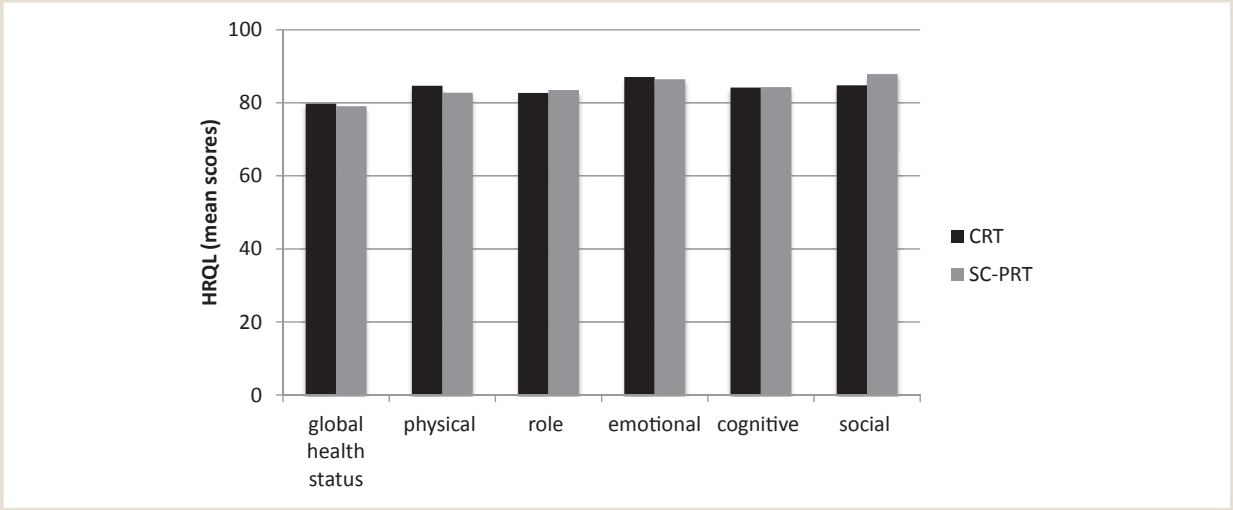
A strength of our study is the high response rate of 81.0% and a median follow-up of 58 months. Also, while some studies excluded patients with a stoma, we included these and even asked specific stoma-related questions. These questions were very useful in our analysis, since 78.8% of the CRT responders had a stoma at time of the HRQL questionnaire. Study patients were treated with CRT, since the Dutch guideline indicated this treatment by this tumor infiltration depth and the lymph node involvement. The patients included in the TME trial had less locally advanced tumors, and were treated with SC-PRT. To be able to correct for this possible confounding by indication, we assessed the influence of the T status, N status, the positive or negative circumferential resection margin, tumor height, type of operation, and the presence of a stoma on HRQL and urinary symptoms in the TME trial. None of these items influenced HRQL. However, gender and age were associated with HRQL, so we corrected for these variables. The finding that the clinical T and N status and tumor location have no or limited influence on HRQL is also supported by an analysis of Guckenberger et al, who also stated that no study in the literature has reported a correlation between HRQL and any clinical T or N stage.[20]

In conclusion, patients who received CRT and SC-PRT reported no clinically relevant differences in long-term HRQL and late symptoms after a median follow-up period of 58 months, apart from less satisfaction with urinary function reported by those who received CRT. These results indicate that both approaches have a comparable impact on long-term HRQL, and a preference for either of them can therefore not be based on long-term HRQL.

Clinical Practice Points

- Both preoperative short-course radiotherapy (PRT) and preoperative long-course chemo radiotherapy (CRT) have shown to reduce local recurrence rates. However, none of these neoadjuvant therapies resulted in an improved overall survival.

Figure 1 Global Health Status and Patient Functioning Scores of the QLQ-C30



Abbreviations: CRT = preoperative long-Course (chemo) radiotherapy; HRQL = health-related quality of life; SC-PRT = preoperative short-Course radiotherapy. A higher Score for functioning represents better functioning.

- After a short follow-up time, no differences in health-related quality of life (HRQL) are reported between both treatment schedules.
- After a median follow-up of 58 months, the only clinically relevant difference in HRQL between the groups was less satisfaction with urinary function indicated by patients who received CRT (mean score for CRT 71.2 vs. 81.2 for SC-PRT; $P < .01$).
- No benefit of CRT over SC-PRT is found based on long-term HRQL, acute toxicity, local control, and survival.
- However, after CRT, more downsizing and down-staging of rectal cancer tumors is reported. On the other hand, tumor regression is also found after SC-PRT followed by delayed surgery.
- Long-term oncological outcomes of new initiatives like the RAPIDO trial have to be awaited before an evidence-based decision about the optimal patient selection and treatment can be made.

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Disclosure

The authors have stated that they have no conflicts of interest.

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Appendix

Items of the Questionnaire on Bowel and Urinary Function
Bowel function
Mean bowel frequency at day and night
Description stool
Anal blood and mucus loss
Fecal incontinence at day and night
Use of pads for fecal incontinence
Ability to delay bowel emptying
Stoma function
Peristomal skin irritation
Stoma smell
Stoma bleeding
Stoma leakage
Painful stoma
Noisy stoma
Blood and mucus loss from stump
Impact of bowel dysfunction on
Work or household activities
Activities outside the house like shopping
Social activities like theater or cinema visiting
Urinary function
Urinary frequency during the day
Frequency urinary incontinence
Relation of urinary incontinence to stress and urge
Use of pads for urinary incontinence
Urine-retention after miction
Need to urinate again within 2 hours
Stream hesitation
Difficulty postponing miction
Weak urinary stream
Difficult to start miction
Satisfaction with bowel and urinary function