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Health-related quality of life (HRQoL) after multimodal treatment for primarily non-resectable rectal cancer. Long-term results from a phase III study

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ABSTRACT

Background: A randomised study in non-resectable rectal cancer showed that preoperative chemoradiotherapy (CRT) resulted in better local control and disease-specific survival, but not overall survival than radiotherapy alone. The present paper presents long-term (>4 years) health-related quality of life (HRQoL) and a comparison between the results and reference values from the Norwegian general population.

Material and methods: A total of 207 patients with primarily non-resectable rectal cancer were randomised to preoperative CRT (2Gyx25 + 5FU/leucovorin) or RT (2Gyx25) before surgery. HRQoL was assessed using EORTC QLQ-C30, completed at baseline and sent to all patients alive in Norway and Sweden ($n = 105$) after a minimum of 4 years post treatment. A difference of $\geqslant 5$ points on the 0–100 scales was considered clinically significant.

Results: Seventy-six (72%) patients answered at follow-up. No statistically significant differences between the CRT and RT groups appeared at follow-up, although clinically significant differences in social functioning, dyspnoea and diarrhoea were found. Over time, a clinically significant reduction in physical functioning was found in both groups. Moreover, reduced social functioning and less diarrhoea in the CRT group and better role functioning and more diarrhoea in the RT group were found. Comparisons between the study group and age and gender matched reference values indicate impaired social functioning and more diarrhoea among the patients.

Conclusion: There were no statistically significant differences in HRQoL between the randomisation groups. In general, despite having impaired social functioning and more diarrhoea, patients reported HRQoL comparable with the reference population several years after treatment.

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1. Introduction

Three randomised clinical trials have shown that preoperative chemoradiotherapy (CRT) gives better local control than radiotherapy (RT) alone in locally advanced rectal cancer.[1–3] In one of the trials, any chemotherapy, whether given pre or postoperatively reduced the risk of local recurrence.[1] Because of the reduced risk of local failure, CRT has become routine in spite of increased acute toxicity. The first two trials[1,2] did not reveal any survival gains, whereas the Nordic study[3] showed statistically significant benefits related to time to treatment failure and cancer-specific survival after treatment of initially non-resectable rectal cancer. Due to lack of a clear survival gain, long-term toxicity and quality of life (QoL) become important. Follow-up of late adverse effects in the Nordic study showed that feacal incontinence and erectile dysfunction were frequent after this combined treatment, and that the problems tended to be more common after CRT than after RT.[4]

So far, only one report has compared long-term health-related QoL (HRQoL) after preoperative long-course RT or CRT in rectal cancer patients.[5] After an interval of more than four years from primary treatment in the EORTC 22921-trial[1] generally high QoL scores after RT were reported, while adding chemotherapy resulted in decreased role- and social functioning, global health and more diarrhoea assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, EORTC QLQ-C30[6] and the colorectal-specific module QLQ-CR38.[7]

A few studies have reported HRQoL after rectal cancer surgery. One study[8] showed that patients receiving RT or CRT pre- or postoperatively did less well than those who had surgery only. Increased feacal incontinence had a negative impact on HRQoL, especially on social functioning. Another study[9] found that patients who required more extensive surgery ($n = 43$, 27 receiving (C)RT) had worse HRQoL than patients with less advanced rectal cancer operated with total mesorectal excision (TME) after short-course RT. In a randomised Polish study[10] no differences were seen in HRQoL and late toxicity one year after preoperative short-course RT or CRT. No differences in global health or physical functioning, but more late toxicity, affecting male sexual functioning and bowel function two years after treatment was seen after preoperative short-course RT compared to selective postoperative CRT in another randomised trial ($n = 563$).[11]

The aims of the present report are to compare long-term HRQoL between the two groups, CRT and RT in the randomised study,[3] to compare baseline and long-term HRQoL and to compare long-term follow-up results with reference data from the general population.

2. Patients and methods

Patients and methods are described in detail in a previous report of this study.[3]

2.1. Patients

From 1996 to 2003, 209 patients from Norway, Sweden and Poland with primarily, non-resectable or locally recurrent rectal adenocarcinoma were randomised to preoperative CRT or RT, and 207 were eligible and analysed. Tumours were considered as non-resectable if digital examination and rigid rectoscopy revealed a fixed tumour, and if CT or MRI indicated overgrowth to the sacrum, pelvic side wall/floor, base of the bladder, or prostate gland. Ninety-eight patients were randomised to the CRT group and 109 to the RT group.

In the period from 2006 to 2008, all patients alive in Norway and Sweden were contacted by mail, totally 105. Patients from Poland were excluded because of logistic difficulties. Seventy-six patients (72%) completed the EORTC QLQ-C30, and 65 of these (62%) responded to the questionnaire at baseline (Fig. 1).

Both the main study and the cross sectional follow-up were approved by the ethical committees at participating sites.

2.2. Treatment

2.2.1. Radiotherapy

A 3 or 4 beam technique (alternatively 2 beams in special cases) was used. The patients were given a daily fraction of

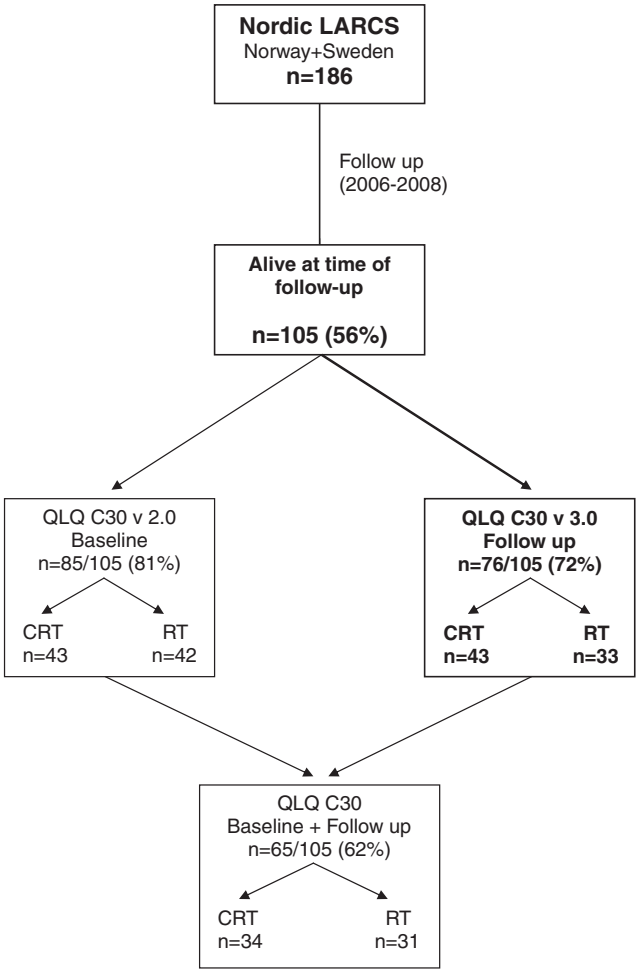

Fig. 1 – Flow chart showing patients randomised in Norway and Sweden and the number of patients answering QLQ-C30 at baseline and long-term follow-up.

2.0 Gy five days a week. Energies between 8 and 21 MV were allowed. The gross tumour volume, plus a 2 cm margin, received 50 Gy. Lymph node stations in the dorsal pelvis received 46 Gy. The upper beam limit was usually at the promontory or slightly above. The anal canal was excluded if an abdomino-perineal resection (APR) was unlikely. All patients' treatment was individually planned using a three-dimensional dose-planning system.

2.2.2. Chemotherapy

Patients randomised to chemotherapy received bolus 5-FU (400 mg/m^2) and leucovorin (Nordic schedule) before the RT fractions 1–2, 11–12, and 21–22.

All patients in the CRT group were scheduled to receive 8 cycles of adjuvant chemotherapy (5FU/leukovorin) starting 4–6 weeks postoperatively, irrespective of pathological stage. Postoperative chemotherapy was also permitted to patients in the RT group.

2.2.3. Surgery

Surgery was performed 5–8 weeks after the last radiation treatment. TME was recommended, and pelvic organs or structures with cancer involvement at diagnoses were resected en bloc if possible. Extended surgery was often required.[3]

2.3. Baseline and follow-up

Follow-up investigations were scheduled every three months during two years, then every six months for two years, and annually thereafter. Evaluation included patient history, clinical examination, blood tests, the EORTC QLQ-C30 version 3.0[6] and WHO toxicity score. Imaging was performed when signs or symptoms indicated recurrent disease.

2.4. HRQoL instrument

Before the start of the treatment, all the patients were asked to fill in EORTC QLQ- C30. It includes one global health scale, five multi-item functioning scales (physical, role, social, emotional, and cognitive functions), three symptom scales (fatigue, nausea/vomiting and pain) and six single symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact). The variable 'financial impact' was not included, as we did not expect it to have an influence after such a long time. The time frame was the past week. The validity and reliability of the Norwegian and Swedish versions of the questionnaire have been established.[12] Reference values are available for the Norwegian[13,14] and Swedish populations.[15] The Norwegian reference values[14] were used in this study, as these data are more recent and because the majority of the study sample (65%) was Norwegians. There are only minor differences between the reference data from Norway and Sweden.[13–15] When this trial was planned in 1995–96, only the QLQ C-30 was available. We considered it more appropriate to use the same questionnaire in the long-term follow up, and therefore no colorectal-specific module (QLQ-CR38) was introduced to the patients.

2.5. Data collection

A large proportion of patients did not complete the EORTC QLQ-C30 longitudinally at the time intervals described in the protocol. Only 8% of patients alive completed the 5-year assessment, which was considered insufficient for further analyses. A separate cross sectional study was therefore conducted after 4–12 years. All patients still alive in Sweden and Norway were sent an information letter, the HRQOL-questionnaire and a prepaid return envelope by mail from the Clinical Trial Office, Oslo University Hospital, Ullevål, Norway. Two reminders were sent to non-responders.

Patient-reported late toxicity, including a structured telephone interview and a questionnaire about sexual functioning, was also collected. These results have been reported separately.[4]

2.6. Statistical analyses

In QLQ-C30 version 2.0, used in the base-line assessment, the first five questions (physical functioning) were responded to in a 'yes – no' dichotomy, while in version 3.0, at the follow-up assessment, the same questions were scored in four categories, (1) 'not at all', (2) 'a little', (3) 'quite a bit' and (4) 'very much'. The items were scored and scaled according to the EORTC Scoring Manual.[16] Raw scores were transformed to a 0–100 point scale. Missing items were imputed if at least half of the items within the scale were completed. High scores on the global and functional scales represent high levels of global QoL and functioning, whereas high scores on the symptom scales/single items represent high levels of symptoms. Expected scale scores were calculated using the method of indirect standardisation with normative age- and gender-specific scores from the Norwegian population.[14]

The effect of treatment on each scale was evaluated using linear regression models including treatment and the potential confounding factors age, gender and stoma. Results from the regression models are presented as mean differences with 95% confidence intervals. Reported p-values refer to Wald tests.

In the interpretation of the QLQ-C30 scores, a difference of $\geqslant$5 points on the 0–100 scale was considered clinically significant. Differences of 5–9 points were considered small, 10–20 as moderate, and >20 as large.[17] All analyses were conducted according to the 'intention-to-treat' principle.

3. Results

3.1. Patient characteristics and compliance

Of the 105 patients alive, 85 (81%) responded to the questionnaire at baseline, and 76 (72%) returned the questionnaire after $\geqslant$4 years post-treatment (median 6 years, range 4–12 years) (Fig. 1). There were no statistically significant differences between the CRT and RT groups in socio-demographic or medical characteristics at follow-up (Table 1). No differences were seen between those who answered at both time points (n = 65) compared to the patients not answering, or only answering at one time point (n = 40) (data not shown).

Table 1 – Patient characteristics.

	CRT	RT
	n = 76	
	n (%)	*n* (%)
Primary cancer	41 (95)	31 (94)
Recurrent cancer	2 (5)	2 (6)
Total	*n* = 43	*n* = 33
Age (years) at follow-up		
median (range)	67 (42–81)	64 (51–78)
⩾70 years	16 (37)	10 (30)
Time (years) from randomisation to follow-up		
median (range)	7 (4–11)	6 (4–12)
Sex	*n* (%)	*n* (%)
Male	27 (63)	20 (61)
Female	16 (37)	13 (39)
Employment status		
Employed	16 (37)	14 (42)
Retired	22 (51)	7 (21)
On social benefits	5 (12)	12 (36)
Surgery		
LAR	19 (44)	18 (55)
APR	20 (47)	14 (42)
Hartmann/other	4 (9)	1 (3)
Additional surgery[a]	11 (26)	13 (39)
No stoma	12 (28)	15 (45)
Treatment failure		
Local recurrence	0	1 (3)
Systemic recurrence	2 (3)	4 (12)
Local + systemic	0	0

LAR: low anterior resection.
APR: abdominoperineal resection.
[a] Pelvic exenteration, hysterectomy/oophorectomy, cystectomy. vaginal resection, bladder resection, small bowel resection.

3.2. *Health-related quality of life at follow-up*

At baseline, there were no statistically significant differences between the randomisation groups in any of the studied HRQoL variables, and no differences appeared at the follow-up assessment. At follow-up, social functioning showed the most prominent clinical difference between the randomisation groups, albeit small. Values comparable to the reference sample were found for most variables (Table 2). The study sample had statistically significantly lower mean score for social functioning than the normal population ($p < 0.05$). There was a slightly higher score for diarrhoea in the RT group than in the CRT group (25 versus 20), and it was statistically significantly higher than in the normal population ($p < 0.05$). There was no difference between CRT and RT groups regarding constipation, nor compared to the normal population. The study sample reported marginally lower pain as compared to the normal population ($p < 0.05$).

The comparison between baseline and follow-up HRQoL, ($n = 65$) showed clinically significant impairment in physical functioning in both groups (CRT: 94–86, RT: 94–87). The same was found for social function in the CRT group (77–68), and improvement in role function was seen in the RT group (80–85). The CRT group improved with respect to diarrhoea (31–20) while diarrhoea in the RT group worsened (15–28).

4. Discussion

This paper presents long-term follow up of HRQoL in a randomised phase III trial comparing long-course preoperative CRT and RT in locally advanced rectal cancer. After multimodality treatment, often with extended surgery, no statistically significant differences in the HRQoL subscales were found between the groups, when adjusting for age, gender and having a stoma or not. When comparing the results with age and gender adjusted data from the Norwegian general population, statistically significant differences in social functioning and diarrhoea in favour of the reference sample appeared.

In the first report from the Nordic study,[3] we described, similar to the two other studies,[1,2] more grade 3–4 acute toxicity, mainly gastrointestinal, in the CRT as compared to the RT group. However, these acute side-effects seem to subside with time, and do not result in impaired HRQoL at the long-term follow-up. However, the present results as well as those previously published[4] show more bowel problems in the CRT group than in the RT group.

Table 2 – Comparison of EORTC QLQ-C30 mean scores at follow up; between randomisation groups and patients versus reference data.

	Mean scale score (SD)					
	CRT (n = 43)	RT (n = 33)	Mean difference[a] and 95% CI	P-value[b]	Mean scale score and 95% CI for the groups combined (n = 76)	Expected[c] scale score
Overall						
Global health status	78 (22)	80 (18)	2 (–8 to 12)	0.72	79 (74–83)	76
Functioning scales						
Physical	86 (16)	88 (18)	1 (–8 to 7)	0.86	87 (83–91)	85
Role	81 (25)	86 (21)	5 (–7 to 16)	0.40	84 (78–89)	83
Emotional	88 (14)	86 (21)	1 (–9 to 7)	0.76	87 (83–91)	85
Cognitive	86 (17)	89 (12)	4 (–4 to 11)	0.31	87 (84–91)	86
Social	71 (30)	78 (22)	10 (–3 to 22)	0.14	75 (69–81)	87
Symptom scales						
Fatigue	22 (24)	20 (21)	3 (–13 to 8)	0.62	21 (16–26)	25
Nausea and vomiting	4 (10)	2 (6)	2 (–6 to 2)	0.27	3 (1–5)	3
Pain	14 (22)	16 (25)	2 (–10 to13)	0.76	15 (10–20)	20
Single items						
Dyspnoea	14 (22)	9 (19)	–4 (–15 to 6)	0.39	12 (7–17)	19
Insomnia	19 (27)	15 (22)	3 (–15 to 8)	0.56	17 (12–23)	21
Appetite loss	6 (22)	2 (12)	–5 (–13 to 4)	0.28	4 (0–9)	5
Constipation	16 (22)	12 (25)	–6 (–16 to 5)	0.30	14 (9–19)	12
Diarrhoea	20 (25)	25 (32)	3 (–10 to 16)	0.44	22 (16–29)	13

[a] Difference between RT and CRT controlling for sex, age, and for having a stoma or not.
[b] P-values for difference adjusted for sex, age and having a stoma or not.
[c] Expected mean scale scores using Norwegian age- and gender-specific normative data.

Radiotherapy for abdominal and pelvic malignancies results in an increased risk of radiation enteritis and diarrhoea.[18] Intestinal mucosa cells are predisposed to radiation-induced damage and the resulting loss of mucosal integrity leads to malabsorption.[19] The total radiation dose and volume of small bowel irradiated are important determinants of the risk of acute and late toxicity.[20,21] Our results showing more late diarrhoea after (C)RT compared to a reference sample, support findings in other studies.[9,22] However, diarrhoea seemed to decrease with time. It should be noted that the mean score for diarrhoea in the reference sample used in this study is higher than in other population-based studies (adjusted for age and gender), with a mean score of 9 in Norway[13] and 5 in Sweden.[15]

Sixty-four per cent of the patients had a stoma at the time of follow-up,[4] but the adjustment for stoma or not in the statistical analyses did not affect the differences between CRT and RT. Studies on HRQoL in rectal cancer comparing colostomy and non-colostomy patients have shown diverging results. Sprangers et al.[23] reported more restrictions of social and sexual functioning in stoma patients, while Engel et al.[24] stated that anterior resection and non-stoma patients had better HRQoL scores than abdominoperineal extirpation and stoma patients, despite suffering micturition and defaecation problems. In contrast to this, Rauch et al.[25] found that patients with a colostomy had better HRQoL than those with an anastomosis. This is supported by others,[8,26,27] and also shown in a meta-analysis.[28]

A small difference between the CRT and RT groups was found with respect to social functioning. There is no obvious explanation of this finding. This, as well as the difference in social functioning between the study sample and the normal population, might be explained by the differences in diarrhoea. Significantly impaired social functioning after (C)RT compared with surgery-only has been reported in other rectal cancer studies.[8,27] Scores for global QoL and the other functioning scales were generally high in the study sample and very close to values in the Norwegian and Swedish general populations. This reflects a generally good HRQoL after this multimodal treatment.

Pain is related to locally advanced rectal cancer growing into adjacent structures, that may have been present at baseline. Interestingly, the study sample reported slightly lower levels of pain at long-time follow-up than the age- and gender-adjusted reference sample. Similar results are reported by Wahlgren et al.[29] studying patients after treatment for prostate cancer. One possible explanation is adaptation or 'response shift',[30–32] indicating changes in internal standards in the conceptualisation of HRQoL that are catalysed by health state changes. Pain and global quality of life are among the HRQoL parameters known to be affected by this phenomenon.

Strengths of this randomised study are related to the use of standardised validated and reliable HRQoL questionnaires and the comparison with normative data. We have used $\geqslant$5 points on the 0–100 scale as clinically significant.[17] New guidelines are recently discussed in a review by Cocks et al.,[33] and the threshold between a trivial and a small clinical difference was still $\geqslant$5 points. A small difference was one believed to be subtle but nevertheless clinically relevant.

A medium difference was defined as likely to be clinically relevant but to a lesser extent than a large one. The present study represents an interesting basis for further evaluation and implementation of the results in the follow-up of rectal cancer.

To our knowledge, no one has reported on these numbers of long-time survivors after treatment for primarily non-resectable rectal cancer before. However, the study has limitations. Thus, the low number of patients in the two groups may have hampered the power to detect statistically significant differences between the groups. A higher response-rate is always beneficial in this respect. However, considering the high age of many patients and the long time after primary treatment, a 72% participation rate can be regarded as satisfactory, also compared to other reports.[27,34] Generalisation should be made by caution as nearly 30% did not respond, and we do not know if attrition was biased when it comes to long-term HRQoL, although no differences were apparent at randomisation.

5. Conclusions

This study showed no difference in HRQoL between the two groups, CRT and RT. Long-term survivors after multimodal treatment for non-resectable rectal cancer have impaired social functioning and more diarrhoea relative to an age- and gender-adjusted reference population. However, these extensively treated patients have a HRQoL comparable with that of the general population in the same age.

Conflict of interest statement

None declared.

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