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PHASE I-III DEVELOPMENT OF THE EORTC QLQ-ANL27, A HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE FOR ANAL CANCER

Running title

Development of the EORTC QLQ-ANL27

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Abstract

Background and Purpose

There is currently no health-related quality of life (HRQoL) measure specific to anal cancer. Our objective was to develop an anal cancer HRQoL module to supplement the EORTC QLQ-C30 questionnaire using EORTC Quality of Life Group Guidelines.

Materials and Method

In order to generate a list of HRQoL issues facing anal cancer patients treated with chemoradiotherapy (CRT), we systematically reviewed the literature and conducted semi-structured interviews with patients and health care professionals (HCPs). Our list was then operationalised into questions using the EORTC Item Library. The provisional question list was pilot tested alongside the EORTC QLQ-C30 with patients from 11 centres across 8 countries.

Results

From our literature review and interviews with 43 patients, we generated a list of 197 issues. The list was then refined to 134 issues and reviewed by 34 HCPs and 10 patients. This review resulted in the retention of 65 issues which were used in the draft questionnaire tested by 100 patients. Our analyses led to the modification and removal of questions resulting in a 27 item questionnaire, the EORTC QLQ-ANL27.

Conclusion

We have developed a 27 item questionnaire to supplement the EORTC QLQ-C30, for use with patients treated for anal cancer. This has been pilot tested and is now available on request for use in clinical trials

Keywords

Anal cancer, chemoradiotherapy (CRT), Health-Related Quality of Life (HRQoL), HRQoL measurement

Background

Anal carcinoma is rare, accounting for 2% of all gastrointestinal malignancies and 10% of all anorectal malignancies, but with increasing incidence over the past 25 years and higher incidence in women [1, 2]. The current standard of care for patients with non-metastatic squamous cell anal cancer is concurrent chemoradiotherapy (CRT) [3-7]. In most cases, this has replaced surgical management and provides definitive treatment with the hope of sphincter preservation. The overall 5 year survival rates reach approximately 75%, colostomy free survival rates are 65-70% and complete clinical response rates around 80-85% [8]. While treatment outcomes are promising, associated toxicities are common, potentially long lasting, and impact on health-related quality of life (HRQoL). Clinician-reported acute grade 3 or 4 toxicities can be as high as 80% [9] with severe late effects (often defined as persisting 5 years or more post-treatment) recorded in about 10% patients [7]. The impact of these toxicities on HRQoL is acknowledged as an important outcome guiding decisions regarding treatment choices [10, 11]. Indeed, achieving good HRQoL alongside loco-regional control and the avoidance of a permanent stoma are identified within clinical practice guidelines as the primary aim of anal cancer treatment [3]. However, currently there is no anal cancer specific HRQoL measure.

In the era of precision radiotherapy where clinical trials evaluating dose escalation and de-escalation are pivotal in improving treatment, the importance of accurate measurement of HRQoL and symptomatic toxicity is key [12]. Complications following CRT include radiation enteritis, diarrhoea, proctitis, skin desquamation, strictures, stenosis, sexual dysfunction, dyspareunia, pelvic fractures, induced menopause, lymphedema, urgency and frequency of defecation, stool incontinence, and urinary tract dysfunction [13]. Our literature review [13] identified a number of reports of treatment complications and toxicities associated with CRT for the treatment of anal cancer. The majority are from small-scale retrospective case reviews. There is limited information on HRQoL and in particular long-term effects of the disease or treatment. Some of the claims regarding HRQoL issues are speculative and not substantiated by formal assessments. The small number of studies assessing HRQoL of anal cancer patients [10, 11, 14-22] use questionnaires validated for use with colorectal cancer patients such as the European Organisation for Research and Treatment of Cancer (EORTC) Colorectal Cancer Specific Quality of Life Questionnaire (EORTC QLQ-CR38 / CR29) [23, 24] and the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) [25]. While anal cancer and colorectal cancer have similar profiles in terms of symptoms and treatment-related side-effects, there are a number of issues, such as skin toxicity, lower limb lymphedema, anal pain and bleeding, which are

specific to anal cancer patients treated with CRT [13]. Many of these issues are not covered at all or are inadequately represented in existing questionnaires. It therefore follows that there is a clear need for a validated HRQoL measure specific to the concerns of anal cancer patients treated with CRT.

The EORTC Core questionnaire, the EORTC QLQ-C30 [26], was designed to capture the generic aspects of HRQoL for cancer patients and while it is appropriate for all cancer types, it is not specific to any tumour site, treatment modality or HRQoL dimension. The EORTC Quality of Life Group (QLG) advocates a modular approach to the development of questionnaires designed to be used alongside the EORTC QLQ-C30. This paper describes the development of an anal cancer specific questionnaire, the EORTC QLQ-ANL27 using EORTC QLG guidelines [27].

Materials and Method

The development of EORTC QLG modules follows four phases [27]. In Phase 1, HRQoL issues are generated through interviews with patients and health care professionals (HCPs), and a literature search. These HRQoL issues are reviewed and revised in Phase 2 and questionnaire items are formulated. In Phase 3, the questionnaire items are pilot tested and a provisional version of the module is developed. In Phase 4 the new module undergoes International field testing. The work reported here describes Phases 1-3. The study protocol was approved by the EORTC QLG. Ethical and research governance approvals were obtained at each centre in accordance with local requirements and all patients provided written informed consent. The study was coordinated from Southampton, UK with additional centres in, Canada, Cyprus, Germany, Greece, Italy, Norway, and Poland. Collaborator meetings were held every six months, with regular email discussion and telephone conferences between these times.

Phase 1a HRQoL issue generation

In order to generate an initial list of HRQoL issues, a systematic review of literature published between January 1996 and March 2014 was undertaken. English language papers describing patients treated with CRT for anal cancer were eligible for inclusion and included randomised controlled trials, case reviews / series, trials of quasi-experimental design, meta-analyses and reviews. Papers reporting conference proceedings and abstracts, study protocols and individual case reports were excluded from the review. Further details of the literature review process are described elsewhere [13].

Patient interviews

Patients with a confirmed diagnosis of primary newly diagnosed or recurrent locoregional anal cancer (squamous or cloacogenic cell cancers with histological confirmation) were invited to participate in semi-structured interviews. Purposive sampling was used to include patients in the acute, early and late treatment phases (< 6 months, 6-24 months and 2-5 years from the start of treatment respectively) as well as a good distribution of males and females although we anticipated a bias in recruitment of females. Patients with a stoma were included in the sample. Recruitment of patients continued until data saturation was achieved.

Patients were asked to describe their experiences relating to diagnosis and treatment with CRT. Issues captured from the literature review were used as prompts. Patients were shown the EORTC QLQ-C30 to engage them in further discussion. Patients were also asked to consider which of the issues raised were most important to them. Sociodemographic and clinical data including performance status (Karnofsky Performance Status [28]) were recorded.

Phase 1b HRQoL issue review

Issues generated from the interviews and the literature review were used to devise a list which was distributed to the project collaborators for feedback and to check for missing issues. This led to the combination of some issues, modifications, and removal of issues with obvious overlap with the EORTC QLQ-C30. The revised list was then reviewed by a separate group of patients and HCPs with expertise in anal cancer. HCPs and patients were asked to rate each issue in terms of importance on a 4-point Likert scale ranging from 1 "Not at all" to 4 "Very much". They were then asked to nominate 10 of the most important issues which should be included in the questionnaire and to identify issues which should not be included.

Phase 2 Construction of the provisional questionnaire

EORTC QLG guidelines were followed to determine which issues should be removed and whether any new issues should be added to the list [27]. Issues were operationalised into items with a response format and time frame compatible with the EORTC QLQ-C30. The EORTC Item Library was the first reference point when devising items to correspond to the issues identified. Attempts were made to harmonise items, where possible, with existing EORTC QLG modules, such as the EORTC QLQ-CR29 [24]. Items were adapted and new questions devised as required. Items were translated into all the languages required for Phase 3, following the EORTC translation guidelines [29].

Phase 3 Pilot testing the provisional Anal Cancer HRQoL Questionnaire

Eleven centres across 8 countries were involved in pretesting the preliminary questionnaire: UK (Leeds, London and Southampton); Cyprus (Nicosia); Canada (Ottawa and Toronto); Poland (Krakow); Germany (Halle); Italy (Florence); Greece (Patras) and Norway (Oslo). The same inclusion criteria were used as in Phase 1. Patients involved in Phase 1 were not eligible to test the questionnaire.

Patients were interviewed and asked to complete the draft questionnaire as well as the EORTC QLQ-C30. Patients were then debriefed and asked to rate whether each of the anal cancer questions had been relevant to them at any time since their diagnosis or treatment, i.e., whether an issue is something they recognise as having happened to them. In addition, if the question was relevant, they were asked to rate how important or bothersome it had been to them using a 4-point Likert scale ranging from “not at all important” to “very much”. Patients were invited to talk through the rating process and comments were recorded. Patients were asked to consider whether any of the questions were particularly irrelevant and also whether any of the questions were ambiguous, upsetting or intrusive. Finally, patients were asked to identify any important omissions. As with Phase 1 interviews, sociodemographic and clinical data were collected, along with a measure of performance status (Eastern Cooperative Oncology Group (ECOG) Performance Status) [30].

The number of items in the questionnaire was reduced by application of a priori agreed decision rules. Items were rejected if <60% patients rated the item as relevant and important (quite a bit or very much); or <70% patients reported the issue applies a little bit, quite a bit or very much; or if there were floor or ceiling effects (<10% patient responses for response options one and two or three and four). In addition, we considered patient comments and clinical judgement. Hypothesised subscales were proposed based on item content; the internal consistency of the proposed subscales was tested using Cronbach’s alpha: alpha ≥ 0.70 was regarded as evidence of adequate internal consistency [31].

Results

Phase 1 HRQoL Issue Generation

Literature review

The results of our literature review are reported elsewhere [13]. In summary, out of 152 publications reviewed, 11 (7%) [10, 11, 14-22] used formal patient reported assessments of HRQoL. For the purposes of issue generation, we considered the HRQoL issues measured as well as physician

rated toxicities which were reported as an outcome measure in 134 (88%) papers reviewed. The following HRQoL issues were identified: diarrhoea, constipation, flatulence bowel control, nausea and vomiting, appetite loss, urinary frequency and urinary incontinence, dyspareunia, reduced sexual interest, impotence, fatigue, insomnia, pain, dyspnoea, anxiety, financial difficulties and stoma-related problems. Overall, bowel functioning issues, in particular diarrhoea, and sexual problems were the most commonly reported issues in the HRQoL literature and were presented as significant concerns in seven studies [10, 11, 14, 16, 20-22]. Additional issues captured from the toxicity literature included haematological complications such as neutropenia and leukopenia, skin reactions (radiation dermatitis and moist desquamation) and bone injury [13].

Phase 1a Interviews

A total of 43 patients was recruited from 7 centres across 5 countries (UK: Southampton and London; Cyprus: Nicosia; Canada: Ottawa and Toronto; Poland: Krakow; Germany: Halle). The socio-demographic and clinical characteristics of patients are shown in Table 1. The majority of patients were female (30 compared with 13 men); mean age 62.9 years. The sample included patients across the disease and treatment spectrum with a slight majority (47%) within 6 months of treatment and 7 patients had a stoma (6 permanent and 1 prophylactic).

Insert Table 1 about here

A total of 197 issues, categorised under 19 sub-headings (bowel function, anal bleeding, urinary, skin, pain / discomfort, fatigue, gastro-intestinal, hair, oedema, psychological / emotional, social, impact on daily activities, sexual, stoma-related, respiratory, cardiac, haematological, oral, and general) were identified from 43 interviews and the literature. Bowel function, in particular diarrhoea and constipation, and skin-related issues such as burning and itchy skin were identified by patients across all research centres. The list of issues is available as supplementary material (*Supplementary material 1*).

Phase 1b Interviews: HCP and patient review

Issues measuring the same underlying construct were removed to produce a list of 134 issues which was then shown to HCPs and patients. Thirty four HCPs from 8 centres across five countries (UK, Cyprus, Canada, Poland and Germany) commented on the issue list. There was an even split of male and female HCPs, mean (standard deviation) age of 43.3 (10.0) years, from five different specialty areas, predominantly radiotherapy (53%). The majority of HCPs (53%) had over 10 years of

experience in the field of anal cancer. Ten patients from the UK who had not been involved in the first phase of interviews also reviewed the list.

The mean rating score for patients and HCPs for the majority of the 134 issues (81 and 123 respectively) was 2 or above implying a high level of importance / relevance attributed to the majority of issues. The majority of issues with low ratings fell in the general miscellaneous section and reflect items with low incidence during the phase 1a interviews. Bowel functioning, skin problems and treatment burden were regarded as the most important issues.

Combination, re-wording or removal of issues led to a revised list of 65 items. HCP and patients ratings as well as the decisions for each issue are available as supplementary material (*Supplementary material 2*).

Phase 2 Creating the provisional item list

For 35 issues, the EORTC QLG Item Library provided a suitable corresponding question and an additional four questions were taken from other EORTC QLG modules in development (cachexia and vulva). For three of these, modifications to the item wording were required. Twenty three issues were not found in the Item Library and required a new question. The list of issues with suitable EORTC QLG items, issues requiring item modifications, and those for which new items were written is available as supplementary material (*Supplementary material 3*).

Phase 3 Pilot testing the draft questionnaire

Patient interviews

One hundred patients were recruited from eleven centres. The socio-demographic and clinical characteristics of Phase 3 patients are presented in Table 1 alongside the characteristics of patients involved in the first round of interviews. Table 1 highlights similarities in sample composition with patients involved in Phase 1 and again is representative for the patient group.

The application of the item decision rules led to the removal of 38 items (Table 3) which left 27 items. Several items with acceptable performance (e.g., worry about one's future health, future of loved ones, and treatment burden) were considered not specific to anal cancer and more suitable to a generic instrument and were therefore removed.

Two items asking about frequent bowel movements at day and night were also removed and combined into one question asking about frequent bowel movements in general.

Of the 65 items, 25 were retained and left unchanged in terms of their original wording. Where an

item did not satisfy the a priori decision rules but was regarded as important from a clinical perspective (e.g., swelling in legs or ankles), the item was retained.

One additional screening question asking about sexual activity was included to provide insight into any missing responses relating to sexual function (painful sexual intercourse). Two additional issues, taste and nail problems, were identified by at least two patients as missing from the anal cancer questionnaire and the EORTC QLQ-C30, however these had already been ruled out for inclusion following an earlier review process (Phase 1) and thus these were not included.

Comments relating to two items asking about interest in sex and impact on sex life indicated that these items are potentially relevant to patients even if they have not been sexually active in the past 4 weeks. Therefore it was decided that these questions should be asked of all respondents irrespective of sexual activity. Phase 3 item review process left 27 items for inclusion in the Anal Cancer Quality of Life Questionnaire (EORTC QLQ-ANL27) (Table 2). The following multi-item subscales were proposed based on content as well as internal and convergent reliability (Cronbach's alpha and inter-item correlations): bowel function, pain or discomfort, sexual function (male or female), and stoma. The remaining five items (frequent urination, keeping clean, proximity to toilet, lower limb oedema, planning activities) did not fit within any of these subscales and are presented as single items. The additional screening question relating to sexual activity does not form part of a subscale. Adequate internal consistency and convergent validity was demonstrated for all sub-scales with the exception of sexual function (male and female). This could be explained by small numbers of patients completing these questions. Further work on confirming these sub-scales and their psychometric properties will be carried out as part of a larger international validation study (Phase 4).

Discussion

The EORTC QLQ-ANL27 was developed for patients with a rare cancer and for which there is both a paucity of and need for research into patient reported outcomes. Before decisions can be made regarding treatment pathways, patients need to be fully informed about all treatment options, together with their complications and outcome. Information on long-term HRQoL is a crucial component for appropriate discussions between the radiation oncologist, nurse navigators and the patient regarding treatment option [32]. The accuracy and accessibility of the information given to patients is important and therefore availability of an anal cancer HRQoL questionnaire is crucial to

providing high quality data to inform decision-making. Even with more advanced, tissue sparing radiotherapy techniques such as IMRT, pelvic chemoradiation can significantly adversely affect patients' quality of life, with an array of problems including skin toxicities, bowel, urinary and sexual dysfunction reported [33-38]. Stoma formation may also lead to permanent alteration in body image, potentially affecting the perception of themselves and their relationship with others [39]. Patients with this knowledge can participate more actively in their consultations, and assume more responsibility for treatment decisions [40].

This paper reports the development of the first tumour- and treatment-specific HRQoL measure for anal cancer patients using rigorous EORTC QLQ module development guidelines [27]. Previously, HRQoL assessment of anal cancer patients has relied on measures designed to be generic to all cancer types or specific to other tumours such as colorectal cancer. These measures inadequately cover the issues faced by anal cancer patients such as radiation-induced skin toxicities. Skin toxicity is only assessed by the EORTC QLQ-CR29 in terms of sore skin around the anal area or stoma site but does not capture the more wide ranging impact on activities of daily living such as walking, lying down or sitting due to pain.

The development process included data from 153 patients at all stages of treatment, from 8 countries, and 34 HCPs with a special interest in the treatment and support of patients with anal cancer. Consistent with previous accounts in the literature, bowel functioning issues, in particular diarrhoea, and sexual problems were commonly reported in our study. Allal et al. [21] described a threefold increase in diarrhoea in their cohort compared with population norms while 31% of patients assessed by Das et al. [10] experienced diarrhoea "quite a bit" or "very much". Das and colleagues also highlighted sexual difficulties including sexual interest (65% patients), reduced enjoyment of sex (71%), difficulties getting aroused (72%), erectile dysfunction (67% of men who responded) and difficulties achieving orgasm (70% of women who responded).

Patient interviews provided a wider range of issues than the literature. Bowel-related issues were reported in all interviews and skin toxicities were frequent. The review process highlighted issues relating to treatment burden. The development process emphasises the importance of patient and HCP input into the selection of issues, in addition to reviewing the literature.

We identified 197 issues which were reduced to 65 questions for pilot testing. Twenty three of these were novel issues not included in the EORTC item library. No additional issues were identified for

inclusion after phase 3 testing, suggesting that the identification of issues during phase 1 had been comprehensive.

Pilot testing resulted in the removal of 40 questions, mainly due to lack of relevance or importance. Two of these questions relating to frequent defecation were combined into one new question asking about frequent bowel movements. Twenty five questions were retained and did not require any modifications to wording. We included one additional screening question asking about sexual activity. We were left with a 27 item questionnaire, the EORTC QLQ-ANL27 with four hypothesised subscales. Certain bowel questions (bowel urgency, feeling of not being able to completely empty one's bowels) were not relevant to patients with a stoma thus separate sections for stoma and non-stoma patients were created, as in the EORTC QLQ-CR29 [24].

Limitations

This paper covers the first three phases of development of the EORTC QLQ-ANL27. We have not examined the scale structure, responsiveness to change and sensitivity to known differences, which will be explored in the Phase 4 validation study. Although our patient cohort was multi-lingual and multi-cultural with recruitment across 8 countries covering different European regions and Canada, further testing of the questionnaire items will be needed to determine acceptability in other cultures.

Assessment of issues relied on patients' judgements of relevance and importance of issues to them at some stage since diagnosis and treatment. Some patients, especially those 2-5 years after treatment, may have found it difficult to recall aspects of their illness and to rate their relevance.

Conclusion

The EORTC QLQ-ANL27 has been developed with a large cohort of patients representing different cultures and languages, to quantify the incidence and extent of the HRQoL impact of anal cancer and its treatment. The measure captures acute and chronic effects of the disease and treatment and is the first anal cancer-specific HRQoL instrument. It is currently available upon request from the EORTC QLQ (<http://groups.eortc.be/qol/>) in 7 languages and is suitable for use in clinical trials as well as clinical practice in promoting engagement and ongoing regular contact with HCPs. In addition to facilitating the management of the late toxicity of anal cancer treatment on urinary,

bowel and sexual function, the EORTC QLQ-ANL27 will also allow clinicians to provide psychological support where needed.

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Conflict of Interest

None of the authors declare any conflict of interest

Ethical Approval

The studies described were subject to review by the Southampton and South West Hampshire Research Ethics Committee (REC nr 13/SC/0287)

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Table 1. Clinical and socio-demographic characteristics of patients recruited in Phase 1a and Phase 3

Variable	Phase 1a N=43	Phase 3 N=100
Patients recruited per country		
Canada	14 (33%)	14
Cyprus	6 (14%)	10
Germany	1 (2%)	7
Greece	—	5
Italy	—	18
Norway	—	6
Poland	6 (14%)	15
UK	16 (37%)	25
Gender		
Female	30 (70%)	64
Male	13 (30%)	36
Age (years)		
Mean (SD)	62.93 (9.32)	62.25 (9.81)
Range	45-85	39-88
Education level		
Less than compulsory	2 (5%)	1
Compulsory school education	14 (33%)	39
Post compulsory school education (college)	16 (37%)	38
University	11 (26%)	22
Employment status		
Full time	9 (21%)	22
Part time	4 (9%)	14

Homemaker	2 (5%)	7
Retired	21 (49%)	39
Sick leave	4 (9%)	3
Disability	—	3
None	1 (2%)	6
Other ¹	2 (5%)	2
Missing	—	4
Living situation		
Alone	15 (35%)	25
Partner	23 (54%)	49
Others	5 (12%)	18
Other ²	—	8
Disease status		
Localised	38 (88%)	85
Locoregional	5 (12%)	9
Missing	—	6
Treatment phase		
Acute	20 (47%)	41
Early	12 (28%)	32
Late	11 (26%)	18
Recurrence	—	9
Stoma		
Yes	7 (16%)	11
Permanent	6 (14%)	6
Temporary	1 (4%)	5
No	36 (84%)	89

Radiotherapy technique		
Intensity Modulated Radiotherapy (IMRT)	27 (63%)	63
Conformal Radiotherapy (CRT)	15 (35%)	33
Volumetric Modulated Arc Therapy (VMAT)	1 (2%)	0
Missing	—	4
Chemotherapy		
Mitomycin C (MMC) and Fluorouracil	35 (81%)	85
MMC and Capecitabine	3 (7%)	4
5FU, MMC and Cisplatin	—	1
Paclitaxel and Carboplatin	—	1
Fluorouracil	1 (2%)	0
Capecitabine	1 (2%)	0
Missing	2 (5%)	8
Co-morbidities ³		
None	21 (49%)	48
Renal	5 (12%)	3
Cardiac	3 (7%)	20
Respiratory	5 (12%)	10
Rheumatic	3 (7%)	4
Diabetes	0	7
Liver	0	1
Other ⁴	12 (28%)	15
Karnofsky Performance Status		
100 (Normal)	12 (28%)	—

90 (Able to carry on normal activity)	14 (33%)	—
80 (Normal activity with help)	8 (19%)	—
75	1 (2%)	—
70 (Cares for self; unable to carry on normal activity or to do active work)	4 (9%)	—
60 (Requires occasional assistance)	1 (2%)	—
50 (Requires considerable assistance and frequent medical care)	1 (2%)	—
40 (Disabled)	2 (5%)	—
ECOG Performance Status		
0 (Fully active)	—	56
1 (Restricted in physical strenuous activity)	—	34
2 (Unable to carry out work activities)	—	6
3 (Limited self-care)	—	4
4 (Completely disabled)	—	0

¹Other employment categories for Phase 1a patients include Semi-retired (n=1); Redundant (n=1) and for Phase 3 participants: Semi-retired (n=1); Application for pension (n=1)

²Other living situations described by Phase 3 patients included Carer (n=1); Nursing home (n=2); Not specified (n=5)

³N=8 (19%) Phase 1a patients and N=19 Phase 3 patient presented with more than one co-morbidity

⁴Other comorbidities presented by Phase 1a patients include: Thyroid problems (n=3); Reflux (n=2); Hypertension (n=1); Multiple sclerosis (n=1); Epilepsy (n=1); Hearing loss (n=1); HIV (n=1); Depression (n=1); Multiple myeloma (n=1). Phase 3 patients presented with Inflammatory bowel disease (n=2); Epilepsy (n=1); Thyroid problems (n=1); HIV (n=3); Skin problems (n=1); Ulcers (n=1); Pulmonary embolism (n=1); and Hypertension (n=5)

Table 2. Issues included in the EORTC QLQ-ANL27 and hypothesised conceptual scales

Conceptual Scale	Issues	Cronbach's alpha	Inter-item correlation (range)
Bowel	Flatulence Bowel incontinence Frequent defecation Bowel urgency Sensation of inability to effectively empty bowels	0.75	0.24 - 0.54
Pain/Discomfort	Painful bowel movements Pain or discomfort in the anus or anal opening Pain while sitting Discomfort in certain positions (e.g lying down) Soreness in treatment area Itchy / irritated skin in treated areas	0.85	0.32 - 0.68
Stoma	Skin reaction around stoma site Leakage of stools from stoma bag Unintentional release of gas / flatulence from stoma bag	0.78	0.32 - 0.83
Sexual	<i>General</i> Sexual interest Affected sex life Painful sexual intercourse		

	<i>Male</i>		
	Impotence	0.28	0.11 - 0.34
	<i>Female</i>		
	Vaginal dryness	0.40	0.02 – 0.74
	Vaginal narrowing		
	Vaginal pain		