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Cancer-Specific Quality of Life Questionnaires: The State of the Art in Europe

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Quality of life (QL) assessment is now regarded as desirable, if not mandatory, by agencies supporting cancer clinical trials around the world, yet doubts persist about the relevance of QL data to clinical practice. A plethora of QL measures is available but the quality of published work remains suboptimal. The appropriate choice of instrument is essential if outcome measures are to be valid and clinically meaningful. This paper reviews the considerations which should determine the choice of QL questionnaire and, taking the specific example of the EORTC approach, aims to provide users with an update on the current state of the art in the development of cancer-specific QL questionnaires.

Key words: quality of life, cancer clinical trials
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INTRODUCTION

THE CONCEPT of quality of life assessment is in vogue but its realisation remains suboptimal. The number of publications including the key words quality of life (QL) has trebled since 1990 [1] but a critique of 75 published QL studies [2] pointed to a lack of: (a) definition of what was to be measured, (b) rationale for selection of measures used, and (c) evidence for the validity of the instruments chosen.

There is an abundance of measures now available. A recently published bibliography [3] listed 177 QL measures used in oncology. The heterogeneity of instruments included in this list is likely to be confusing to the uninitiated, yet choosing the appropriate tool is essential if outcome measures are to be valid and clinically meaningful.

The aims of this paper are to emphasise the considerations which should determine the choice of a QL questionnaire and to review the current state of the art in the development of cancer-specific QL questionnaires, with particular reference to the EORTC approach.

CONSIDERATIONS IN SELECTING A QL MEASURE

There can be no single universal QL measure for all purposes. Sufficient consensus has been reached internationally on a broad working definition of QL to shape the development of a number of multidimensional QL instruments. Yet the onus remains with the investigator to define the QL question with sufficient precision to guide the selection of an appropriate measure for a specific study. The study question may call for a detailed exploration of a limited number of symptoms, e.g. pain and fatigue. In that case, a specific measure for the symptom in question [4], a diary card approach [5] or a symptom checklist [6] and an appropriately precise title for the study are indicated. If the study question is framed in terms of the impact of symptoms and side-effects on patients' functioning, or if different treatments are associated with different psychosocial trade-offs, then a multidimensional approach to QL assessment is appropriate.

It is important to check that any candidate questionnaire covers the relevant content area. Established measures should be used in their entirety and this is mandatory if the instrument is protected by copyright. Items should not be discarded without regard to the scale structure of the questionnaire and any proposed changes should, where possible, be discussed with the test developer. Additional items, provided they are appended to and not incorporated within an established questionnaire, are acceptable.

Evidence of reliability and validity is important. Instruments developed for one purpose should not be uncritically used for another because the psychometric criteria required to ensure that the measure fulfils its function are different in different settings. For example, measures developed for clinical trials do not meet the standards of reliability or validity required for screening, diagnosing or monitoring individual patients in clinical practice [7] and the threshold scores for screening measures, e.g. the Hospital Anxiety and Depression Scale [8], may vary with patients' disease and treatment status [9].

One aspect of validity rarely studied is whether patients interpret questionnaires in the same way as the researchers who report the results. A recent study measured agreement between patients' self-reported responses and an observer's

rating of the patients' open-ended responses to the same questionnaire administered as an interview. Agreement was generally high, but qualitative data revealed that selective reporting by patients may on occasion lead to systematic errors, e.g. when patients report only what they consider to be relevant symptoms [10].

If an instrument is to be used in a hitherto undocumented way, some pilot work should be undertaken as a minimum and, ideally, a validation exercise should be undertaken to establish the psychometric performance of the questionnaire in that setting.

Confusion also arises about which measure to use when QL data are to be collected alongside an economic evaluation. The only utility approach designed specifically for use in oncology is the Q-TWiST (Quality Adjusted Time Without Symptoms and Toxicity) [11]. Since this does not measure patients' preferences directly it falls outside the scope of this paper.

Measures that can be used across cancer patient populations offer investigators the opportunity of developing familiarity with and expertise in the use of that measure and of developing a generic database to allow comparison of data across studies. Generic measures, however, may fail to capture those aspects of patients' experience that are of major clinical interest in a specific clinical setting. In order to address this problem, the state of the art in QL assessment in cancer clinical trials is the modular approach.

THE EORTC APPROACH: AN UPDATE

The modular approach, proposed by the EORTC QL Study Group [12], consists of a core, patient self-report QL questionnaire covering physical, emotional and social health issues and symptoms relevant to a broad range of cancer patients. This is supplemented, in modular fashion, by disease- and/or treatment-specific questionnaire(s) to assess issues not (sufficiently) covered by the core instrument. A similar approach is adopted in the Functional Assessment of Cancer Therapy (FACT) Scales [13].

Questionnaire development is a time-consuming and continuously evolving process. There is an inevitable lag in scientific reporting, thus data published in current journals often refer to an earlier version of the measure than that which is currently advocated. The following summary should help to clarify the current status of the EORTC QLQ-C30.

EORTC QLQ-C36

The first-generation 36-item core questionnaire was developed in 1987. International field testing showed promising psychometric results overall [14] but some areas were open to improvement. A few informative items were discarded and the eight-item emotional functioning scale which showed inadequate reliability was reduced to four items.

EORTC QLQ-C30 (version 1.0)

This second-generation core was field tested in 13 countries to confirm the hypothesised scale structure, to establish reliability and to evaluate validity [15]. This resulted in further refinements being proposed: (a) an alternative role-functioning scale, which incorporated a broader spectrum of role activities (i.e. not only work and household jobs but also hobbies and leisure activities) and a wider range of response categories (i.e. a four-point Likert scale instead of dichotomous response choice), and (b) a revised overall health status/QL scale in which less weight is placed on the specifically physical aspects of health. The first version of EORTC QLQ-C30 is now being phased out and should not be used in new studies. Recently published data [16] demonstrated the high test–retest reliability of the QLQ-C30 in patients with various cancer diagnoses whose condition was stable over the period of assessment.

EORTC QLQ-C30 (+3)

This test version of the questionnaire consists of the original EORTC QLQ-C30 plus the revised items. This version will be phased out but it has been retained for the meantime to allow users with pre-existing data sets based on the first version of EORTC QLQ-C30 to maintain comparability with their earlier studies, while benefiting from progress in instrument development.

EORTC QLQ-C30 (version 2.0)

This is the most up-to-date version of the core QL questionnaire currently available, incorporating all the tested revisions. It remains a 30-item questionnaire consisting of five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting), a global health status/QL scale and a number of single items assessing symptoms (dyspnoea, loss of appetite, sleep disturbance, constipation and diarrhoea) and perceived financial impact of the disease. In this version only the first five items, assessing physical functioning, have dichotomous yes/no responses.

The EORTC approach has been to field test the core questionnaire internationally in large, relatively homogeneous patient populations, i.e. lung, breast, head and neck cancer, to test its psychometric and cross-cultural performance. Data from trials conducted by the NCI Canada [17] confirm the QLQ-C30 as a psychometrically robust instrument which discriminates well between varying severity of disease, different levels of ECOG performance status and is responsive to the effects of chemotherapy. The instrument is now in use in >300 clinical investigations.

Officially approved EORTC QL questionnaires are copyright to protect their proper use and should not be used without the prior written conent of the QL Unit at the EORTC Data Center. The EORTC QLQ-C30 and its scoring manual are available free of charge for academic use. A licence fee is charged for its use in studies sponsored by the pharmaceutical industry. A prospectus of terms for contracts with industrial users is available from the QL Unit.

The core questionnaire is available in 26 languages: Bulgarian, Chinese, Czech*, Danish, Dutch, English, Finnish, French*, German, Greek*, Hebrew, Hungarian, Italian*, Japanese, Norwegian, Polish*, Portuguese* (Portugese & Brazilian), Russian, Slovak* Slovenian, Spanish* (Castillian Spanish, Hispanic and Argentinean), Swedish and Turkish (*denotes availability of separate forms for men and women). Translations are in preparation in Afrikaans, Croatian, Lithuanian, Romanian, Serbian and Sotho.

Further minor revisions of the EORTC QLQ-30 can be anticipated [18]. Data are urgently needed from studies comparing the EORTC QLQ-C30 and other QL measures to clarify their relative merits. Future developments are likely to focus on the development of modules and on revisiting the whole concept of a generic instrument for special patient populations where the core issues are somewhat different, e.g. children.

MODULE DEVELOPMENT

A proliferation of *ad hoc* modules prompted the EORTC QL Study Group to publish guidelines to promote a standard methodology for developing supplementary modules in an effort to ensure uniformly high psychometric quality [19]. These specify four phases of module development:

(1) Generating relevant issues by consulting the literature, clinicians and patients, with defined procedures for selecting the most salient issues.
(2) Translating issues into questionnaire items and scales in a format compatible with EORTC QLQ-C30, observing recognised rules for questionnaire construction.
(3) Pre-testing the provisional module to identify any problems in its administration, e.g. items to be reworded, deleted or added.
(4) Field testing in a larger international group of patients to test the module's psychometric performance.

Modules developed by the EORTC QL Study Group are submitted to formal processes of peer review following stage 3 to ensure quality control of the provisional modules proceeding to field test.

The aim now is to develop a database to facilitate communication and optimise consistency in module construction. This is no mean task, given the number of centres now involved in module development but it is essential if duplication of effort is to be avoided.

EORTC MODULES

Progress in the development of modules is rapid. Up-to-date information about the availability of modules should be checked with the QL Unit of the EORTC Data Center.

Breast Cancer Module QLQ-BR23 [20]

This module consists of 23 items assessing disease symptoms, side-effects of treatment (surgery, chemotherapy, radiotherapy and hormonal therapy), body image, sexuality and future perspective. Having performed satisfactorily on field studies in the Netherlands, Spain and the U.S.A., it is currently undergoing more extensive international field testing—EORTC Protocol 15931.

Head and Neck Cancer Module QLQ-H&N37 [21]

This module consists of 37 items assessing disease symptoms and side-effects of treatment, social function, body image and sexuality and is currently being field tested internationally—EORTC Protocol 15941.

Oesophageal Module QLQ-OES24 [22]

This module consists of 24 items assessing dysphagia, nutrition, upper gastrointestinal symptoms, pain, burden of disease and treatment and other symptoms. It performed satisfactorily on pretesting in the U.K., Spain and Sweden and an international field study will be undertaken in 1997.

Colorectal Module QLQ-CR38

This module consists of 38 items assessing disease symptoms, side-effects of treatment (sphincter-saving resection, rectal extirpation, radiotherapy and chemotherapy), body image, sexuality and future perspective. Nineteen questions are completed by all patients, the remainder are completed by subsets of patients (e.g. males or females; patients with or without a stoma). Information about this module may be obtained from the QL Unit at the EORTC Data Center.

Lung Cancer Module LC13

This 13-item questionnaire was developed in collaboration with the clinicians of the EORTC Lung Cancer Group and used in the first field studies of the QLQ-C36 and QLQ-C30, i.e. prior to the formal methodological guidelines. It consists of a multi-item scale to assess dyspnoea and a series of single items to assess cough, sore mouth, dysphagia, peripheral neuropathy, alopecia and haemoptysis. Results from two field studies have confirmed that the module is a clinically valid tool, although some refinements were proposed, e.g. changes to the assessment of pain and additional items to assess neuropathy [23].

A number of other modular supplements to the EORTC QLQ-C30 are in preparation, e.g. for bladder, brain, ovary, myeloma and prostate. Until they have been published, modules remain the intellectual property of those who develop them. However, the EORTC approach emphasises international collaboration and modules may be made available prepublication subject to agreement about publication rights and sharing data relevant to the psychometric validation of the modulation.

There is clearly an urgent need to develop more disease- and treatment-specific modules to meet the demands of the clinical trial agenda. There are also QL dimensions transcending disease site which may be crucial to treatment outcome for patients, e.g. body image, sexuality, cognitive function. The depth of questioning that is appropriate is likely to vary from study to study and validation of short and longer forms of scales to assess these dimensions would now be invaluable.

CROSS-CULTURAL ISSUES

Clinical trials are often international and the state of the art in QL assessment requires questionnaires of proven cross-cultural applicability.

The benefit to the EORTC QL Study Group of its culturally diverse membership has been the development of a core questionnaire that translates with relative ease into other languages and has proven applicability internationally. The same must be true of modules.

Emphasis is placed on maximising cross-cultural collaboration at every stage of the EORTC module development process. Good quality translations are required and the Group has developed formal guidelines for the translation process with the aim of producing translations that are clear, conceptually equivalent to the original and expressed in language in common use.

This requires an iterative backward–forward process and, crucially, for translations to be pilot tested in the country in which they are to be used. The whole translation process is documented and submitted to peer review before the translated module is deemed ready for use.

ISSUES IN SCORING AND ANALYSING QL DATA

The state of the art is that manuals are becoming available for established QL questionnaires and these should be used to ensure consistency of scoring procedures across studies.

For the EORTC QLQ-C30, scores are derived for each scale from the unweighted sum of scores for the items of that scale and averaged to give a raw score. Raw scores are

standardised by linear transformation so that scores range from 0 to 100. A higher score represents a higher (i.e. better) level of functioning. On symptom scales, a higher score represents more symptomatology.

There is no total global score based on all the items although there is a two-item scale for global health status/QL which can be used as a summary measure. A comparison of the directly assessed (DA) and aggregate methods of measuring overall QL using the QLQ-C30 [24] confirmed that DA-global QL is a separate construct not fully captured by aggregating scores for the five functional domains. Measuring global health-related QL directly is therefore preferable to the aggregate score approach.

Item bias analysis is a statistical method of testing whether information obtained from individual items is preserved in a summary scale score. It has recently been suggested [25] that this technique offers a way of checking whether differences between groups of patients in scores on QL scales show biases, e.g. by age, sex or treatment, which may distort or dilute the effect being measured. The authors rightly comment that the clinical importance of this approach depends on whether it can be shown to prevent misinterpretations of data sufficiently often to justify the extra work involved.

A brief manual is now available for the EORTC QLQ-C30 with information about scoring the QLQ-C30 using BMDP, SPSS and SAS statistical packages and conventions for dealing with missing values [26]. The manual contains supporting documentation, a bibliography and information about modules.

If the patient misses out one question of a multi-item scale, it may be acceptable to impute the missing value but it is important to be aware of the potential for bias introduced by this procedure. A series of checks on the dataset have been proposed [27] before any decision is made about how to handle missing items but the best advice is wherever possible to institute procedures to prevent missing items from occurring.

There is no generally agreed best approach to the problem of data that are missing because the patient became too ill to complete QL questionnaires. Informative censoring of this kind is common in longitudinal QL studies in oncology and there are a number of statistical modules for dealing with it [28]. The prevailing advice for researchers is to be aware of the problem, to seek expert statistical help and to report exactly the method used.

A reference manual of comparative data to assist in the interpretation of QLQ-C30 scores will be available from the QL Unit in 1997. Data from 14 studies using the EORTC QLQ-C30 have recently been analysed to examine the interplay between QL scale scores and clinical data [29]. Generally the largest differences in QL scores were between groups of patients of different performance status and the smallest differences were between those with local and metastatic disease. Data of this kind are important in the interpretation of the clinical meaning of differences in QL scores between treatment arms of clinical trials and in providing sample size estimates for a range of differences for future studies.

With experience of illness and treatment over time, cancer patients may adjust their internal standards for assessing their QL and this response shift may jeopardise the validity of conclusions that can be drawn from longitudinal studies. Methods of correcting for this potential source of bias are being explored [30].

In the present state of the art investigators should not incorporate QL assessment into their studies without knowing in advance how the data will be scored and analysed.

A checklist has recently been published to assist authors reporting QL data from clinical trials [31].

IMPLEMENTATION ISSUES

Many of the difficulties in using QL questionnaires in the past have arisen not from the questionnaires themselves but from poor design of the studies in which they were implemented. There are now published guidelines for incorporating QL assessment in Phase III clinical trials [32] based on the highly successful experience of the Quality of Life Committee of the National Cancer Institute of Canada's Clinical Trials Group.

In the current state of the art it is important to have named individuals responsible for collecting QL data and to invest in the training of these individuals. There is great interest in reducing the burden for staff by employing electronic methods of data collection [33] and prototypes are being evaluated in a number of countries.

The problem that arises when some patients are, or are likely to become, unable to complete QL questionnaires has led to a revisiting of the role of significant others as proxy raters. In one comparison of ratings by patients with brain tumours, their care givers and doctors [34], the doctors were better at detecting changes in physical function than patients but less good at assessing change in pain or social function. Relatives' ratings were close to patients'. In another study of patients with advanced melanoma [35], relatives proved more appropriate proxies than attending nurses. However, agreement in ratings between proxies and brain tumour patients is likely to be lower for more cognitively impaired patients, particularly those who are confused [36].

More studies are needed to examine the relative reliability and validity of patient and proxy responses. Where it can be anticipated that proxy ratings will be needed these should be obtained in parallel with patient ratings at each assessment point and not merely introduced as a substitute for missing patient data.

CONCLUSIONS

Much progress has been made in the development of an integrated modular system for assessing the QL of cancer patients in international clinical trials. Much remains to be done: to accelerate the rate of the development of new modules; to provide documentation to inform well-designed QL protocols; to ensure the infrastructure for good quality QL data to be collected and to continue scientific work including support for appropriate statistical analysis and interpretation of QL data. All of these developments are necessary if the information derived from cancer-specific QL questionnaires is to impact on routine oncology practice.

Health care services, organisations supporting clinical trials, the pharmaceutical industry and regulatory agencies are all increasingly interested in assessing QL outcomes but the question of financial support remains a vexed one. Although in the current state of the art we now have cancer-specific QL questionnaires for use in Europe, the need to support continuing scientific development work in QL should not be overlooked.

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