

DEVELOPMENT OF A EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER MODULE TO ASSESS THE QUALITY OF LIFE OF PATIENTS WITH PROCTITIS AFTER PELVIC RADIOTHERAPY FOR MALIGNANCY

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Purpose: To describe the development of a proctitis-specific quality-of-life module to supplement the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Methods and Materials: The module was developed according to EORTC guidelines, which consisted of an extensive literature review to identify previously described issues and interviews conducted with seven health professionals and 10 patients to rationalize the item list for construction into a provisional module. The module developed was then pretested with 28 patients and five health professionals.

Results: The final module contains 21-items that are suitable to obtain information about the patients' quality of life after high-dose pelvic irradiation. The questionnaire has now been translated into four languages and commenced field testing in late 2007.

Conclusions: The EORTC QLQ-C30, supplemented by EORTC QLQ-PRT21, will enable health professionals to more accurately monitor the side effects that patients experience after pelvic irradiation. © 2008 Elsevier Inc.

Radiotherapy, proctitis, quality of life, pelvic cancer, rectal bleeding, treatment side effects.

INTRODUCTION

Radiotherapy is commonly used to treat cancers in the pelvic region. Radiation proctitis, one of the side effects experienced by patients after receiving radical doses of pelvic irradiation (50–70 Gy), is an unpleasant recurrent clinical syndrome characterized by bouts of anorectal pain, profuse rectal bleeding or blood clots, explosive bowel urgency, frequent diarrhea, profuse mucous discharge, and fecal and/or mucous incontinence (1, 2). The most common presenting complaint is adverse rectal bleeding (3–7). Approximately 85% of patients who experience radiation proctitis develop symptoms within the first 2 years after treatment (3). These symptoms may persist in some patients and therefore have profound social and psychological consequences for the patient and their family (8, 9).

The reported incidence of chronic radiation proctitis ranges between 2% and 20% in retrospective studies of varying

sample size, radiation doses, and types of pelvic malignancy treated (2, 3). However, the true incidence of radiation proctitis is likely to be underestimated because most reports rely on medical practitioner-based evaluation of symptoms, often utilizing toxicity scales that focus on rectal bleeding and do not include assessment of urgency or defecation and/or mucous/fecal incontinence. The move to conformal radiation techniques and intensity-modulated radiotherapy has helped to reduce toxicity of pelvic treatment (10). However, more recently there has been an increase in the range of indications for pelvic radiation (e.g., use of neoadjuvant bowel radiotherapy and postprostatectomy radiotherapy) (11), and there has also been a trend toward dose-escalation studies (12). Given that the diagnosis of radiation proctitis has traditionally been made reluctantly, there is a risk that radiation proctitis will become a bigger issue for patients, particularly if it continues to be unrecognized and managed in the future. Prospective

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trials are needed to establish the true incidence of the condition and the effect it has on patients' quality of life and to determine the best forms of treatment. These should include valid QoL scales to reliably assess the effectiveness of treatment in patients incapacitated by the condition (13).

Quality-of-life instruments provide a reliable and valid method of assessing the impact of treatment on patients' lives and evaluating topical, medical, nutritional, and surgical options (14). Recent research by Olopade *et al.* (15) reported that the Vaizey incontinence questionnaire and a modified inflammatory bowel disease questionnaire can be used to assess patients' gastrointestinal chronic toxicity and disability experienced after pelvic radiotherapy. Although the combined questionnaires ask patients about side effects after pelvic irradiation they do not focus on determining the severity of radiation proctitis and how this is impacting on the patients' quality of life. To date, there has been only one questionnaire developed to measure the quality of life of patients with radiation proctitis (8). However, this questionnaire does not cover all issues related to proctitis or allow easy comparison with other measures of core quality of life issues, because it is a stand-alone instrument. Therefore, there is a need to develop a questionnaire that can be used to adequately and reliably measure the severity of proctitis and other side effects after pelvic irradiation.

The European Organization for Research and Treatment of Cancer (EORTC) has developed a standard 30-item questionnaire, the EORTC QLQ-C30, which can be used to assess the quality of life of cancer patients. This questionnaire 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 (16). It is designed to be used in conjunction with specific modules that focus on the patient's diagnosis and symptoms. Quality-of-life modules have previously been developed for cervical cancer (CX24) and prostate cancer (PR25). The cervical cancer module has already been validated, and the module for prostate cancer is in its final phase of development and is already being used to assess quality of life in some prostate studies (17, 18). Although these modules are useful for identifying disease-specific issues, they fail to adequately cover the problems associated with radiation proctitis. Currently there is no specific questionnaire that comprehensively assesses the quality of life concerns of patients who are experiencing proctitis. The aim of this study was to develop and test a proctitis-specific quality-of-life module that can be used in conjunction with the EORTC QLQ-C30 quality-of-life questionnaire. The proposed proctitis module has the potential to enable health professionals to identify issues that can easily be overlooked in a busy clinic situation and act as a measure to record change and provide a robust outcome measure in this neglected area.

METHODS AND MATERIALS

Ethics approval was gained from Edith Cowan University and the hospitals involved. All participants were provided with a relevant information sheet, and written informed consent was obtained.

Guidelines for the development of EORTC modules (19) were followed. However, the module development process was interrupted because of resource constraints, during which time the EORTC substantially changed the module development process to improve the robustness of the procedure (20). Nonetheless, the EORTC Quality of Life Executive Committee guided our latter development of the questionnaire and enabled us to incorporate our earlier work into the phases that are recommended for module development. The EORTC guidelines on module development recommend that the following phases be used: Phase 1: generation of quality-of-life issues; Phase 2: construction of items for the provisional module; Phase 3: pretesting; and Phase 4: field testing (20).

Phase 1a: generation of quality-of-life issues

A list of relevant quality-of-life issues was developed by (1) conducting a literature search, (2) interviewing health professionals, and (3) conducting patient interviews as recommended by the EORTC guidelines for module development (20).

The literature was searched for quality-of-life issues after pelvic irradiation and for existing questionnaires on proctitis using two databases: MEDLINE from January 1966 to June 2000 and PSYCHINFO from January 1992 to June 2000. The following key words were used: rectal bleeding, proctitis, quality of life, radiotherapy side effects, pelvic irradiation, and bowel dysfunction. A provisional list of items was developed.

Phase 1b: interviews with health professionals and patients

The provisional list and core instrument were presented at the "Radiation Induced Rectal Injury Scientific Workshop" held in Port Douglas, Queensland, Australia, in June 2000, and participants were invited to provide feedback on the appropriateness of content and breadth of coverage. Health professionals were also asked to identify any other issues that they thought should be included and which items they thought should be rephrased or removed. Finally, health professionals were invited to indicate the five most important items they believed should be included.

Radiation oncologists in Western Australia and South Australia recruited patients. Patients were eligible if they had been experiencing proctitis symptoms for more than 1 year. The provisional list of issues and the QLQ-C30 were discussed with each patient on an individual basis. Patients were asked whether they understood the questions, how relevant the issues were to them, whether they felt any additional issues should be included, and which five symptoms were most relevant to them and therefore should be included in the questionnaire.

Phase 2: construction of items for the provisional module

Phase 2 began in 2005 and followed the 2002 EORTC revised guidelines for module development (20). First, an additional literature search was conducted to ensure that no new articles on radiation proctitis measurement had been published between June 2000 and June 2005. Next the EORTC QLG Item Bank (21) was consulted to determine whether any of the items already existed. Finally, new items were constructed to be consistent with the Item Bank, and a revised questionnaire was developed. Questions were designed so that they were compatible with the response categories of the EORTC QLQ-C30, relevant to patients within a 1-week time frame, not too confronting or upsetting to patients, requiring patients to consider experiences of stress rather than just change in behavior, and finally, worded positively when referring to patients' experiences of receiving support.

Phase 3: pretesting

The aims of pretesting the module were to identify and solve potential problems in its administration, to determine the need for additional questions and/or the elimination of others, and to determine the overall degree of eliciting attention and interest. During this phase, patients individually completed the self-administered EORTC QLQ-C30 and provisional proctitis-specific module and were then interviewed on an individual basis. Patients were eligible for this phase if they were receiving or had completed a radical course of pelvic irradiation (50–70 Gy) during 2005 or 2006, experiencing side effects from their treatment, and able to converse freely in English.

The interview protocol followed the EORTC guidelines (20) and consisted of a total of six specific questions and two general questions: (1) Were there questions that you found difficult to answer? (2) Were there questions that you found annoying? (3) Were there questions that you found confusing? (4) Were there questions that you found upsetting? (5) Were there questions that you found intrusive? (6) Were there questions that you found irrelevant? (7) Do you have other comments about these questions? (8) Can you think of additional issues that are relevant for you but are not included in this questionnaire?

In addition to patient interviews, health professionals familiar with proctitis symptoms reviewed the proposed module and participated in an interview about the module.

The results obtained were summarized according to the prevalence of each problem, the severity of each problem, and the range of responses recorded for each question. Cut-off points to retain items were as follows: mean score for patient responses of ≥ 1.5 (patients scored items from 1 = not at all to 4 = very much); range for patient responses of ≥ 2 points; prevalence ratio for patients experiencing the symptoms $>30\%$; priority given to item by $\geq 15\%$ of patients; and identified as high priority by health professionals.

The EORTC guidelines (20) suggest that items meeting at least three of these five criteria may be retained in the list and that items meeting two or fewer criteria can be deleted. Additional items identified by more than one third of patients were considered as additional questions to be added to the module, unless they were already covered in the core module. Items were rewritten if patients had difficulty answering them or if health professionals recommended that changes be made.

This phase was conducted in two stages in Australia. After the module had been tested on 10 patients, the questionnaire was modified appropriately. Stage 2 consisted of further pretesting to increase the sample size and ensure that the revisions made were acceptable to the patients.

Phase 4: field testing

During Phase 4 the proposed module will be administered to large numbers of patients who are undergoing pelvic irradiation. This phase will begin once Phase 3 is completed internationally and approved by the EORTC module development committee.

RESULTS

Phase 1a: generation of quality-of-life issues

Seventy-two articles were identified and evaluated for relevance in relation to radiation proctitis and quality of life. Thirty-three of these articles described validated and nonvalidated questionnaires that had been used to evaluate cancer patients' quality of life after pelvic irradiation. Among these, only one questionnaire was designed to assess radiation pro-

ctitis (8), and six questionnaires (21–26) included a section examining bowel function after pelvic radiation. A list of 38 relevant quality-of-life issues (e.g., rectal pain) was developed. Examples of these issues include rectal pain and flatus. These issues were then compiled into the following seven categories: (1) incontinence (flatus, mucous, solids, liquids, nocturnal), (2) pain (abdominal bloating, pain and cramps, anal pain, rectal pain), (3) bleeding (fresh or dark clots from rectum), (4) social function (limits social engagements because of fear incontinence), (5) role and performance (limits daily activity, difficulty bending due to bowel problem, avoids certain foods), (6) fatigue (reduction in energy due to bowel problem), and (7) emotional function (feeling anxious, frustrated, unattractive, embarrassed).

Phase 1b: interviews with health professionals and patients

Seven health professionals (two radiation oncologists, one gastroenterologist, two general surgeons interested in this area, and two radiation oncology nurses) were interviewed after the presentation that was made in Queensland in June 2000. The number of health professionals interviewed in this phase is consistent with the EORTC guidelines, which recommend that at least three to five health professionals be interviewed about issues to be included in the module (20). Participants provided feedback on the appropriateness of content and breadth of coverage of the issues and indicated the five most important items they believed should be included.

Interviews were conducted with 10 patients (7 prostate cancer patients and 3 cervix cancer patients) who had been experiencing significant radiation-induced proctitis. Patients graded the relevance of each issue and described the symptoms they had experienced. Patients found it difficult to prioritize which five symptoms were most relevant to them. The number of patients included in this phase of the study is consistent with the EORTC guidelines, which state that 5–10 patients be included in this phase of the study so that it is possible "to determine the extent to which patients have experienced the problems, limitations or positive experiences during the period of their disease and to check for any significant omissions." (19, p. 8).

As a result of the interviews with health professionals and patients, a number of issues were reworded to overcome phrasing ambiguity. Four issues were combined as they overlapped. Each of the categories described in Phase 1a was incorporated into items apart from the category on fatigue because this category was adequately covered by the QLQ-C30. Eight issues were deleted because they did not add new information or were covered in QLQ-C30. Four new issues were identified. After rewording, removing, adding, and condensing of issues, 26 issues remained.

Phase 2: construction of items for the provisional module

The EORTC Quality of Life Group has developed a database known as the "Item Bank," which provides users with a list of all items that have been included in quality-of-life assessments and the modules that contain each of the items. In 2005 the existing 26 issues were compared with the Item

Bank, and after deletion and addition of new items the resulting questionnaire had 25 questions or items. An example item was, “Have you had a bloated feeling in your abdomen?” Twenty-two of the questions were structured in the EORTC Likert response format, whereby patients were required to specify their response (range from “not at all” to “very much”). Two questions specified yes/no answers: “Have you needed to take medication to control diarrhoea?” and “Would you like more assistance with your bowel problem?” One question asked patients to enter the maximum number of times they have opened their bowels in a 24-h period during the past week. Although these latter three questions did not follow the EORTC guidelines, participating health professionals thought they were important because they identified the patients’ need for help in dealing with their proctitis symptoms.

Phase 3: pretesting

This phase was completed in two stages. Five health professionals and 28 patients were interviewed.

Stage 1. Five health professionals who were familiar with radiation proctitis were interviewed: one consultant, one registrar, one nurse manager, one registered nurse, and one enrolled nurse.

Ten eligible patients completed the module and were interviewed. Patient profiles are shown in Table 1.

Analysis of the interview responses were as follows. Two questions (“Have you had any unintentional release (leakage) of formed stools?” and “Have you lost control of your bowels when asleep?”) were deleted because they were associated with a low severity (mean <1.5), a low variability (range <2), and a prevalence ratio of <30%, and health professionals rated these two questions as irrelevant.

Nine questions were rephrased because patients and/or health professionals thought that the phrasing was difficult. Four additional items were requested by the health professionals and two by patients. Of these, five items were already addressed in the QLQ-C30 (relating to fatigue and social interference issues), and one related to urinary dysfunction and hence was not relevant to this module. The module was revised to contain 21 items with an additional optional feedback question that investigators could include if they wanted real-time feedback (“Would you like more assistance with your bowel problem?”). This revised module was submitted to the EORTC and approved for translation.

Stage 2. The 21-item module (EORTC QLQ-PRT21) was further tested with 18 patients to confirm that the revisions made were acceptable. Although two questions met the criteria for deletion because they had low prevalence ratios and means, they were retained because the symptom problems, although not common, were rated as very important by participating health professionals as manifestations of severe proctitis. No additional items were identified, and no further rewording was required.

The EORTC guidelines for module development recommend that 10–15 patients be included in this phase of the study, so that it is possible to identify any problems in its

Table 1. Patient characteristics for Phase 3 (Stages 1 and 2)

Patient characteristics	Stage 1	Stage 2
Patients in each stage	10	18
Age (y)		
Mean (SD)	72.60 (5.83)	71.7 (10.31)
Range	65–82	58–87
Male (%)	80	77.7
Diagnosis		
Prostate	8	10
Bladder	1	2
Rectum		2
Anal canal		3
Pelvic non-Hodgkin’s lymphoma		1
Uretic	1	
On treatment: high-dose pelvic radiation	5	8
Off treatment (<1 month)	2	7
Off treatment (<6 month)	2	
Off treatment (<1 year)	1	2
Off treatment (>1 year)		1

Values are *n* unless otherwise noted.

administration and to determine whether additional items needed to be added or alternatively items need to be removed (19). During Stage 1 of this phase 10 patients completed the module and were interviewed. The researchers then modified the module and further tested it with an additional 18 patients to further ensure its appropriateness for this population of patients. This phase of module development therefore extends beyond the recommended number of participants that should be included during Phase 3 of the study, further demonstrating its acceptability for people who have received pelvic irradiation.

The module developed is shown in Fig. 1. This module has been translated into Norwegian, Swedish, German, and French and is currently being pretested in these languages before large-scale field testing begins.

DISCUSSION

By collaborating directly with the EORTC Quality of Life Group in the development of this questionnaire, we believe that we have developed a provisional instrument that comprehensively captures the major and relevant proctitis symptoms experienced by patients who have undertaken high-dose pelvic irradiation. It can be self-administered by patients and is designed to be completed in conjunction with the EORTC-QLQ-C30 questionnaire. In 2000, at the time of commencement of our module development, there were only seven published articles that included a section on examining bowel function after pelvic radiation; only one (8) investigated radiation proctitis directly, and none can be considered as a criterion standard for the assessment of this condition. A recent literature search (January 2007) did not produce any additional references on questionnaires for the assessment of radiation proctitis.

The items included in our proctitis module (EORTC QLQ-PRT21) are designed to capture the specific bowel side effects experienced by patients who have received pelvic

EORTC QLQ –PRT21 Module used during Phase 3 of Study**EORTC QLQ – PRT21**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had a bloated feeling in your abdomen?	1	2	3	4
32. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
33. Have you had excessive gurgling noise from your abdomen?	1	2	3	4
34. Have you had any unintentional release (leakage) of wind or mucous?	1	2	3	4
35. Have you had any unintentional release (leakage) of liquid stools?	1	2	3	4
36. Have you needed to get up at night to open your bowels?	1	2	3	4
37. Have you had abdominal pain or cramping not related to a bowel movement.	1	2	3	4
38. Have you had pain /discomfort related to your anal opening (back passage)?	1	2	3	4
39. Have you had pain in your rectum (deep inside the back passage)?	1	2	3	4
40. Have you had bright blood in your motions?	1	2	3	4
41. Have you had dark blood clots in your motions?	1	2	3	4
42. Does passing water cause your bowels to act immediately?	1	2	3	4
43. Have you had to wear a pad because of your bowel problems?	1	2	3	4
44. Have you had difficulty going out of the house, because you needed to be close to a toilet, because of bowel problems?	1	2	3	4
45. Have your daily activities been limited by your bowel problems?	1	2	3	4
46. Did your treatment restrict the types of food you can eat due to your bowel problems?	1	2	3	4
47. Did you worry about your bowel problem?	1	2	3	4
48. Did you feel embarrassed by your bowel problem?	1	2	3	4
49. How unhappy would you feel if you lived the rest of your life with your bowel habit as it is now?	1	2	3	4
50. Have you needed to take medication to control diarrhoea?	Yes		No	
51. What was the highest number of times you had to open your bowels in the last 24 hours? Please indicate number in box				<input type="text"/>
52. Would you like more assistance to manage your bowel problem? (optional question)	Yes		No	

Fig. 1. Proctitis-specific quality-of-life module to supplement the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PRT21), used during Phase 3 of the study.

irradiation. This module differs from the EORTC modules for cervical cancer (CX24) and prostate cancer (PR25) by focusing on the following bowel functions: incontinence, pain, bleeding, social function, role and performance, fatigue,

and emotional function. In comparison, the cervical cancer module focuses specifically on symptoms relating to the treatment of the vagina and cervix, and the prostate cancer module focuses on broader side effects that may occur as

a result of receiving surgery or radiation therapy to the prostate or more general androgen suppression side effects.

Three questions included in this proctitis module were not consistent with the EORTC's question formatting recommendations. Two questions were included for clinical interpretation because they identified issues not amenable to Likert scale categorization but important for interpreting symptom state (requirements for diarrhea and the maximum number of times patients had opened their bowels in a 24-h period within the past week). We believe they were useful and common indicators of severity. An additional optional question ("Would you like more assistance with your bowel problem?") was designed to prompt the reviewer of the patient's responses that the patient has a problem that requires additional assistance. Nonetheless, this question is proposed as an optional question only. Although the module focuses on determining the impact that radiotherapy has on patient's quality of life, it is anticipated that this instrument will also be suitable for use with non-radiation-induced proctitis, with only minor modifications.

Although the EORTC quality-of-life guidelines for module development changed over the 7 years of our development period, we were able to take steps to ensure that the module complied with the evolving EORTC requirements. Essentially this was through regular liaison with EORTC Quality of Life Development Committee for guidance, support, and annual provision of progress reports. The introduction of the revised EORTC guidelines (20) assisted the researchers in improving the methods used to develop the initial questions for the questionnaire and revising items that were included before further testing of the module. Testing of the module with 28 patients demonstrates that the module seems to capture the breadth of issues important to patients experiencing proctitis-related symptoms.

At this stage, only Australian data using an "Australian-English" module is available. Culturally appropriate translations are now required by the EORTC, for the different languages and countries likely to be involved in the final

prospective field criterion validation study. For this study the EORTC has translated the module into four European languages (French, German, Norwegian, and Swedish) for piloting in late 2007. It is anticipated that this module will also be translated, piloted, and field tested in other countries at a later stage.

CONCLUSIONS

The proctitis-specific module, EORTC QLQ-PRT21, presented in this article has been developed under EORTC guidance for the assessment of quality-of-life experience of patient with specific conditions—radiation proctitis. The authors believe that the proctitis module will facilitate a broader and more comprehensive characterization of the problem that patients experience. Such characterization offers the opportunity to improve the sensitivity and specificity of the diagnosis of the condition and the ability to detect small changes in the severity of the condition, and to act as a surrogate endpoint for effective clinical investigation of its prevalence and response to therapy. However, before this questionnaire is implemented into regular clinical practice it needs to be formally tested for validity and reliability with a larger sample of patients who are experiencing radiation proctitis (Phase 4). This process will include confirming its cultural applicability, and this process could lead to some refinement of the content and structure of the current questionnaire. This is being conducted, with the intention of the final field validation study to begin in 2008. Once field testing has been conducted, guidelines will be made available to advise health professionals on the use of the questionnaire and how to manage participant responses. Although this module was developed with patients experiencing radiation-induced proctitis, the EORTC and authors of this report encourage other researchers to investigate its role in assessing other potentially similar conditions, such as non-radiation-induced proctitis.

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