Development and validation of a patient reported outcome measure for health-related quality of life for locally recurrent rectal cancer: a multicentre, three-phase, mixed-methods, cohort study

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Summary

Background Locally recurrent rectal cancer (LRRC) occurs in 5–10% of patients following previous treatment of rectal cancer. It has a significant impact on patients' overall health-related quality of life (HrQoL). Major advances in surgical treatments have led to improved survival outcomes. However, due to the lack of disease-specific, validated patient-reported outcome measure (PROM), HrQoL, is variably assessed. The aim of this study is to develop a disease-specific, psychometrically robust, and validated PROM for use in LRRC.

Methods A multicentre, three phase, mixed-methods, observational study was performed across five centres in the UK and Australia. Adult patients (>18 years old) with an existing or previously treated LRRC within the last 2 years were eligible to participate. Patients completed the proposed LRRC-QoL, EORTC QLQ-CR29, and FACT-C questionnaires. Scale structure was analysed using multi-trait scaling analysis and exploratory factor analysis, reliability was assessed using Cronbach's and the intra-class coefficient, convergent validity was assessed using Pearson's correlation, and known-groups comparison was assessed using the student t-test or ANOVA.

Findings Between 01/03/2015 and 31/12/2019, 117 patients with a diagnosis of LRRC were recruited. The final scale structure of the LRRC-QoL consisted of nine multi-item scales (healthcare services, psychological impact, pain, urostomy-related symptoms, lower limb symptoms, stoma, sexual function, sexual interest, and urinary symptoms) and three single items. Cronbach's Alpha and Intraclass correlation values of >0.7 across the majority of scales supported overall reliability. Convergent validity was demonstrated between LRRC-QoL Pain Scale and FACT-C Physical Well Being scale ($r = 0.528$, $p < 0.001$), LRRC-QoL Psychological Impact scale with EORTC QLQ CR29 Body Image ($r = 0.680$, $p < 0.001$) and the FACT-C Emotional Well Being scale ($r = 0.326$, $p < 0.001$), and LRRC-QoL Urinary Symptoms scale with EORTC QLQ-CR29 Urinary Frequency scale ($r = 0.310$, $p < 0.001$). Known-groups validity was demonstrated for gender, disease location, treatment intent, and re-recurrent disease.

Interpretation The LRRC-QoL has demonstrated robust psychometric properties and can be used in clinical and academic practice.

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Research in context

Evidence before this study

Phase I of this project evaluated the current landscape for health-related quality of life (HrQoL) assessment in locally recurrent rectal cancer (LRRC). A systematic literature search was performed across three databases: MEDLINE (1966–January 2013), EMBASE, and CINAHL, with searches limited to the English language. The syntax contained the term LRRC in combination with the terms 'HrQoL', 'QoL', 'symptom control', 'questionnaires', 'physical distress', 'psychological distress', and 'psychosocial distress'. This identified twelve studies reporting HrQoL in LRRC using a combination of non-validated, generic, and ad hoc PROMs, with no disease-specific measure for use in LRRC identified. Supplementary interviews with patients and healthcare professionals identified a total of twenty-one HrQoL categories organised into six themes. On comparison of these identified categories and themes with existing questionnaires, it became apparent that there were several HrQoL issues missing that were relevant to patients with LRRC. Phase II of the project led to the design of the provisional LRRC-QoL questionnaire, ensuring its relevance, comprehension, and acceptability using cognitive patient interviews prior to psychometric testing.

Added value of this study

In Phase III of this project, we assess the psychometric properties of the LRRC-QoL, in terms of its scale structure, reliability and validity. The revised LRRC-QoL consists of nine multi-item scales (healthcare services, psychological impact, pain, urostomy-related symptoms, lower limb symptoms, stoma, sexual interest, and urinary symptoms) and three single items. The LRRC-QoL should be administered to patients undergoing all treatment for LRRC, including surgery, chemotherapy ± radiotherapy, to assess HrQoL in a standardised manner.

Implications of all the available evidence

The LRRC-QoL promises to be the new standard for health-related quality of life assessment in patients with locally recurrent rectal cancer. It is ready to be used in clinical and academic practice.

Introduction

Locally recurrent rectal cancer is a complex clinical entity, occurring in approximately 5–10% of patients. Given the global incidence of colorectal cancer was 1,931,590 cases in 2020,[1] with a third being rectal cancer, locally recurrent rectal cancer (LRRC) affects a significant proportion of patients worldwide. LRRC represents a heterogenous patient cohort requiring tailored treatment strategies based on previous oncological and surgical treatments, recurrent tumour characteristics and operability, and patient factors. The management of LRRC has undergone a significant evolution over the last decade,[2–4] leading to significant clinical and oncological improvements, with curative resection rates (R0) of 65% and 5-year survival of 51%.[4–6]

National and international initiatives such as the Association of Coloproctologists of Great Britain and Ireland Improving outcomes in Advanced Colorectal Tumours (IMPACT) and the PelvEx Collaborative have helped drive improvements in LRRC through signposting clinical services and techniques, establishing referral pathways, and developing clinical guidance.[7,8] PelvEx has led the way in creating a data-driven, evidence-based approach to managing patients with LRRC, with international open outcome reporting of a range of post-operative clinical outcomes.[9] However, in recent times, there has been a growing recognition that health-related quality of life (HrQoL) also needs to be appropriately measured with integrated reporting in this patient population.[10] This will provide broader based, patient-centred, contextual relevance to clinical and oncological outcomes such as morbidity, recovery, and survival. Dual outcome reporting of clinical and patient-reported outcome data aligns well with patient priorities in this setting, with equal value placed on overall survival and maintaining HrQoL.

To date, HrQoL assessment in this cohort of patients has been variable and methodologically flawed, primarily due to the use of multiple, non-validated patient-reported outcome measures (PROMs) to measure the complex and wide-ranging issues experienced by this cohort of patients.[11–13] The majority of available, validated PROMs used for primary rectal cancer, do not adequately measure, assess, or report the issues relevant to patients with LRRC, with less than fifty percent coverage of key HrQoL issues in LRRC.[14] Furthermore, the significant heterogeneity in outcome assessment of HrQoL outcomes prevents meaningful comparison and data synthesis of current best evidence. HrQoL is a complex construct and must be appropriately assessed, interpreted, and reported to obtain meaningful results which are relevant and applicable to the target population. The aim of this study was to develop and validate a psychometrically robust, disease-specific PROM for use in patients with LRRC.

Methods

Study design and participants

A multicentre, international, three phase mixed-methods, observational study was performed between 01/01/2012 and 31/12/2019 across five centres in the UK and Australia. The study was approved by Yorkshire and The Humber Research Ethics Committee (REC reference: 12/YH/0518) in the UK and by the Sydney Local Health District Ethics Committee in Australia.

Patients with LRRC were recruited from prospectively held registries at each participating site. Eligible patients were approached for participation and were appropriately consented for enrolment into the study. Patient inclusion criteria included age ≥18 years old, with an existing resectable LRRC undergoing neo-adjuvant treatment(s) or had undergone surgically treatment for a LRRC within the last two years or had undergone non-surgical palliative treatment of LRRC and were able to read and write English, and provide written, informed consent. Exclusion criteria included patients who declined treatment based on individual choice or were considered too frail to pursue either surgical or oncological treatments.

The development of the LRRC-QoL is in keeping with guidance on PROM development from several organisations including the U.S. Food and Drug Agency,[15,16] The Medical Outcomes Trust,[17] the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[18,19] and the European Organisation for Research and Treatment of Cancer (EORTC).[20,21] Based on this collective guidance, three distinct phases of LRRC-QoL were developed; Phase I: Development of a Conceptual Framework, Phase II: Design and Pre-testing of the LRRC-QoL, and Phase III: Psychometric Analysis. Phase I and II design and results are summarised below, with the main focus of this manuscript being on Phase III.

Phase I: development of a conceptual framework

Content validity for the LRRC-QoL was established in Phase I by identifying HrQoL issues relevant to patients with LRRC using a top-down, bottom-up approach through dedicated systematic reviews and patient focus groups.[12,13] This underpinned the development of a conceptual framework, consisting of five domains: symptoms, sexual function, psychological impact, role and social functioning, and future perspective. The details of this phase have been previously published.[22]

Phase II: design and pre-testing of the LRRC-QoL

A pragmatic decision was made to design the LRRC-QoL based on the EORTC questionnaires, with the aim to use the LRRC-QoL as a modular questionnaire with the EORCT core questionnaire, EORTC QLQ-C30. HrQoL issues identified in Phase I were converted into a list of sixty-six questions (items) utilising the EORTC item bank[23] and the PROQUOLID database. A modified Delphi exercise was undertaken to ensure clarity, breadth of coverage, and to determine item inclusion into the preliminary LRRC-QoL. A total of seven healthcare professionals and six patients participated from the two lead sites (Leeds and Sydney). This modified Delphi consisted of seven leading healthcare professionals with significant experience and expertise in managing patients with LRRC. Six patients were selected locally from these two sites to reflect the broad and heterogenous nature of LRRC and its treatments. Three rounds of online Delphi surveys were used to identify key items to include in the LRRC-QoL questionnaire. Participants were asked to score items for inclusion into the LRRC-QoL based on their importance. Each item was scored on a numerical Likert scale ranging from 1 to 9, with 1 being the least important and having the least impact on HrQoL and 9 being the most important with the most impact on HrQoL. Rankings of 1–3 were considered of low importance, 4–6 were considered of moderate importance and 7–9 were considered of high importance. Patients were instructed to score all items, irrespective of whether this was personally applicable or relevant to them. Each round was open for four weeks with weekly email reminders. The frequency of scores in each category of importance (low, moderate and high) and the mean overall scores were calculated for healthcare professionals and patients for each consecutive. Results for each participating group were shown between each consecutive Delph round. Following all three Delphi rounds an online consensus meeting was held to review all items which had achieved consensus and discuss items which did not reach consensus. Items that had a discrepancy in scores between healthcare professionals and patients and items which could be amalgamated were discussed and real time online polling was used to identify whether consensus had been achieved.

All 13 participants completed three rounds of Delphi voting and the final consensus meeting, leading to the identification of 29 high priority items, the amalgamation of 24 items into 14 items and the rejection of 13 items (Supplementary Material—Fig. S1). These forty-three items were mapped to the EORTC QLQ-C30 questionnaire, with overlapping items removed, leaving thirty-nine items in the provisional item list. These 39 items were operationalised into the following domains Symptoms, Psychological Impact, Sexual Function, Future Perspective, and Healthcare Services to design the preliminary LRRC-QoL questionnaire.

The preliminary LRRC-QoL underwent pre-testing using cognitive interviews in 27 patients. The Question Appraisal System (QAS-99) was used to identify and categorise any issues with items including reading, instructions, clarity, assumptions, knowledge, sensitivity/bias, response, and other problems.[24] Similar issues were identified by the UK and Australian populations (Supplementary Material—Table S1), with all issues solved by consensus through discussion by the LRRC-

QoL expert panel. This led to a preliminary version of the LRRC-QoL consisting of 32 questions organised into five domains: Symptoms, Sexual Function, Psychological Impact, Future Perspective, and Healthcare Services ready for psychometric testing in Phase III.

Phase III: psychometric analysis

A cross-sectional, observational study was undertaken across five centres: 3 UK and 2 Australian between 01/03/2015 and 31/12/2019. All eligible patients were invited to participate in the study. A self-complete pack was sent to eligible patients, consisting of a Patient Information leaflet explaining the premise of the study, a consent form, a baseline demographics questionnaire, the LRRC-QOL questionnaire, as well as additional quality of life measures including the EORTC QLQ-CR29, and FACT-C. Information concerning gender was self-reported by participants and collected using the demographics form. A self-addressed stamped envelope was provided to return the questionnaires back to the clinical centre. All patients were invited to participate in completing a second questionnaire pack 10–14 days following the return of the first questionnaire pack.

Patients were appropriately sampled across the spectrum of disease for LRRC ensuring appropriate representation of the wider population. A purposive sampling strategy was employed to ensure appropriate representation across gender, pelvic recurrence subtype and treatment strategies. This purposive sampling strategy aimed to target equal number of male and female patients across each pelvic recurrence subtype (i.e. anterior, central, lateral and posterior). This strategy was employed to ensure representativeness of the patient population this purposive sampling strategy was previously employed in Phase 1.[22] There is no formal sample size calculation for the development of PRO measures, however, recommended guidelines state 5–10 patients should be recruited per item within the questionnaire.[20]

Data analysis

All data were analysed using SPSS for Mac, version 22 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL). This manuscript was prepared in accordance with the Strobe reporting guidelines.[25,26] Data analysis was undertaken in a stepwise approach (Supplementary Material—Fig. S2). Descriptive analyses of the demographic and clinical characteristics of all participants were performed.

Data completeness was analysed to identify missing data at an item and scale level, the distribution of responses and floor/ceiling effects, and descriptive analyses of items. The criteria for acceptable levels of missing data are <10% for items, <50% for computable total scale scores, and for maximum endorsement frequencies is <80% (floor/ceiling effects <80%).[27,28] Handling of missing data for each scale was conducted using simple imputation using half-mean imputation. This is a valid and robust manner of missing data imputation for validating multi-item, multi-scale questionnaires.[29,30] The Shapiro–Wilk test was undertaken to assess the distribution of the data.

The scale structure of the LRRC-QoL was assessed using the principles of multi-trait analysis and exploratory factor analysis. Multi-trait scaling was used to determine whether the hypothesised items of the LRRC-QoL fit within the proposed scale structure. The item internal consistency was determined by measuring the item intercorrelation and the item-to-total correlation. Values of 0.3–0.7 were considered to be indicative of item intercorrelation. Item-to-total correlations are a measure of convergent validity, with a recommended value of 0.3. Item discriminant validity was indicated when the correlation for an item and its hypothesised scale is more than two standard errors higher than its correlations with another scale.[31,32] Item discriminant validity was also supported when correlations of <0.4 were observed between an item and other scales in the questionnaire. Scaling errors were considered to occur when items consistently correlated more highly with another scale or did not correlate with its hypothesised scale.

If multiple scaling errors were identified using multitrait scale analysis an exploratory factor analysis (EFA) would be conducted to identify clusters of items which were not previously hypothesised into a scale. Items which highly correlate together will load onto the same factor. The suitable of the data for EFA was determined using the Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy and Bartlett's Test of Sphericity. A KMO of >0.50 and a significant Bartlett's Test of Sphericity (<0.05) were considered to be suitable for EFA.

Reliability was assessed using Cronbach's Alpha coefficient and the Intraclass coefficient (ICC). Cronbach's Alpha assesses internal consistency, which is a measure of the homogeneity of a scale, with a magnitude of >0.70 considered to be acceptable. The ICC (test-retest measure) assesses the stability of the LRRC-QoL over a period of time during which the patient's clinical status remains stable. The ICC was used to measure the strength of agreement between repeated measures between baseline and 10–14 days. An ICC score of 0.7 or above is recommended to ensure good test-retest reliability. The ICC was calculated using a fixed effects analysis of variance (ANOVA) model[30] and reported along with 95% confidence interval values.

Convergent validity reflects the correlation between individual assessment tools measuring the same underlying concepts. This was assessed using Pearson's correlation between items and scales of the LRRC-QoL, EORTC CR29, and FACT-C based on a priori hypotheses. Five *a priori hypotheses were generated to demonstrate convergent validity following the confirmation of the scale structure (Supplementary material)*. Values of greater than 0.45 are considered to be highly correlated.

Known-groups comparison was evaluated to explore the ability of the LRRC-QoL to discriminate between patients differing in clinical status. The clinical parameters hypothesised to form mutually exclusive patients for subgroup comparison included disease stage (local recurrence versus local recurrence and metastatic disease), recurrent disease location (central, anterior, lateral, or posterior), treatment intention (curative versus palliative), and pre-operative treatments (chemoradiation versus none) and disease re-recurrence (distant versus local). Nine *a priori hypotheses were generated to demonstrate known-groups comparison following the confirmation of the scale structure (Supplementary material)*. The independent student t-test was used to examine differences in mean scores in 2 groups and the one-way analysis of variance (ANOVA) for more than 2 groups.

LRRC-Qol patient and public involvement and engagement (PPIE)

A dedicated PPIE group for the LRRC-QoL study was setup to provide oversight of the study from a patient perspective. The membership of this group was flexible to take into account the variable health status of the participants. Throughout the duration of the LRRC-QoL study there were six PPIE members overall, with a minimum of three members at any one time. There were four male members and two female members, representing the broad spectrum of LRRC. The PPIE group reviewed the LRRC-QoL at the start and completion of each phase of the study to ensure patient acceptability, representativeness and to limit patient burden.

Role of the funding source

This study received no financial support.

Results

A total of 243 patients were approached for participation in the psychometric analysis of the LRRC-QoL, with a total of 117 (48.1%) patients participating, with 84 (71.8%) male participants with a median age of 66 years (IQR 59–71). Median interval between primary rectal cancer and recurrence was 2 years (range 1–4). Seventy-four (63.2%) patients were treated with curative intent and 21 (17.9%) were treated with palliative intent, with missing data for 22 (18.8%) patients. Overall patient and disease characteristics are outlined in Table 1 with characteristics for non-responders available in the supplementary material (Table S3).

Data completeness

At baseline assessment seven items were considered to have a high rate of missing data (range 15.2%–32.5%), with six of these items assessing gynaecological symptoms or sexual function and one item related to the delivery of healthcare services. A pragmatic decision was made to retain all items related to gynaecological

Variable	Number of patients (percentage)
Gender	
Male	84 (71.8)
Female	33 (28.2)
Median age	66 (IQR 59–71)
Marital status	
Married	90 (76.9)
Living common law	5 (4.3)
Widowed	3 (2.6)
Separated	2 (1.7)
Divorced	4 (3.4)
Single	3 (2.6)
Unknown	10 (8.5)
Education status	
Secondary school	45 (38.5)
College	25 (21.4)
University	27 (23.1)
Other	9 (7.7)
Unknown	11 (9.4)
Employment status	
Self-employed	15 (12.8)
Home maker	1 (0.9)
Full time employment	8 (6.8)
Part time employment	6 (5.1)
Unemployed	1 (0.9)
Sick leave	10 (8.5)
Retired	63 (53.8)
Unknown	13 (11.1)
Mode of detection	
Surveillance	60 (51.3)
Symptomatic	27 (23.1)
Unknown	30 (25.6)
Pattern of recurrence	
Anterior	12 (10.3)
Central	25 (21.4)
Lateral	27 (23.1)
Posterior	20 (17.1)
Unknown	
Presence of metastatic disease	
Yes	71 (60.7)
No	12 (10.3)
Unknown	34 (29.1)
Treatment intent	
Curative	74 (63.2)
Palliative	21 (17.9)
Unknown	22 (18.8)
Palliative treatment	
Chemotherapy	16 (76.2)
Chemoradiation	4 (19.0)
Surgery	1 (4.8)
Pre-operative treatment	
None	24 (29.8)
Chemoradiation	36 (48.6)
Short course radiotherapy	1 (1.4)
Unknown	15 (20.3)

(Table 1 continues on next page)

Variable	Number of patients (percentage)
(Continued from previous page)	
Margin status	
R0	44 (59.5)
R1	17 (23.0)
Unknown	13 (17.6)
Post-operative treatments	
Chemotherapy	10 (13.5)
None	46 (62.2)
Unknown	18 (24.3)
Current disease status	
Disease free	43 (36.8)
Distant disease recurrence	4 (3.4)
Local disease recurrence	13 (11.1)
Unknown	57 (48.7)

Table 1: **Psychometric analysis: patient characteristics.**

symptoms and sexual function, given the personal nature of these questions and their impact on overall HrQoL. The item regarding frequency of consultations was excluded from further analysis. All items demonstrated response rates of <80% for single scores demonstrating low potential for floor/ceiling effects. Data completeness of >50% was observed for total computable scale scores for all the scales.

Scale structure of the LRRC-QoL

The initial multi-trait scaling analysis failed to demonstrate unidimensionality across several of the hypothesised scales including symptoms, sexual function, psychological impact and future perspective. The healthcare services scale was the only scale which demonstrated stable scale structure with good item internal consistency with a mean item intercorrelation value of 0.692, equal item-to-total correlations, and good item discriminant validity (Table 2). The future perspective scale demonstrated good item internal consistency and equal item-to-total correlations, it failed to demonstrated item discriminate validity as all items in the scale correlated with the psychological function scale. In view of this an EFA was performed, with a KMO measure of sampling adequacy of 0.684 and the Bartlett's statistic of 2171, df 435 $p < 0.001$. Nine factors emerged with an eigenvalue of 1.00, supported by the scree test criterion (Supplementary Material—Fig. S3). Based upon the extractions these nine scales were renamed healthcare services, psychological impact, urostomy related issues, urinary symptoms, sexual function, sexual activity, lower limb function, pain and discomfort, and stoma and wound issues. The extracted scales were further refined using the principles of multi-trait scaling analysis, which identified the pain and discomfort scale and the stoma and wound issues scales failed to illustrate unidimensionality (Table 3). Both these scales were further revised with removal of items that did not correlate, which led to the development of the pain scale, stoma scale, and three individual items.

Scale reliability

The LRRC-QoL demonstrated good reliability, with Cronbach's Alpha values of >0.7 for the majority of the scales (Table 4). The ICC values were all >0.7 indicating good temporal stability.

Scale validity

Convergent validity was demonstrated between the LRRC-QoL Pain Scale and the FACT-C Physical Well Being scale ($r = 0.528$, $p < 0.001$), the LRRC-QoL Psychological Impact scale with the EORTC QLQ CR29 Body Image ($r = 0.680$, $p < 0.001$) and the FACT-C Emotional Well Being scale ($r = 0.326$, $p < 0.001$), and the LRRC-QoL Urinary Symptoms scale with the EORTC QLQ-CR29 Urinary Frequency scale ($r = 0.310$, $p < 0.001$) (Supplementary Material—Tables S4 and S5).

The LRRC-QoL was able to discriminate between several clinically relevant groups, including gender, disease location, treatment intent, and re-recurrent disease (Supplementary Material—Tables S6–S8). Men reported significantly higher scores of sexual dysfunction, as measured by the Sexual Interest ($p = 0.006$) and Sexual Function ($p < 0.001$) scales. The Psychological Impact scale identified higher scores, indicating greater impact, in the patients with posterior recurrences ($p = 0.008$). The Urinary Symptoms scale identified higher scores, indicating a higher burden of symptoms and worse HrQoL, in patients with central recurrence ($p = 0.024$). Patients undergoing curative treatment

Scale	No of items	Mean item intercorrelation	Item discriminant validity (range of scores)	Item to total correlations
Symptoms	17	0.170	−0.04 to 0.588	−0.013 to 0.557
Psychological function	2	0.379	−0.005 to 0.218	0.289
Sexual function	4	0.426	−0.029 to 0.197	0.337–0.681
Future perspective	3	0.644	0.103–0.502	0.690–0.727
Healthcare services	4	0.692	0.118–0.328	0.759–0.817

Table 2: **Multitrait scaling analysis hypothesised LRRC-QoL scale structure.**

Scale	No of items	Mean item intercorrelation	Item discriminant validity (range of scores)	Item to total correlations
Healthcare services	4	0.634	−0.089 to 0.168	0.759–0.817
Psychological impact	5	0.503	−0.127 to 0.159	0.465–0.782
Sexual function				
Female	2	0.870	−0.068 to 0.273	0.326–0.371
Male	2	0.759	−0.143 to 0.378	0.443–0.508
Pain	4	0.295	−0.058–0.412	0.248–0.594
Urostomy related symptoms	3	0.833	−0.212 to 0.178	0.835–0.917
Lower limb symptoms	3	0.601	−0.078 to 0.296	0.603–0.711
Stoma	2	0.617	−0.009 to 0.326	0.766
Sexual interest	2	0.609	−0.019 to 0.261	0.609
Urinary symptoms	3	0.399	−0.157 to 0.571	0.391–0.535

Table 3: **Multitrait scaling analysis extracted LRRC-QoL scale structure.**

reported worse scores on the Sexual Function scale (p = 0.004). Patients with local re-recurrent disease reported higher pain scores as assessed by the Pain scale (p = 0.032).

Discussion

This study highlights the development of a psychometrically robust, disease-specific outcome measure for use in locally recurrent rectal cancer, demonstrating the LRRC-QoL's scale structure, reliability, and validity. The final scale structure of the LRRC-QoL consists of nine multi-item scales (healthcare services, psychological impact, pain, urostomy-related symptoms, lower limb symptoms, stoma, sexual interest, and urinary symptoms) and three single items as supported by multitrait scaling analysis and exploratory factor analysis. The LRRC-QoL captures and assesses the wide-ranging nature of issues which effect patients with LRRC, reflecting the heterogenous nature of the disease and its' management.

Scale	Cronbach's alpha (95% confidence intervals)	ICC (95% confidence intervals)
Female sexual function	0.95 (0.92–0.96)	0.92 (0.89–0.94)
Male sexual function	0.87 (0.82–0.91)	0.84 (0.79–0.88)
Psychological impact	0.79 (0.72–0.85)	0.85 (0.80–0.89)
Urostomy	0.93 (0.91–0.95)	0.88 (0.84–0.91)
Healthcare services	0.81 (0.74–0.86)	0.83 (0.77–0.87)
Lower limb symptoms	0.79 (0.71–0.85)	0.88 (0.84–0.91)
Urinary symptoms	0.62 (0.45–0.74)	0.77 (0.69–0.83)
Sexual interest	0.62 (0.45–0.74)	0.70 (0.60–0.78)
Stoma	0.75 (0.64–0.83)	0.88 (0.84–0.91)
Pain	0.70 (0.59–0.78)	0.81 (0.75–0.86)

Table 4: **LRRC-QoL reliability testing.**

For a patient reported outcome measure to have utility in clinical and academic practice it needs to be relevant, acceptable, and valid in its target patient population. The design of the LRRC-QoL ensures all of these three key facets have been addressed through its design and evaluation. The LRRC-QoL is underpinned by a robust conceptual framework ensuring all relevant and disease-specific HrQoL issues are addressed and operationalised into its framework.[22] Patient acceptability, comprehension, and relevance were evaluated and demonstrated using the Question Appraisal System. Psychometric evaluation was performed in a pre-specific, multi-step manner, with appropriate revision and refinement, thus ensuring the development of a streamlined, well-balanced, acceptable, reliable, and valid PROM. Using a combination of multitrait scaling analysis and factor analysis led to the development of a functional and logical systems-based structure to the items and scales within the LRRC-QoL. This ensured the underlying construct validity of the measure, whilst facilitating a modular and flexible system for future outcome assessment. This flexible, modular approach will enable the tailored use of the LRRC-QoL in certain population subsets, for example, the urostomy scale will be applicable to patients undergoing total pelvic exenteration or lower limb scale in patients undergoing sciatic nerve resection.

The LRRC-QoL demonstrates a robust scale structure, as confirmed by multitrait scaling analysis and exploratory factor analysis. The questionnaire includes six items with high levels of missing data (15.2–32.5%) at an individual item level. These items were included as they address gynaecological symptoms and sexual function. These were considered to be important items by the expert panel and our PPIE group. Furthermore, it is well acknowledged, that QoL items which are

considered to be of a personal nature have a higher rate of missing data.[33] The higher rates of missing data associated with these items are unlikely to be random in nature, it is likely that participating patients chose not to complete these items as there were considered embarrassing or not relevant. Furthermore, despite the higher rates of missing data, all these items performed well at multitrait scaling analysis and at EFA, suggesting their valid contribution to their underlying scale. The LRRC-QoL demonstrates excellent temporal and scale reliability, with high ICC and Cronbach's Alpha values of >0.70 for the majority of the scales, confirming the ability of the LRRC-QoL to produce highly reproducible scores on repeated applications. The convergent validity of the LRRC-QoL was relatively good, with the majority of a priori hypotheses correctly confirmed, with moderate to high correlations demonstrated between the LRRC-QoL, the FACT-C, and the EORTC CR29 questionnaires. This provided supporting evidence that the LRRC-QoL scales measure what they purport to measure. The LRRC-QoL was able to discriminate scores between clinically relevant and important groups of patients, including gender, disease location, treatment intent, and disease re-recurrence.

The LRRC-QoL has the potential to transform outcome assessment in LRRC, by attributing a value or range of values to HrQoL in patients with LRRC and integrate this with clinical and oncological data. The use of a disease-specific, validated measure will ensure greater accuracy, consistency, and sensitivity in outcome assessment. Its implementation into clinical and academic practice will help homogenise HrQoL assessment and outcome reporting. In clinical practice, the LRRC-QoL can be used to quantify patient symptoms, experience and overall satisfaction. The LRRC-QoL will assist in improving the overall reporting of symptoms and impact on HrQoL, leading to the disclosure and identification of potential issues not routinely reported and will aid the early detection and subsequent monitoring of symptoms. The LRRC-QoL is ideally suited for assessing symptoms in this manner as it encapsulates the wide range of potential symptoms patients can experience and can therefore help guide clinical decision-making. Given the significant burden of treatment for LRRC, utilising LRRC HrQoL scores as an additional outcome is of huge relevance in this cohort. By equating a value or a range of values to HrQoL using the LRRC-QoL and combining this data with oncological and surgical outcome data, will ensure the presentation of a balanced and measured perspective when discussing and considering potential treatment options. The combined presentation of quantitative data including LRRC HrQoL, oncological and surgical outcomes should be provided to patients when counselling for potential treatments during the decision-making process. The values derived using the LRRC-QoL can be integrated with established survival data to provide a dual 'quality of survival' measure to help guide clinicians and patients with clinical decision–making, including, type of treatment initiated and emphasis of treatment i.e. curative versus palliative. The key strength of the LRRC-QoL is that it assesses a wide range of HrQoL issues relevant to patients with LRRC. This overcomes the tradition approach to HrQoL assessment in this cohort of patients of using multiple, generic, non-validated assessment measures addressing a variety of different HrQoL issues. This will help reduce patient burden and help minimise attrition, thus overcoming the current methodological limitations of assessing HrQoL in LRRC.

LRRC represents a relatively rare occurrence following previous curative surgery, however, despite its low overall incidence, it can have a significant and debilitating impact on patients. There is growing emphasis to appropriately assess the impact of rare diseases from a patient perspective, particularly on daily lives, HrQoL and function.[34] The development and validation of the LRRC-QoL reflects the recommendations from the ISPOR Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials Task Force Report.[35] The LRRC-QoL has been designed to be widely generalisable and to reflect the clinical heterogeneity associated with LRRC, this is reflected in the broad range of patient characteristics that were included in its' development and validation. This includes patients treated with varying pelvic tumour location, patients treated with palliative intent with a range of palliative treatments, patients with metastatic disease, and with re-recurrent disease. This approach focuses on the core HrQoL issues relevant to all patients with LRRC and will ensure the utility of the measure across the entire LRRC patient population. The trade-off with this approach, is the recruitment of small number of patients within certain subpopulations i.e. urostomy, which meant that the known groups validity could not be robustly assessed across all patient characteristics. Further limitations include the overall small sample size, although within the context of a rare disease this is acceptable, and the inclusion of English-speaking patients alone. The relative inclusion of a small sample size of female patients (n = 33, 28.2%) must also be considered a potential limitation as it may not reflect the health status of female LRRC-QoL patients within this validation study. This is likely to reflect the overall higher incidence of primary rectal cancer, and therefore LRRC, in men compared to women. To address this we adopted a purposive sampling strategy targeted to disease recurrence pattern and gender in Phase I to ensure we appropriately identified and incorporated the opinions, testimony and HrQoL issues relevant to female patients.[22] In Phase II, a total of 27 patients (18 males, 9 females) participated. We employed a similar purposive sampling strategy in Phase III. However, given the nature of LRRC, and the

gender disparity, with a higher proportion of men affected, we acknowledge the relatively lower proportion of women included in our study and the potential bias this represents. However, despite the lower sample size of female participants, the Female Sexual Function domain achieved excellent item intercorrelation (0.870), item discriminant validity scores (range –0.068 to 0.273), item to total correlation (0.326–0.371), Cronbach's Alpha of 0.95 and an ICC of 0.92. The LRRC-QoL patient cohort is broadly generalisable to the overall patient population with LRRC, reflecting the anatomical pattern of disease, the combined local and distant metastatic disease states, and the different treatment modalities. However, further validation works needs to be done in groups that were underrepresented including female patients and patients with urostomies. Furthermore, as the radicality of surgical options have evolved to include high sacrectomy and extended lateral sidewall excision (ELSiE),[36–38] it is important, that these groups are appropriately incorporated into an external validation study to ensure the LRRC-QoL is relevant and applicable in this cohort. Although, overall, the purposive sampling strategy we employed in Phase III facilitated targeted to recruitment to ensure broad generalisability, it is a non-probabilistic sampling technique which has the potential for selection bias. There is a risk that researchers will preferentially approach patients with clinical characteristics as targeted by the purposive sampling strategy, rather than approach all consecutive patients.

Several *a priori hypotheses* were generated with regards to known-groups comparison, with the LRRC-QoL able to fulfil some of these, including, urinary symptoms and pelvic disease location, treatment intent and sexual function and re-recurrent disease and pain. These observations are clinically relevant and meaningful, which contributes to the ability of the LRRC-QoL to discriminate scores between appropriate groups of patients. However, it did not fulfil all *a priori hypotheses,* this in part due to the small sample sizes in certain disease populations, i.e. urostomy (n = 16), palliative patients (n = 21) and chemoradiation (n = 36). Future works must focus on confirming the known groups comparison validity in a larger sample size, with a focus to include underrepresented groups based on patient and clinical characteristics to ensure the LRRC-QoL is able to discriminate between all relevant patient populations. Specifically, this must include female patients, patients with metastatic disease, patients treated palliatively and patients with a urostomy. To enhance the overall future utility of the LRRC-QoL further additional work should include cross-cultural adaptation and translation to further enhance and promote international collaboration in this complex cohort of patients.

The further development of the LRRC-QoL on an international platform will help improve the utility of this outcome measure in this complex disease setting. The LRRC-QoL provides a unique opportunity to document disease-specific QoL in patients with LRRC and therefore will generate a large volume of PRO data which can be used in a variety of ways, including, assessing the effectiveness of a variety of treatment strategies, integrating survival data with QoL data to help guide joint decision-making between clinicians and patients, and potentially using QoL data, in particular, baseline data as a prognostic marker.[39–41] Furthermore, as the number of clinical studies expand in this area, a validated dataset of QoL data will be extremely useful for power calculations to potentially inform the design of future clinical trials.

In conclusion, the LRRC-QoL has been designed in a systematic and methodologically robust manner, incorporating guidance from several authorities on PROMs development with continual patient input and engagement throughout all key phases. This approach has ensured all key disease-specific HrQoL issues relevant to this cohort of patients have been appropriately captured and assessed, including, stoma and urostomy related issues, lower limb symptoms, urinary symptoms, sexual function, sexual interest, pain, psychological impact, and utilisation of healthcare services, and have been incorporated into a psychometrically robust outcome measure, which is ready for use in clinical and academic practice.

Contributors

DH conceived the study concept, the study was designed by DH, JMB, GV, and PMS. Data acquisition was undertaken by DH, CK, MJS, BG, ME, AH, and PMS, these authors have accessed and verified the data collected. DH, CK, and NM had access to all the data undertook the statistical analysis and generated tables and figures. DH drafted the manuscript, all authors have read and approved the manuscript for final submission.

Data sharing statement

De-identified individual participant data collected during the study will be made available to request following publication, access to this data will be granted to researchers who provide a methodologically sound proposal. Proposals should be directed to Miss Deena Harji Deena.Harji@mft.nhs.uk. The study protocol is available in the appendix of this Article.

Declaration of interests

GV has received consulting fees from Pfizer, Eisa and Roche. She has received honoraria from Novartis, AstraZeneca and Pfizer. She sits on advisory boards for Sanofi and Seattle Genetics. The other authors have no declared conflicts of interest. NM is undertaking a PhD funded by from Bowel and Cancer Research UK.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101945.

References

1 World Health Organization. *Colorectal cancer*. WHO; 2020. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf. Accessed September 7, 2022.
2 Solomon MJ. Redefining the boundaries of advanced pelvic oncology surgery. *Br J Surg*. 2021;108(5):453–455.
3 Harji DP, Sagar PM. Advancing the surgical treatment of locally recurrent rectal cancer. *Br J Surg*. 2012;99(9):1169–1171.

4 PelvEx Collaborative. Changing outcomes following pelvic exenteration for locally advanced and recurrent rectal cancer. *BJS Open*. 2019;3(4):516–520.
5 Fadel MG, Ahmed M, Malietzis G, et al. Oncological outcomes of multimodality treatment for patients undergoing surgery for locally recurrent rectal cancer: a systematic review. *Cancer Treat Rev*. 2022;109:102419.
6 Hagemans JAW, van Rees JM, Alberda WJ, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. *Eur J Surg Oncol*. 2020;46(3):448–454.
7 Vallance AE, Harji D, Fearnhead NS, IMPACT Collaborative. Making an IMPACT: a priority setting consultation exercise to improve outcomes in patients with locally advanced, recurrent and metastatic colorectal cancer. *Eur J Surg Oncol*. 2019;45(9):1567–1574.
8 PelvEx Collaborative. Perioperative management and anaesthetic considerations in pelvic exenterations using Delphi methodology: results from the PelvEx Collaborative. *BJS Open*. 2021;5(1):zraa055.
9 PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *Br J Surg*. 2018;105(6):650–657.
10 PelvEx Collaborative. Contemporary management of locally advanced and recurrent rectal cancer: views from the PelvEx collaborative. *Cancers (Basel)*. 2022;14(5):1161.
11 Denys A, van Nieuwenhove Y, Van de Putte D, et al. Patient-reported outcomes after pelvic exenteration for colorectal cancer: a systematic review. *Colorectal Dis*. 2022;24(4):353–368.
12 Harji DP, Griffiths B, Velikova G, Sagar PM, Brown J. Systematic review of health-related quality of life in patients undergoing pelvic exenteration. *Eur J Surg Oncol*. 2016;42(8):1132–1145.
13 Harji DP, Griffiths B, Velikova G, Sagar PM, Brown J. Systematic review of health-related quality of life issues in locally recurrent rectal cancer. *J Surg Oncol*. 2015;111(4):431–438.
14 Harji DP. *The development and validation of a patient-reported outcome measure of health-related quality of life in locally recurrent rectal cancer*. University of Leeds; 2017.
15 Turner RR, Quittner AL, Parasuraman BM, Kallich JD, Cleeland CS, Group MFP-ROCM. Patient-reported outcomes: instrument development and selection issues. *Value Health*. 2007;10 Suppl 2:S86–S93.
16 Research USDoHaHSFCfDEa, Research USDoHaHSFCfBEa, Health USDoHaHSFCfDaR. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes*. 2006;4:79.
17 Aaronson N, Alonso J, Burnam A, et al. Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual Life Res*. 2002;11(3):193–205.
18 Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity–establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1–eliciting concepts for a new PRO instrument. *Value Health*. 2011;14(8):967–977.
19 Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO good research practices task force report. *Value Health*. 2009;12(4):419–429.
20 Sprangers MA, Cull A, Groenvold M, Bjordal K, Blazeby J, Aaronson NK. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. EORTC quality of life study group. *Qual Life Res*. 1998;7(4):291–300.
21 Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC study group on quality of life. *Qual Life Res*. 1993;2(4):287–295.
22 Harji DP, Koh C, Solomon M, Velikova G, Sagar PM, Brown J. Development of a conceptual framework of health-related quality of life in locally recurrent rectal cancer. *Colorectal Dis*. 2015;17(11):954–964.
23 EORTC Quality of Life Item Bank. http://groups.eortc.be/qol/itembank. Accessed July 2016.
24 Willis G, Lesser JT. *Question appraisal system: QAS 99*. National Cancer Institute; 1999.
25 von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495–1499.
26 Ghaferi AA, Schwartz TA, Pawlik TM. STROBE reporting guidelines for observational studies. *JAMA Surg*. 2021;156(6):577–578.
27 Ware JE, H W, Gandek B, Rogers BW, Reese PR. *MAP-R for windows: multitrait/multi-item scale analysis software*. Boston, MA: Health Assessment Lab; 1997.
28 Yurdugül H. Minimum sample size for Cronbach's coefficient alpha: a Monte-Carlo study. *Hacettepe Üniversitesi Eğitim Fakültesi Dergisi*. 2008;35:397–405.
29 Guadagnoli E, Velicer WF. Relation of sample size to the stability of component patterns. *Psychol Bull*. 1988;103(2):265–275.
30 Müller R, Büttner P. A critical discussion of intraclass correlation coefficients. *Stat Med*. 1994;13(23–24):2465–2476.
31 MacCallum RC, Widaman KF, Preacher KJ, Hong S. Sample size in factor analysis: the role of model error. *Multivariate Behav Res*. 2001;36(4):611–637.
32 Hogarthy K, H C, Kromrey JD, Ferron JM, Mumford KR. The quality of factor solutions in exploratory factor analysis: the influence of sample size, communality and overdetermination. *Educ Psychol Meas*. 2005;65:202–226.
33 Lemanska A, Chen T, Dearnaley DP, Jena R, Sydes MR, Faithfull S. Symptom clusters for revising scale membership in the analysis of prostate cancer patient reported outcome measures: a secondary data analysis of the Medical Research Council RT01 trial (ISCRTN47772397). *Qual Life Res*. 2017;26(8):2103–2116.
34 *European organisation for rare disorders position paper: patients' priorities and needs for RD research 2014-2020*. 2011.
35 Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials: an ISPOR COA emerging good practices task force report. *Value Health*. 2017;20(7):838–855.
36 Harji DP, Griffiths B, McArthur DR, Sagar PM. Surgery for recurrent rectal cancer: higher and wider? *Colorectal Dis*. 2013;15(2):139–145.
37 Dozois EJ, Privitera A, Holubar SD, et al. High sacrectomy for locally recurrent rectal cancer: can long-term survival be achieved? *J Surg Oncol*. 2011;103(2):105–109.
38 Shaikh I, Aston W, Hellawell G, et al. Extended lateral pelvic sidewall excision (ELSiE): an approach to optimize complete resection rates in locally advanced or recurrent anorectal cancer involving the pelvic sidewall. *Tech Coloproctol*. 2015;19(2):119–120.
39 Harji DP, Williams A, McKigney N, et al. Utilising quality of life outcome trajectories to aid patient decision making in pelvic exenteration. *Eur J Surg Oncol*. 2022;48(11):2238–2249.
40 Wenzel L, Osann K, McKinney C, et al. Quality of life and adverse events: prognostic relationships in long-term ovarian cancer survival. *J Natl Cancer Inst*. 2021;113(10):1369–1378.
41 Jörling M, Rutzner S, Hecht M, Fietkau R, Distel LV. Deterioration of health-related quality of life scores under treatment predicts longer survival. *Biomed Res Int*. 2020;2020:3565238.