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# Quality of life during radiotherapy for rectal cancer

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**Abstract**

The aim of this study was to assess symptoms and health-related quality of life (HRQL) during (neo)adjuvant radiotherapy for rectal cancer. Patients receiving pelvic radiotherapy 50 Gy for rectal cancer, were studied prospectively ($n=42$). The European Organization for Research and Treatment of Cancer (EORTC) questionnaires quality of life-core 30 QLQ-C30 and QLQ-CR38 and a 5-day symptom diary were completed at the start and end of radiotherapy and 4–6 weeks later. At the end of radiotherapy, mean scores of diarrhoea, fatigue and appetite loss had significantly increased ($P<0.01$) compared with pretreatment scores, but this was not observed for scores for nausea or pain. At the end of radiotherapy, diarrhoea, fatigue, appetite loss, physical function, social function and global quality of life (QL) were significantly worse than the population-based norms. 64% of the patients reported an increase in fatigue and 52% an increase in diarrhoea during radiotherapy. HRQL scores had returned to pre-treatment levels 4–6 weeks after radiotherapy. Thus, diarrhoea, fatigue and appetite loss increased transiently during pelvic radiotherapy.


*Keywords:* Quality of life; Radiotherapy; Radiation; Colorectal neoplasms; Rectal cancer; Diarrhoea; Fatigue

## 1. Introduction

In Norway, 1035 new cases of rectal cancer were diagnosed in 1998. The age-adjusted incidence rates per 100 000 were 15.5 for males and 10.7 for females [1]. The main treatment is surgery. Patients with a non-resectable primary tumour or a locally recurrent tumour are recommended preoperative radiotherapy in order to reduce their tumour size prior to a new evaluation for surgery. After an operation for rectal cancer, patients with a high risk of local recurrence, and who have not received preoperative radiotherapy, are recommended for postoperative radiotherapy combined with chemotherapy. The primary goals of this treatment are to reduce the risk of local recurrence and improve survival.

Efficacy of cancer treatment is traditionally measured in terms of survival, treatment toxicity and functional outcome as assessed by the physician. However, during the past years, the understanding of the multidimensional quality of life concept has evolved. Reliable and validated questionnaires enable us to assess how patients themselves evaluate their health-related quality of life (HRQL). The European Organization for Research and Treatment of Cancer (EORTC) has developed a cancer-specific core questionnaire [2] and a disease-specific colorectal cancer module [3]. Standardised instruments enable comparison of results from prospective trials or cross-sectional studies, as well as comparison with population-based norms [4].

It is well known that radiotherapy results in acute as well as late normal tissue damage. The principal symptom of acute radiation enteritis is diarrhoea, although other symptoms like nausea and abdominal pain are also reported [5,6]. Little is known about how the patients themselves perceive these adverse effects during the course of curatively intended radiotherapy. There have been few studies investigating the HRQL of patients undergoing adjuvant or neoadjuvant radiotherapy for rectal cancer [7]. Knowledge of how patients perceive the treatment-related toxicity is important, in order to prepare future patients for what to expect during and after treatment. Thorough pretreatment information may lead to an improved tolerance of toxicity, and may enable better prophylactic and symptomatic treatment. The aim of this prospective study was to

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assess how patients with rectal cancer perceive the acute toxicity of adjuvant or neoadjuvant radiotherapy for rectal cancer, to what degree the dimensions of HRQL were affected by the treatment, and if patients had recovered within 4–6 weeks.

## 2. Patients and methods

### 2.1. Patients and treatment

Patients with rectal cancer scheduled to receive pelvic radiotherapy (RT) with curative intent were followed prospectively. Patients with locally advanced rectal cancer at diagnosis (T4) or locally recurrent rectal cancer received preoperative radiotherapy. Patients who had been operated upon and were at a high risk of recurrence received postoperative radiotherapy with concomitant 5-fluorouracil (5-FU)-based chemotherapy.

Consecutive patients were included provided they had a performance status of Eastern Cooperative Oncology Group (ECOG) $\leqslant 1$, age $<80$ years, no previous other cancer, and no previous major abdominal or pelvic surgery for reasons other than rectal cancer. All patients were examined with blood tests, chest X-ray, and ultrasound of the liver, and were without evidence of distant metastases. The patients were treated at the Norwegian Radium Hospital between November 1997 and June 2000. The regional ethical committee approved the study. Written informed consent was obtained from all of the participants.

All patients received 50 Gy in 2-Gy daily fractions, five treatments per week. Preoperative radiotherapy was preferably given by a three-field technique with one posterior and two lateral portals (Fig. 1). The superior and inferior borders of the treatment volume were the L5-S1 space and the perineum, respectively. Lateral borders of the posterior–anterior (PA) field were 1 cm outside the true bony pelvis. The posterior and anterior borders of the lateral fields were 1 cm behind the sacrum and the centre of the femoral heads, respectively. Patients were treated in the prone position, preferably with a full bladder. In patients with extensive anterior infiltration, a two-field technique (opposing AP–PA fields) was used. The clinical target volume received 46 Gy, and the gross tumour volume an additional 4 Gy boost. Four weeks after radiotherapy, the patients were re-evaluated, and if the tumour was considered resectable, surgery was performed shortly thereafter. Postoperative radiotherapy was applied by the three-field technique, the clinical target volume receiving 50 Gy. Patients $<75$ years of age received concomitant chemotherapy (modified Nordic schedule, 5-FU 400 mg/m$^2$ intravenous (i.v.) bolus followed by leucovorin 100 mg i.v. bolus, before fractions 1,2, 11,12, 21 and 22) [8].

### 2.2. Assessment of HRQL and symptoms

HRQL was assessed by the cancer-specific core questionnaire EORTC QLQ-C30 version 2.0 (QLQ-C30) [2] and the colorectal cancer module EORTC QLQ-CR38 (QLQ-CR38) [3]. The QLQ-C30 covers aspects of HRQL considered relevant to most cancer patients, and includes a global quality of life (global QL) scale. The QLQ-CR38 provides additional information relevant to

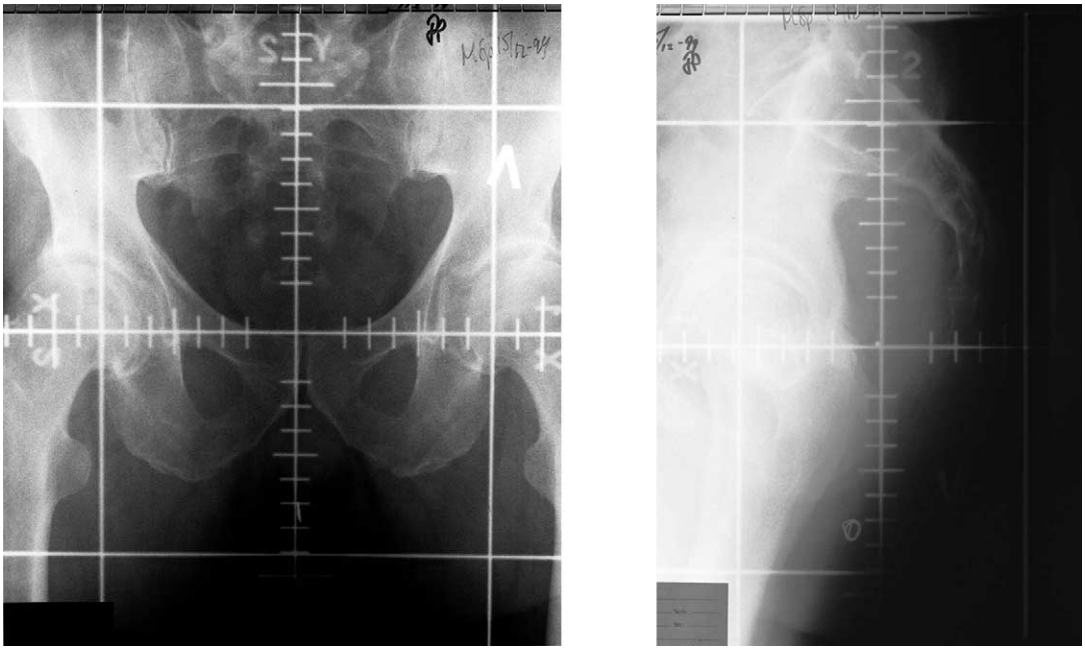

Fig. 1. Radiotherapy treatment fields: (a) posterior–anterior (PA) field; (b) lateral field.

patients with colorectal cancer. As the translation process was still ongoing when the present study started, a preliminary version was used, with minor deviations from the final version. The patients completed the QLQ-C30 and CR38 at the start of radiotherapy (baseline), at the end of the treatment period when subjective toxicity was expected to be worst, and 4–6 weeks after the completion of radiotherapy when toxicity was expected to have receded.

A self-report 5-day diary of defecation habits and symptoms was completed at the same assessment times. Patients with a preserved sphincter function recorded the number of daily bowel movements, patients with colostomy the number of daily stoma bag changes. Furthermore, the consistency of the stools, blood in the stools, faecal incontinence, nocturnal defecation, appetite, nausea and pain were recorded, as well as medication taken for these problems. Pain, diarrhoea, nausea and vomiting were graded from 0 to 4 based on the Common Toxicity Criteria (CTC) [9].

### 2.3. Interpretation of HRQL data

Missing items were handled according to the QLQ-C30 scoring procedures [10]. The responses were linearly transformed to range from 0 to 100, and related items were combined to function or symptom scales. A high function score indicated a good function, whereas a high symptom score indicated more symptoms. A change in mean score between 5 and 10 was interpreted as small, between 10 and 20 as moderate, and a change greater than 20 as large [11]. Changes $\geqslant 10$ points were considered clinically significant [4,11]. In addition, patients reporting "quite a bit" or "very much" were identified as those scoring $>50$ on a scale from 0 to 100, and the proportions of these patients were reported.

Reference data for the QLQ-C30 are available from the Norwegian general population [12]. For each patient, the expected score for each scale according to gender and age group was identified, and was compared with the actual score observed. Differences between the observed and expected scores $>10$ were considered clinically significant.

### 2.4. Statistics

The changes with time were analysed by different methods; paired samples *t*-test, Wilcoxon signed ranks test, repeated measures ANOVA with complete data sets, and repeated measures ANOVA with imputed data (last observation carried forward). The main results remained consistent with all these methods, and thus final data analyses were performed with repeated measures ANOVA, including those patients who returned QLQ-C30 and CR38 forms ($n=42$) or the 5-day diary ($n=45$) at all three times.

Comparisons at baseline were analysed with Mann–Whitney U tests. Comparisons with expected scores from population-based norms were analysed with one-sample *t*-tests. Correlations were analysed by Pearson correlations.

As multiple tests were performed, only *P* values $<0.01$ were considered statistically significant.

Table 2
Patients and treatment ($n=42$)

| | *n* (%) |
|---|---|
| Gender | |
| Male | 25 (60) |
| Female | 17 (40) |
| Indication for radiotherapy | |
| Preoperative | 26 (62) |
| • Primary tumour | 15 |
| • Recurrent tumour | 11 |
| Postoperative | 16 (38) |
| Radiotherapy technique | |
| Three-field | 34 (81) |
| Two-field | 8 (19) |
| Concomitant chemotherapy | |
| During postoperative radiotherapy | 13 of 16 |
| Stoma | |
| Yes | 23 (55) |
| No | 19 (45) |

Table 1
Study population and compliance

| | *n* | QL | PhysF | RoleF | EmF | SocF | BodIm | FutPer | Fatigue | Nausea | App | Pain | Dia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **All available data** | 56 | 68 (3.2) | 75 (3.6) | 85 (2.3) | 81 (2.5) | 70 (4.3) | 81 (2.6) | 57 (4.0) | 33 (3.6) | 10 (2.5) | 17 (3.7) | 23 (4.4) | 26 (3.6) |
| -withdrew from study | 4 | 46* (7.2) | 51 (12.0) | 58** (4.8) | 53** (7.6) | 38* (14.2) | 44** (6.4) | 25* (8.3) | 67** (13.6) | 45** (12.5) | 58* (21.0) | 50* (9.6) | 25 (16.0) |
| -other missing forms | 10 | 64 (6.5) | 73 (9.4) | 87 (4.8) | 83 (7.2) | 72 (12.4) | 86 (4.7) | 63 (9.2) | 28 (7.6) | 10 (7.1) | 20 (7.4) | 23 (12.0) | 26 (9.3) |
| **Complete data** | 42 | 72 (3.8) | 78 (4.0) | 87 (2.5) | 84 (2.4) | 72 (4.6) | 84 (2.7) | 59 (4.5) | 31 (3.9) | 6 (2.0) | 13 (3.8) | 21 (4.9) | 26 (4.2) |

Mean scores for global QL and selected function and symptom scales at baseline. Standard error of the mean (SEM) shown in parenthesis. Patients with missing data were compared to patients with complete data sets. Mann-Whitney U test, * $P<0.05$, ** $P<0.01$. QL, global QL; PhysF, physical function; RoleF, role function; EmF, emotional function; SocF, social function; BodIm, body image; FutPer, future perspective; App, appetite loss; Dia, diarrhoea.

## 3. Results

### 3.1. Compliance

Of the 56 patients who returned the baseline questionnaire, 42 (75%) returned QL questionnaires at all three assessment times and were included in the final analysis. 4 patients withdrew from the study after the first or second assessment, while 10 had occasionally missing forms. Those who withdrew had worse mean scores at baseline for several function and symptom scales than had the 42 who complied throughout the study. However, those with occasionally missing forms did not have significantly different baseline scores (Table 1).

### 3.2. Patients and treatment

Patient and treatment characteristics of the 42 patients are shown in Table 2. The median age was 67 years (range 38–78 years), and 60% were male. 26 patients had preoperative radiotherapy, while 16 were treated postoperatively. Of the latter, 13 received concomitant 5-FU/leucovorin. Most patients (81%) were treated by the three-field technique. Approximately half of the patients (55%) had a colostomy or ileostomy throughout the investigation period. 3 patients needed a treatment break (for 7, 17 and 20 days, respectively), but all patients completed the treatment. Of the patients treated preoperatively, 80% underwent surgery after completion of radiotherapy. At start of radiotherapy, the mean body mass index was 26.0 kg/m$^2$ (range 18.4–40.4), mean haemoglobin (Hgb) 133 g/l (range 98–157), and mean albumin 38.5 g/l (range 27–46).

### 3.3. Health-related quality of life

From baseline to the end of radiotherapy, the mean score of diarrhoea increased from 26 to 46 on a 0–100 scale ($P=0.002$), fatigue from 31 to 45 ($P<0.001$), and appetite loss from 13 to 26 ($P=0.003$) (Fig. 2). These changes were both clinically (difference $\geqslant 10$) and statistically ($P<0.01$) significant. There was no significant change in nausea or pain during treatment as assessed by the QLQ-C30. A small ($<10$), and significant, increase was observed in the mean score of other gastrointestinal problems (from 16 to 25, $P=0.001$), while a small, non-significant, increase was observed in mean score of micturition problems (from 20 to 27, $P=0.036$). At the end of radiotherapy, increased fatigue (score increased by $\geqslant 10$) was reported by 64% of the patients, increased diarrhoea by 52%, and worse appetite by 36%.

At the end of radiotherapy, no clinically significant changes were observed in the mean scores of any functional scales (Fig. 3). Small ($<10$), statistically significant, reductions in mean scores were observed in physical function (from 78 to 70, $P=0.006$) and body image (from 84 to 77, $P=0.002$). A small, statistically non-significant, reduction was observed in mean score of global QL (from 72 to 63, $P=0.037$).

At follow-up 4–6 weeks after radiotherapy, all mean scores had returned to near pretreatment levels (Figs. 2 and 3). At this time, neither function nor symptom scales were significantly different from the values obtained at baseline.

The proportion of patients reporting a fatigue score $>50$ (i.e. "quite a bit" or "very much") at the start of radiotherapy was 17%, at the end of radiotherapy 31%,

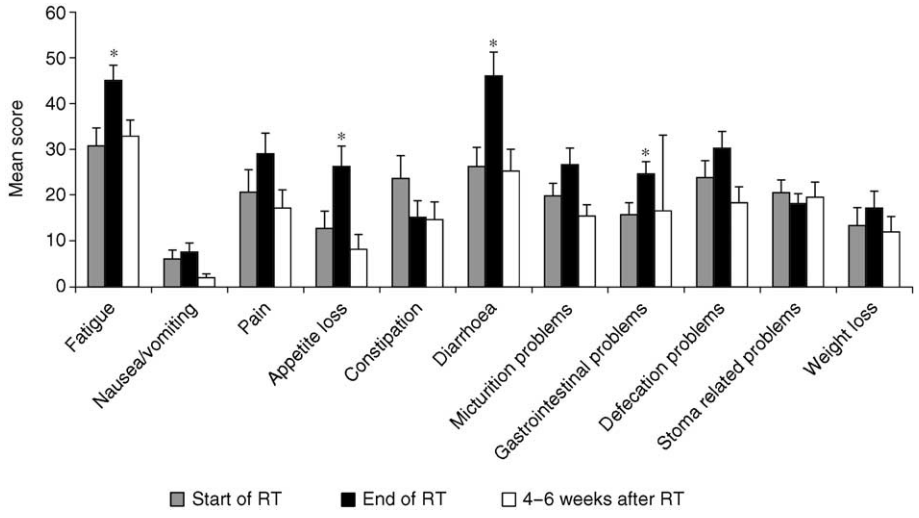


Fig. 2. Mean score of symptom scales and single items. The three bars indicate the start of radiotherapy (RT), the end of radiotherapy and 4–6 weeks after radiotherapy. *Repeated measures ANOVA, change from start to end of radiotherapy, $P<0.01$.

and after 4–6 weeks 20%. Similar proportions for diarrhoea were 19, 38 and 22%, and for appetite loss 10, 19 and 5%, at the three assessment times.

### 3.4. Comparison with population-based norms

Comparisons with the population-based norms when adjusted for gender and age group are shown in Fig. 4. At the start of radiotherapy, only the mean diarrhoea score was significantly worse than the population-based norms (difference 17, $P<0.001$). At the end of radiotherapy, mean scores of global QL (difference 10, $P=0.003$), physical function (difference 14, $P=0.003$), social function (difference 13, $P=0.004$), fatigue (difference 16, $P<0.001$), appetite loss (difference 19, $P<0.001$), and diarrhoea (difference 36, $P<0.001$) were significantly worse than the population-based norms. Four to six weeks after completion of radiotherapy, only the mean role function score was significantly better (difference 11, $P<0.001$), and the mean diarrhoea score significantly worse (difference 16, $P=0.002$), than the population-based norms.

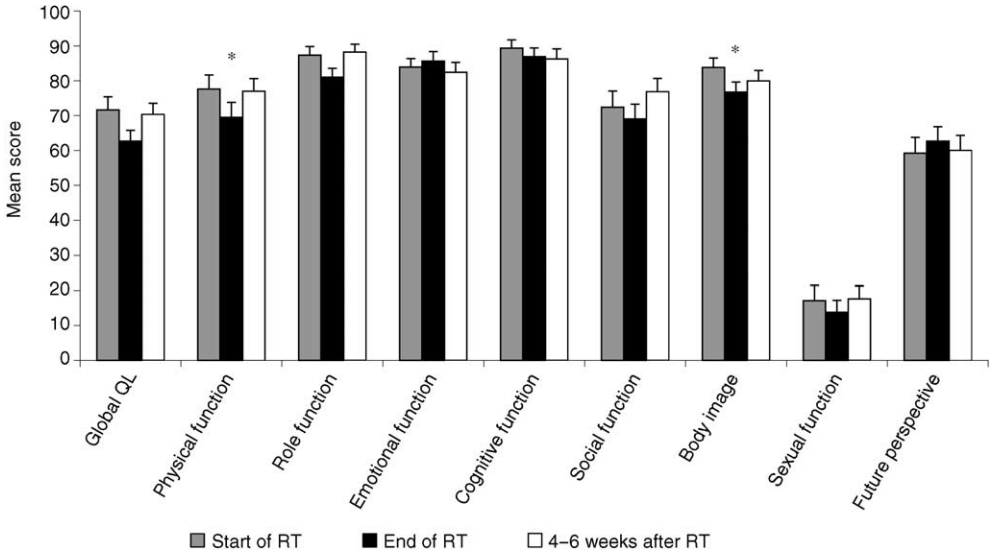


Fig. 3. Mean score of global QL and function scales. The three bars indicate the start of radiotherapy (RT), the end of radiotherapy and 4–6 weeks after radiotherapy. *Repeated measures ANOVA, change from start to end of radiotherapy, $P<0.01$.

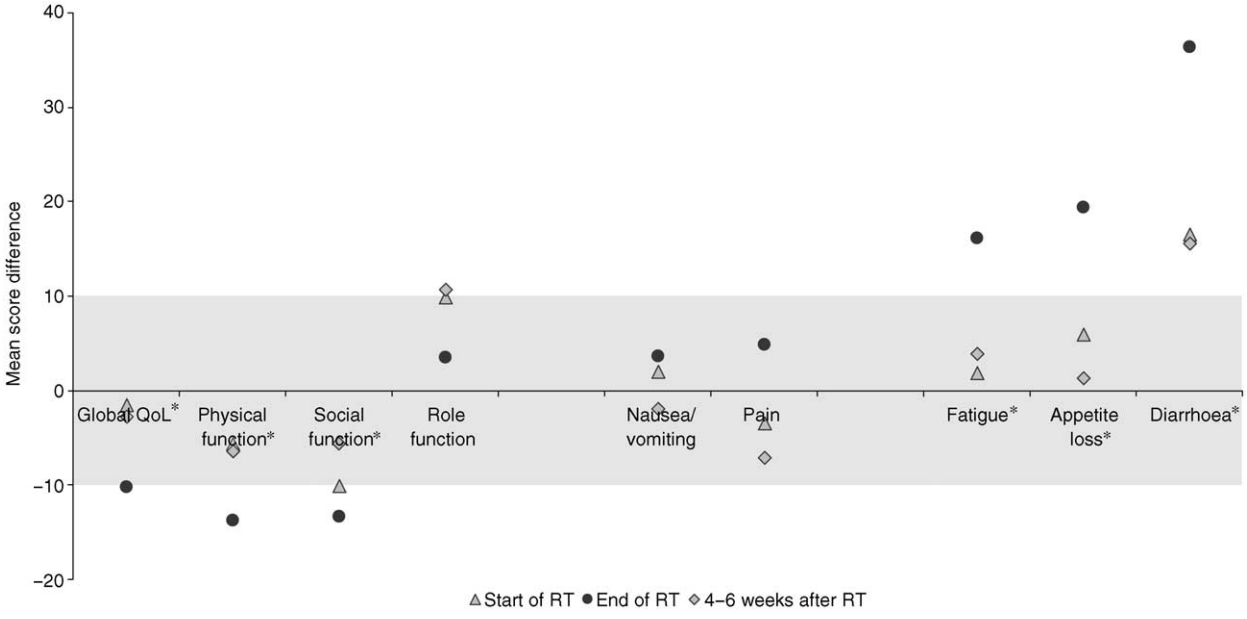


Fig. 4. Comparison with population-based norms, adjusted for gender and age group. Mean differences between observed values and expected norm values are shown at the three assessment times. *Difference $\geqslant 10$ points and $P<0.01$ (one-sample $t$-test) at the end of radiotherapy.

### 3.5. 5-day diary

According to the 5-day diary, the stools became looser ($P<0.001$). Diarrhoea according to the CTC grading increased ($P=0.001$) during radiotherapy (Table 3). The percentage of patients with grade 3 or 4 diarrhoea increased from 11 to 20%; 4–6 weeks later it was still 16%. Medication for diarrhoea was used by 10% of the patients at the end of radiotherapy, but not at the other assessment times. Laxatives were used by 43, 48 and 36% at the three assessment times, respectively, mostly by patients receiving preoperative radiotherapy.

There were no significant changes in nausea or vomiting. Daily antiemetics were used by 5% of the patients at the end of radiotherapy, but not at the other assessment times.

There was a small, non-significant, increase in pain according to the CTC criteria during radiotherapy ($P=0.027$) (Table 3). However, the percentage of patients with grade 3 or 4 pain (taking opioid medication) was 18–20% throughout the investigation period. Daily analgesics were used by 26, 31 and 21% at the three assessment times, respectively.

### 3.6. Fatigue and haemoglobin

Mean serum Hgb was reduced during radiotherapy from 133 g/l to 129 g/l ($P=0.010$), and was 130 4–6 weeks later. During radiotherapy, 4 patients received transfusions with 1–4 units of erythrocytes; in these patients, further Hgb values were excluded from analyses. No patients received erythropoietin. There was no correlation between fatigue scores and Hgb at any of the assessment times, and patients with Hgb below the reference range did not differ in fatigue scores from patients with Hgb within the reference range.

## 4. Discussion

The present study describes the treatment-related symptoms experienced during curatively intended radiotherapy for rectal cancer. Diarrhoea, pain and nausea were evaluated by two separate questionnaires. Five weeks of radiotherapy resulted in significantly increased diarrhoea, fatigue and appetite loss, while global QL was not significantly reduced, and there was no significant increase in nausea or pain. The changes were transient, and had returned to pretreatment levels 4–6 weeks after completion of treatment. At that time, all symptom scores except diarrhoea were comparable with those of the general population.

Diarrhoea was increased at the end of radiotherapy, which was evident by two independent questionnaires, the QLQ-C30 and the 5-day diary. Diarrhoea is a well-known side-effect of pelvic and abdominal radiotherapy, due to the damage of intestinal mucosa cells, and has been described during radiotherapy for rectal cancer [13]. It has been suggested that diarrhoea may predict late radiation injury [14], which may be progressive and difficult to control [15]. A recent review of acute and late radiation injury of the rectum describes some possible mechanisms currently being investigated, such as leucotrienes, cytokines and growth factors [16]. Radiation-induced diarrhoea is related to the radiation dose, fractionation pattern, and the volume of small bowel irradiated [17–19]. Surgical techniques have been used to exclude the small bowel from the pelvis [19]. Diet intervention (low fat, low lactose) has been shown to reduce diarrhoea during pelvic radiotherapy in patients with gynaecological malignancies [20]. Several drugs have been investigated as prophylactic agents [16,19], but none are commonly used. Preventing radiation enteritis is a major concern also in modern radiotherapy using multiple fields, multileaf collimator, and treatment in the prone position with a distended bladder.

Fatigue is a well-known side-effect of radiotherapy, although the aetiology is unclear [21]. Fatigue during radiotherapy gradually increases during the treatment, then declines with time, and has normally returned to pre-treatment levels 1–2 months after treatment [22,23]. It even occurs in tumour-free patients, for instance patients receiving adjuvant radiotherapy after breast-conserving surgery [22]. In the present study, 64% of the patients reported an increase in fatigue by more than 10 points, comparable to a recently published study of patients with rectal cancer in which 67% reported increased fatigue during chemoradiation [24]. Radiation-induced fatigue was observed although most patients had Hgb levels within the normal range. No correlation was found between fatigue and Hgb levels.

Although the appetite was reduced, most patients had an adequate energy intake, as there was only a small weight reduction of approximately 0.5 kg (data not shown) during radiotherapy. In contrast to our general understanding, nausea did not increase, when assessed by the QLQ-C30 or by the 5-day diary, although a small

Table 3
Patient-based symptom registration graded according to the common toxicity criteria (CTC)

| | Start of RT | | | | | End of RT | | | | | 4–6 weeks after RT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Grade | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| Symptom | | | | | | | | | | | | | | | |
| Diarrhoea[a] | 35 | – | 5 | 5 | – | 15 | 12 | 9 | 8 | 1 | 31 | 4 | 3 | 7 | – |
| Nausea | 39 | 5 | 1 | – | – | 33 | 8 | 4 | – | – | 41 | 3 | 1 | – | – |
| Vomiting | 42 | 1 | 2 | – | – | 43 | 2 | – | – | – | 44 | – | 1 | – | – |
| Pain | 27 | 6 | 4 | 8 | – | 19 | 10 | 7 | 9 | – | 28 | 6 | 3 | 7 | 1 |

Number of patients reporting different grades of toxicity.

[a] Change from start to end of radiotherapy, repeated measures ANOVA, $P<0.01$.

percentage (5%) used daily antiemetics. The mean scores were comparable to those of the general population at all of the assessment times. This was surprising, as nausea is often considered a side-effect of pelvic radiotherapy [5].

During radiotherapy, there was no significant increase in the pain score when measured by the QLQ-C30. When assessed by the 5-day diary, there was a trend towards a significant increase, mainly in pain not requiring opioids. While the QLQ-C30 scores the degree of pain as perceived by the patient, the 5-day diary registers the type of analgesic needed to alleviate the pain. At all assessment times, opioids were used by 18–20% of patients, although the dose was not recorded. As the patients in this study did not report more pain (QLQ-C30) than the general population, it seems that pain was adequately relieved.

This prospective study, although descriptive, yields new information regarding HRQL during pelvic radiotherapy. A recently published study showed a deterioration in many subscales of HRQL after chemoradiation and surgery, when compared with baseline [25]. The present study assessed subjective toxicity and HRQL before and after the radiotherapy course, and found that prior to subsequent surgery, patients had recovered from the acute radiation-induced toxicity. Larger studies are ongoing [26] which will provide further information on HRQL during radiotherapy.

We have previously shown that after radiotherapy followed by surgery including urinary diversion, disease-free rectal cancer patients did not have worse HRQL than the general population, although they had severely impaired sexual function and persistent diarrhoea [27]. Patients experiencing a life-threatening disease have been shown to adjust their internal standards, a phenomenon called 'response shift' [28].

All patients admitted for (neo)adjuvant radiotherapy from this particular health region were eligible for the study. The patient sample was restricted to patients in whom curative radiation was planned and who had good performance status (ECOG $\leqslant 1$). With the exception of diarrhoea, pretreatment HRQL was comparable to that of the general population. The results may thus be applicable only to patients in initially good general condition.

Missing forms represent a frequent problem in studies assessing HRQL, and may produce biased results. They are frequently of the same magnitude as in our study [25,29]. We compared the baseline scores of patients with complete data sets to those with missing forms. The patients who withdrew from the study (7%) had a poorer baseline HRQL. However, most of the missing forms were missing for reasons other than study withdrawal, and these patients did not have a worse baseline HRQL. Nevertheless, the results may be moderately biased by this missing data. It is reasonable to assume that the present study provides a small or moderate underestimation of the subjective toxicity. However, the results seem robust, as they remained consistent throughout analyses with different data sets; all available data, imputed data, and complete data sets. Since 75% of the patients included returned the questionnaires at all time points, it seems reasonable to conclude that pelvic irradiation results in temporary clinical deterioration in appetite, diarrhoea and fatigue in the majority of rectal cancer patients with a good baseline performance status and HRQL.

Five weeks of irradiation resulted in a small reduction in global QL (nine points on a 0–100 scale), with a non-significant $P$ value of 0.037. However, the patients had significantly reduced overall QL at the end of radiotherapy when compared with the general population ($P = 0.003$). In contrast, Bye and colleagues did not observe any significant reduction in overall QL at the end of radiotherapy in patients receiving radiotherapy for gynaecological malignancies [30]. Whether pelvic irradiation results in a clinically significant reduction in overall QL needs to be determined in larger, prospective studies which are currently ongoing [26]. Other future studies are needed regarding symptomatic or prophylactic treatment of fatigue and diarrhoea. Meanwhile, thorough pretreatment information may enable patients to cope better with subjective toxicity, as symptoms may be better tolerated when they are anticipated.

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