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research article

Quality of life in patients after combined modality treatment of rectal cancer: Report of a prospective phase II study

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Background. *The literature reports are unclear whether a permanent stoma reduces the quality of life (QOL) of patients with locally advanced rectal cancer (T3-4 and/or N+). Our aim was to compare the QLQ of patients with abdominoperineal resection and with restorative surgery, treated with preoperative radiochemotherapy in a prospective phase II clinical trial.*

Methods. *Fifty-seven patients were irradiated to 45 Gy in 25 fractions over 5 weeks to the pelvis concomitantly with oral capecitabine 825 mg/m^2, twice a day, including weekends. Surgery was scheduled 4-6 weeks after the completion of the chemoradiotherapy. Four courses of chemotherapy were planned postoperatively. Patients still alive and without recurrence of the disease, with a minimum follow up of 2 years, were surveyed with two self-rating questionnaires developed by the European Organisation for Research and Treatment of Cancer (EORTC): one was cancer specific (EORTC QLQ-C30) and one was site specific (EORTC QLQ-C38).*

Results. *QLQ was assessed in 28 of 32 patients eligible (87.5%). The median time from surgery to filling in the questionnaires was 35 months. For all scales of EORTC QLQ-C30 and EORTC QLQ-C38, no significant differences in median scores were observed between the two groups of patients.*

Conclusions. *QOL did not differ in patients with abdominoperineal resection from patients with sphincter-sparing surgery.*

Key words: preoperative radiochemotherapy; rectal cancer; quality of life

Introduction

The preoperative chemoirradiation has become a standard part of treatment protocols in stage II and III rectal cancer. Compared to postoperative chemoradiotherapy, the advantage of preoperative application of chemotherapeutics and irradiation includes improved compliance, reduced toxicity and down staging of the tumour in a substantial number of patients. The latter can potentially increase the feasibility of sphincter-saving resection in low-sited tumours.[1] The impairment of anorectal, voiding and sexual function is a frequent adverse effect of the multimodality treatment. Thus, the addition of radiotherapy (RT) to surgery

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improves the oncologic outcome but, potentially, adds morbidity to that associated with surgery.[2] A poor functional outcome after the restorative surgical technique may effect on the patient's quality of life (QOL). The construction of permanent colostomy following an abdominoperineal resection (APR) may be associated with one or more physical and psyhosociological problems as well. In the past, prospective studies with rectal cancer patients have focused on the tumour response, local control, survival and treatment related toxicity as primary end-points. Although these parameters remain central in the evaluation process, there is an increasing recognition of the need to assess more systematically the impact of cancer and its treatment on the functional, psychological and social health of the individual. As MRI has become incorporated in the diagnostic procedure of rectal disease,[3] the measurement of the functional outcome and QOL in rectal cancer patients, treated with preoperative radiochemotherapy and surgery has also become incorporated in clinical trials over the past decade.[4]

The aim of the present study was to assess QOL outcomes in patients treated with restorative procedures, compared with those in patients after APR by using a recommended and proven method.

Patients and methods

Patients

Between June 2004 and January 2005, fifty-seven patients with locally advanced resectable rectal cancer were treated with preoperative radiotherapy and concomitant capecitabine. Thirty-two patients, who were alive and without evidence of disease progression at a minimum follow-up of 2 years, were asked to participate in QOL study. Twenty-eight participated after having given informed consent. The characteristics of patients who answered the questionnaires are listed in Table 1.

Table 1. Characteristics of patients who answered the questionnaires

Characteristics	Number (%)
Number of responders/eligible patients	28/32 (87.5)
Median age (range) years	67 (37-81)
Gender	
Male	20 (71.4)
Female	8 (28.6)
WHO performance status	
Stage 0	27 (96.4)
Stage I	1 (3.6)
Tumour distance from the anal verge (cm)	6.5 (1-12)
Clinical TNM stage	
Stage II	14 (50.0)
Stage III	14 (50.0)
Permanent stoma	
Yes	9 (32.1)
No	19 (67.9)
Postoperative chemotherapy	
Yes	27 (96.4%)
No	1 (3.6%)
Median time (range) from surgery to answering (ra	35 (26-39)

Treatment

The details of both the patients and the treatment have been reported previously.[5] Briefly, the prospective phase II trial has been approved by the Republic Ethic Committee. The entry criteria included: histologically verified adenocarcinoma of the rectum, clinical stage II or III (IUCC TNM classification 2002); no prior radiotherapy and/or chemotherapy; World Health Organisation (WHO) performance

status <2; age at diagnosis of 18 or older; adequate bone marrow, liver, renal and cardiac function (no history of ischemic heart disease), and written informed consent.

Radiotherapy was delivered using 15 MV photon beams and four-field box technique, once per day, 5 days weekly. The small pelvis received 45 Gy in 25 fractions over 5 weeks. Three-dimensional CT-based treatment planning was performed. The clinical target volume (CTV) was defined to cover the small pelvis from the L5-S1 interspace to 5 cm below the primary tumour. The lateral borders were 5 mm outside the true bony pelvis. The posterior margin covered the sacrum, and the anterior margin encompassed the posterior one-third to one-half of the bladder and/or vagina. An additional 1 cm in all directions was added to the CTV to obtain the planning target volume (PTV). The dose was prescribed to cover the PTV with a 95% reference isodose (95% of the ICRU point dose). Patients were treated in the prone position. They were instructed to have a full bladder during irradiation, and no devices were used to displace the small bowel out of the irradiated volume. A multileaf collimator was used for shaping the fields and for the protection of normal tissues.

Chemotherapy was administered concomitantly with radiotherapy and consisted of capecitabine administered orally at a daily dose of 1650 mg/m^2, divided into two equal doses given 12 hours apart. One of the doses was taken 2 hours prior to irradiation. The chemotherapy started on the first day of radiotherapy and finished on the last day of radiotherapy (including weekends).

According to the protocol, surgery was planned for 4-6 weeks after the completion of the chemoradiotherapy. Although TME was the preferred surgical technique, it was not mandatory. Abdominoperineal resection (APR) was carried out in 17 (30.9%) patients, anterior resection (AR) in 4 (7.3%) patients, low anterior resection (LAR) in 32 (58.2%) patients, exenteration of the small pelvis in 1 (1.8%) patient and Hartmann's resection in 1 (1.8%) patient. As determined by the histopathological examination of surgical specimens, the resection was radical (R0) in 54 (98.2%) patients. A temporary colostomy was required in 32 (88.8%) patients.

Four courses of chemotherapy were planned postoperatively. It was administered in 44/55 (80%) of patients. Eighteen (40.9%) patients received adjuvant 5-Fluorouracil/Leukovorin and 26 (59.1%) patients received capecitabine.

QLQ assessment

QLQ was assessed using two validated questionnaires developed by European Organisation for Research and Treatment of Cancer (EORTC). One questionnaire assessed the cancer specific QOL (the third version of the Quality of life Questionnaire Core 30 items, i.e. QLQ-C30)[6] and the other site - specific (colorectal) QOL (Quality of life Questionnaire Core 38 items, *i.e.* QLQ-C38).7

The QLQ-C30 is a 30-items questionnaire. It includes a total of nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Separate six single items are included to measure gastrointestinal symptoms (diarrhoea and constipation), dyspnoea, appetite loss, sleeping disturbances and economic consequences of the disease.

The QLQ-C38 questionnaire comprises 38 questions, of which 19 are completed by all patients and the remaining by a subset of the patients (men or women; patients with or without stoma). It incorporates two functional scales (body image and sexuality) and seven symptom scales (micturition

problems induced by irradiation, chemotherapy side effects, gastrointestinal general symptoms, defecation problems, stoma - related problems, and sexual dysfunction in men and women). The remaining single items assess future perspectives and weight loss.

Both questionnaires contain questions related to the previous week. Four response categories, from 1 (not at all) to 4 (very much), are possible.

Statistical analysis

The scoring was performed according to the EORTC QLQ-C30 scoring manual.[8] The principle of scoring was to estimate the average of the items that contributed to the scale; this was the raw score. A linear transformation was used to standardize the raw score, so that all scores ranged from 0 to 100. The higher scale score for the functional scale or the global health status/QOL represents a higher level of functioning, or higher QOL; whereas the higher level of symptoms/problems for the symptom/item scales represents a higher level of symptomatology, or dysfunction. Missing values were calculated such that if at least one-half the items from the scale had been completed, it was assumed that the missing items would have had values equal to the average of the items present.

Demographic and clinical data were calculated using descriptive statistics. Results of QOL information were expressed as means and medians. The nonparametric Mann-Whitney *U*-test was used to compare median scores of QOL scales between the two treatment groups of patients. A 5% level of statistical significance was used for variables ($P<0.05$). Data were analyzed using SPSS for Windows (version 13.0; SPSS, Chicago, IL, USA).

We hypothesized that at least some scores of various scales would vary between subgroups of patients in favour of patients with restorative type of surgery.

Results

Oncological outcome

Before the therapy, an abdominoperineal resection was planned in 24 out of 55 patients who had definitive surgery. After the completion of chemoradiotherapy, the sphincter-conserving surgery was successfully performed in 7 of these 24 patients. Among 31 patients in whom the sphincter-conserving surgery was planned before having had any therapy, this was not possible in two patients, which resulted in an ultimate sphincter preservation rate of 65.5% (36/55).

A local relapse has occurred in 1 (1.8%) patient and a dissemination in 13 (24.1%) out of 54 patients with a median time to progression of 23 months (range 3-23 months). Second malignancies have occurred in 2 patients. The median 2-year overall survival, disease-free survival and disease-specific survival rates were 84.2%, 72.5% and 92.4%, respectively, and local control was 98.2%.

QOL evaluation

Of 32 eligible patients from the prospective phase II trial, 28 (87.5%) completed the EORTC QLQ-C30 and QLQ-C38 questionnaires: 19 patients with sphincter conserving surgery and 9 patients with APR. Three patients refused to participate in the study and one was judged ineligible because of serious comorbidities. Surveys were completed a median of 35 (26-39) months after the surgery.

The general results of QLQ-C30 for all patients with or without stoma are given in Table 2. The global quality of life scores, representing the overall health and quality

Table 2. EORTC QLQ-C30 mean and median functional scale and single-item scores according to the type of surgery

	APR (8 patients)		Restorative surgery (20 patients)		
Item	Mean (s.d.)	Median (range)	Mean (s.d.)	Median (range)	*P*
Global QOL	69 (24)	71 (25-100)	65 (28)	71 (0-100)	0.86
Functional scale					
Social function	75 (28)	83 (33-100)	80 (24)	92 (17-100)	0.71
Cognitive function	67 (35)	75 (0-100)	82 (23)	83 (17-100)	0.26
Role function	69 (31)	67 (17-100)	83 (24)	100 (17-100)	0.30
Emotional function	73 (34)	83 (0-100)	81 (22)	88 (33-100)	0.64
Physical function	78 (19)	83 (47-100)	81 (24)	93 (20-100)	0.47
Symptom scale					
Pain	25 (24)	25 (0-50)	18 (29)	0 (0-100)	0.36
Fatigue	36 (37)	33 (0-100)	25 (23)	22 (0-67)	0.57
Nausea and vomiting	10 (15)	0 (0-33)	3 (6)	0 (0-17)	0.30
Single items					
Dyspnoea	21 (40)	0 (0-100)	8 (24)	0 (0-100)	0.64
Insomnia	21 (35)	0 (0-100)	33 (29)	33 (0-100)	0.22
Appetite loss	13 (25)	0 (0-67)	3 (10)	0 (0-33)	0.53
Diarrhoea	17 (36)	0 (0-100)	17 (25)	0 (0-100)	0.67
Constipation	17 (18)	17 (0-33)	15 (23)	0 (0-67)	0.71
Financial impact	29 (33)	17 (0-67)	17 (25)	0 (0-67)	0.41

of life of patients, were similar. There was no difference in medians for all other scale scores. Patients having had APR seem to have less sleep disturbances (0 versus 33; p=0.22) and they tended to report lower levels of role functioning (67 versus 100; p=0.3) and cognitive functioning (75 versus 83; p=0.26) than did patients having had restorative resection.

The results of QLQ-C38 for the two surgical groups are given in Table 3. No significant differences in median scores were observed between the two surgical groups for any of the scales. However, APR group of patients tended to report a lower body image score (61 versus 89; p=0.16). The sexual functioning score and sexual enjoyment score were very low in both groups, but in the APR group the sexual functioning score was higher (33 versus 17; p=0.11).

Discussion

The abdominoperineal resection (APR) was long considered the standard treatment of tumours lying in the lower third of the rectum, providing a good local control. A more precise understanding of tumour biology and of failure patterns, has lead to the acceptance of short distal resection margins. Advances in surgical stapling and coloanal anastomoses technique have made it possible to treat many low rectal cancers by the sphincter-saving low anterior resection in preference to an APR. The survival and lo-

Table 3. EORTC QLQ-C38 mean and median functional scale and single - item scores according to the type of surgery

	APR (8 patients)		Restorative surgery (20 patients)		
Item	Mean (s.d.)	Median (range)	Mean (s.d.)	Median (range)	*P*
Functional scale					
Body image	67 (23)	61 (33-100)	81 (20)	89 (44-100)	0.16
Future perspectives	46 (43)	50 (0-100)	56 (35)	67 (0-100)	0.56
Sexual functioning	40 (32)	33 (0-100)	19 (21)	17 (0-67)	0.11
Sexual enjoyment	44 (34)	33 (0-100)	29 (28)	33 (0-67)	0.49
Symptom scale					
Micturition problems	33 (28)	33 (0-78)	22 (22)	11 (0-56)	0.39
General gastrointestinal	17 (21)	7 (0-60)	19 (14)	20 (0-40)	0.48
Defecation problems			23 (17)	24 (0-57)	
Stoma- related problems	26 (20)	21 (5-67)			
Sexual dysfunction of males	0 (0)	0 (0-0)	0 (0)	0 (0-0)	1.0
Sexual dysfunction of females	17	17 (17-17)	17 (24)	17 (0-33)	1.0
Weight loss	8 (15)	0 (0-33)	5 (17)	0 (0-67)	0.62

cal recurrence rate was not compromised.[9]

There are many other factors, which impact the decision, which surgical procedure to undertake for low-lying cancers: patient gender, preoperative sphincter function, stage of the disease, potential distal resection margin and surgeon preference. The avoidance of permanent colostomy has been used to judge the quality of the rectal cancer surgery. Although the avoidance of a permanent stoma following rectal cancer excision is regarded as a favourable outcome measure, the bowel function after the sphincter-sparing procedures may be greatly altered, resulting in faecal urgency and incontinence.[10] Patients receiving preoperative radiochemotherapy for rectal cancer may develop also other unpleasant symptoms, such as micturition problems and sexual dysfunction. These symptoms, which occurred in a substantial proportion of patients, have been reported previously.[11] Our aim was to evaluate the effect of these symptoms on the health-related QOL as an important endpoint.

It is difficult to evaluate the QOL after the rectal cancer surgery. For that purpose, non-cancer-specific or nonstardized questionnaires with a different methodology for scoring were used, *i.e.* self-reported by patients or scored by physicians. Additionally, the authors provided different types of preoperative or postoperative treatment. The evaluations of QOL were mostly of retrospective nature with a different time for questionnaire administration and evaluated on small sample sizes. So, the heterogeneity in the evaluation of QOL after the rectal cancer surgery gave rise to inconsistent and conflicting findings. Any comparison between data reported by different authors might be misleading. The use of standardized questionnaires is necessary. In our study, the evaluation of health-related QOL of patients was assessed by using EORTC cancer and site specific questionnaires,

which are validated and preferred measures in recent clinical trials.

Some studies have suggested that patients with a colostomy have a poorer QOL when compared to those who had restorative resection.[12,13] In the present study no significant differences in median scores were observed in any of the function scales of QLQ-C30 questionnaire studied (physical, role, social, emotional, cognitive functions and overall QOL) between the two groups. Our finding is in agreement with the observation reported by Allal *et al*.[14] and Camilleri-Brennan *et al*.[4] In a prospective study, Grumann *et al.*[15] showed that following LAR patients had even a lower QOL than those who underwent APR. A recent analysis of eight studies in a Cochrane Database Systemic Review showed mixed results. Half of the studies revealed no difference with regard to QOL between APR and LAR, in one the QOL in patients with stoma was only slightly affected and others revealed that the formation of stoma significantly affected the patients QOL.[16] The similarities in QOL in stoma and non-stoma patients may be due to the adaptation and the phenomenon of "response shift",[17] in which patients who have survived life-threatening disease seem to have new internal standards and, thereby, often report good QOL. Even patients who have undergone pelvic exenteration report having good QOL.[18] In agreement with other authors, we found that APR was associated with a lower perception of body image (feeling less attractive) than LAR.

Defecation-related problems, such as urgency, incontinence and incomplete bowel emptying, are well-known side effects of sphincter-preserving surgery.[11] Interestingly, the assessment of gastrointestinal problems on the QLQ-C38 and constipation on the QLQ-C30 showed similarities in the two groups. Camilleri-Brennan *et al.* found that patients who had sphincter saving resection had more problems with constipation.[4] Scores for stoma-related problems in both studies were comparable low, probably due to better stoma care. Standardized training by the specialized nurse is performed in every stoma patient in our department. That might lead to a better perception of QOL in our study.[19]

While most of the studies have suggested that the sexual function was impaired in patients receiving permanent stomas,[15,20,21] in present study, no difference in this dimension of the QLQ-C38 was revealed. Unexpected, the sexual functioning score tended to be higher in patients with APR than in patients with LAR, although the difference was not significant. Because of a small sample size and older age of our patients than in other studies, no valid conclusion can be made regarding this issue. Urinary problems were more frequently encountered after APR than after LAR. These differences are probably surgeon dependent.

The present study is limited by a lack of control measurements before the treatment. In addition, the number of evaluated patients was small, as only patients without evidence of disease treated in one clinical trial were surveyed. So a lack of statistical power might also be relevant. To obtain a large, unselected patient sample, we started to evaluate the QOL of all patients with rectal cancer, treated with preoperative radiochemotherapy, prospectively: before preoperative treatment, 1 year and 3 years after the operation.

In conclusion, consequences of the multimodality treatment of rectal cancer have an important bearing on QOL. Patients after the combined modality treatment with restorative surgical procedures do not necessary have a better QOL, mainly due to the impairment of the bowel function. In addition to traditional endpoints, such a disease control and survival, assessing restrictions

in QOL are necessary to provide a comprehensive understanding of the outcome of the combined modality treatment.

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