

Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18

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Abstract

Measurement of quality of life (QoL) in hepatocellular carcinoma (HCC) requires assessment of factors related to chronic liver disease, as well as issues related to the primary tumour and its treatment. This study describes the development of a questionnaire module in patients from Europe, as well as Taiwan and Hong Kong. The questionnaire was developed according to the European Organisation for Research and Treatment of Cancer (EORTC) QoL Group guidelines. Twenty nine QoL issues were identified from a literature search. Semi-structured interviews with patients ($n = 32$) and health-care professionals ($n = 10$) reduced the issues to 22 items forming a provisional questionnaire. This was tested in 158 patients from three countries. Descriptive statistics and clinical judgement reduced the module to 18 items conceptualised as containing six scales and two single item. This study recommends the EORTC QLQ-HCC18 to accompany the QLQ-C30 to measure QoL in clinical trials in HCC.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the world's most common malignancies, with a marked heterogeneous geographical distribution [1]. In high-risk areas, such as Asia and Africa, annual incidence rates are between 10 and 120 per 100,000 population, whereas in low-risk areas, Northern Europe, United States of

America (USA) and India, annual incidence rates are below 3 per 100,000 population [1]. Over the past decade, advances in diagnostic techniques and multi-disciplinary management of HCC have led to small improvements in survival, although outcomes remains poor with overall one year survival being less than 20% [2,3]. Trials evaluating systemic chemotherapy show very little benefit [4]. Local arterial infusion of cytotoxic agents or cytotoxic agents in combination with lipiodol may increase survival in well selected patients [5,6]. Percutaneous approaches with ethanol, or radio-frequency ablation can be used for unresectable HCC

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and there is currently interest in the role of octreotide [7]. Potentially curative treatments, including resection, percutaneous ablation or liver transplantation can be offered to patients with small lesions confined to the liver and five year survival may reach 50% [5]. Treatment strategies are aimed at incorporating prognosis estimation with potential treatment advancements [8]. Although survival data and information about the side-effects of treatment are widely available, much less is known about how treatment for HCC impacts upon patients' health-related quality of life (QoL). Self-reported QoL data includes measures of physical, social and emotional well-being and this is valuable for patients and clinicians in decision-making [9]. Self-reported health data may also predict survival in patients with cancer and in other populations [10].

The most widely used instruments in assessing QoL in cancer patients within the context of clinical trials are the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the Functional Assessment of Cancer Therapy (FACT) generic questionnaire [11,12]. These both use a general core questionnaire and may be supplemented by disease-specific modules. A module for hepatobiliary cancers has been published by the FACT group [13]. This is designed for patients with cancer of the head of pancreas, colorectal liver metastases, primary liver cancer and cholangiocarcinoma. It has 18 items that may be aggregated to produce a FACT-Hep scale. The EORTC group has taken a more focused approach, by developing separate modules for pancreatic cancer, colorectal hepatic metastases and primary liver cancer [14,15]. This approach was followed because these cancers have different aetiologies, epidemiology, clinical problems, treatments and disease progression. This paper describes the development of the EORTC questionnaire, module to accom-

pany the EORTC QLQ-C30 to comprehensively assess QoL in patients with HCC.

2. Patients and methods

2.1. Study design

The development of the provisional module was performed according to the EORTC Quality of Life Group (QLG) published guidelines for questionnaire development [16–18]. These guidelines are summarised in Table 1. The final part of module development (Phase 4) consists of psychometric testing and is not part of this paper.

2.2. Subjects

Patients for the interviews carried out in Phase 1 were recruited from the United Kingdom (UK), The Chinese University of Hong Kong and Egypt. In Phase 3 of the study, patients from the UK, Taiwan, the Chinese University of Hong Kong and Queen Mary Hospital Hong Kong were included. Eligible patients were required: (a) to have been diagnosed with HCC; (b) to have no other concurrent malignancy; (c) to speak and understand the respective language of the questionnaire; (d) to give full informed consent. Ethical committee permission was obtained.

2.3. Data analysis

Descriptive statistics were used to analyse results of the interviews in Phases 1 and 3. Mean scores of <2.0 for the professionals and patients were used as cut-off points for consideration of deletion of an issue in

Table 1
Guidelines for development of an EORTC disease-specific QL module

Phase	Aim	Process
1	Generation of QoL issues relevant to the selected group of patients	1. Literature search 2. Semi-structured interviews with health-care professionals and patients 3. Analysis of qualitative and quantitative data 4. Combination of results from interviews to produce a list of issues
2	Construction of a provisional questionnaire	1. Consultation of the EORTC QoL group item database 2. Construction of new items 3. Translation of provisional questionnaire
3	Pretesting the questionnaire for acceptability and relevance	1. Patients complete module with interview 2. Analysis of quantitative and qualitative data 3. Modification of questionnaire 4. Formal development report reviewed by EORTC QoL group
4	International field testing	Psychometric testing of the reliability, validity and sensitivity of the module

EORTC, European Organisation for Research and Treatment of Cancer; QoL, quality of life.

Phase 1. In Phase 3, mean scores <1.5 were used for consideration for deletion from the final module. Items scores were considered in conjunction with qualitative comments made during the interviews [19,20].

3. Results

3.1. Phase 1: Generation of QoL issues

3.1.1. Literature search

Literature searches were performed in three databases: MEDLINE (1966–June 2002), EMBASE (1980–June 2002), and CINAHL (1982–April 2002). The searches were limited to the English language. The major subject heading, HCC was combined with surgery, QoL, questionnaires, chemotherapy, alcohol ablation, chemoembolisation, physical distress, psychological distress, psychosocial distress and physical symptoms. This identified 2055 articles. Nine papers described QoL questionnaires used with patients with HCC, but only two had supporting psychometric data and may be used for all patients with HCC [13,21]. These articles produced a list of 33 potentially relevant QoL issues.

3.1.2. Interviews with health-care professionals

Ten health-care professionals (two surgeons, four specialist nurses, three gastroenterologists and an oncologist) were interviewed. Mean scores were above 2.0 for all QoL issues except six. An additional 14 issues were suggested and 47 issues were therefore presented to patients in Phase 1. Fig. 1 summarises the module development process.

3.1.3. Interview with patients

Patients were recruited from six hospitals in the UK, Taiwan, Egypt and Hong Kong. Socio-demographic and clinical details are shown in Table 2. Analyses of mean relevance scores, discussion of qualitative interviews and scrutiny for overlapping issues resulted in exclusion of 18 issues (29 issues remaining).

3.2. Phase 2: production of the provisional questionnaire

The 29 QoL issues were discussed in detail with the EORTC QLG. Issues that overlapped with items in the core questionnaire or with each other were merged. There were two new issues that were added: ‘the need to take pain killers’ and ‘worry about nutrition’. This process resulted in 22 items (Fig. 1). Eight items were obtained from QLQ Item Bank and 14 new items developed. The provisional module, the EORTC QLQ-HCC22, was reviewed and approved by two members of the EORTC QoL Group and subsequently translated

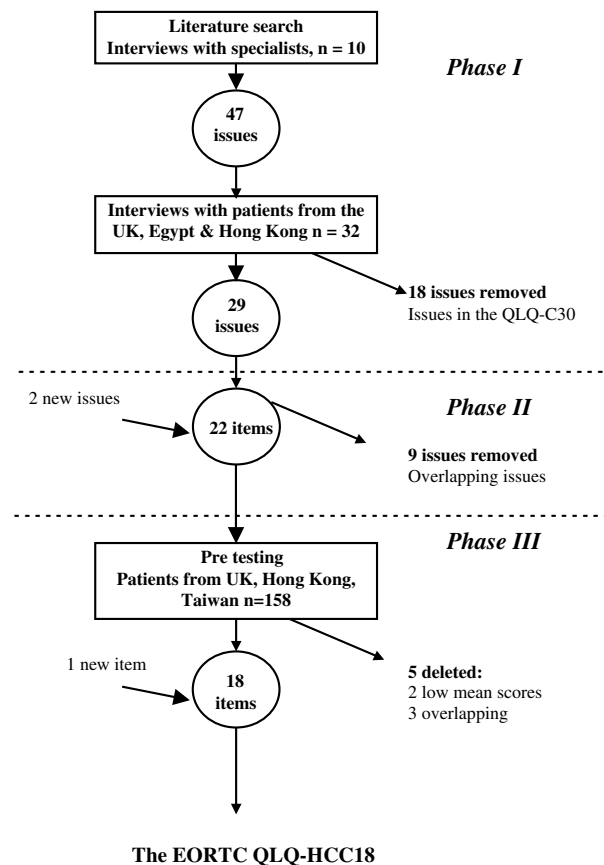


Fig. 1. QLQ-HCC18 – summary of module development. UK, United Kingdom; EORTC, European Organisation for Research and Treatment of Cancer.

according to the strict translating guidelines into Taiwanese and Chinese [22].

3.3. Phase 3: pre-testing in the EORTC QLQ-HCC22

Pre-testing was performed in 158 patients (Table 2). On the basis of descriptive statistics and interviews, two single items were deleted (need to take pain-killers and swollen ankles/legs). Three other items had low mean scores: ‘Have you had pain in your upper abdomen?’, ‘Have you had problems with your sense of taste?’ and ‘Did you have night sweats?’ After discussion and because of clinical importance, it was decided to retain these items. The wording of the item addressing abdominal pain was changed to synchronise with EORTC modules. The item ‘Did you have night sweats’ was split into two items, ‘Have you had fevers’ and ‘Have you had chills?’.

All six fatigue items in Phase 3 had high patient mean scores (>1.78). These were considered alongside the three fatigue items in the QLQ-C30 and three were deleted because of perceived content overlap. The resultant questionnaire consisted of 18 items and has been named the EORTC QLQ-HCC18. This is hypothesised to

Table 2
Socio-demographic and clinical details of patients interviewed in Phases 1 and 3

	Phase 1, <i>n</i> = 32	Phase 3, <i>n</i> = 158
Mean age (range)/years	60 (29–77)	58 (35–83)
<i>Gender (%)</i>		
Male	23 (72)	133 (84)
<i>Marital status (%)</i>		
Single	3 (9)	9 (6)
Married or living with partner	24 (75)	139 (88)
Separated/divorced/widowed	5 (16)	10 (6)
<i>Cohabitation status (%)</i>		
Living alone	4 (13)	14 (9)
Living with family	27 (84)	138 (87)
Living with other adults	1 (3)	6 (4)
<i>Education (%)</i>		
Less than compulsory school	7 (22)	45 (28)
Compulsory school	12 (38)	60 (38)
Post-compulsory school	13 (41)	51 (32)
Unknown	0(0)	2 (1)
<i>Employment (%)</i>		
Employed or homemaker (full-time/part-time)	14 (44)	56 (35)
Retired	15 (47)	62 (39)
Unemployed	1 (3)	32 (20)
Other	2 (6)	8 (5)
<i>Centre (%)</i>		
Edinburgh Royal Infirmary, UK	17 (53)	3 (2)
Bristol Royal Infirmary, UK	0 (0)	15 (10)
National Taiwan University, Taiwan	0 (0)	40 (25)
Chinese University of Hong Kong	11 (34)	60 (38)
Queen Mary Hospital, Hong Kong	0 (0)	40 (25)
Medical Research Institute, Alexandria, Egypt	4 (13)	0 (0)
<i>Timing of treatment (%)</i>		
Before start of treatment	2 (6)	30 (19)
During treatment	7 (22)	33 (21)
Post-treatment	23 (72)	95 (60)
<i>Treatment group (%)</i>		
Hepatectomy alone	7 (22)	33 (21)
Hepatectomy and chemoembolisation	3 (9)	14 (9)
Hepatectomy and percutaneous ablation	1 (3)	9 (6)
Hepatectomy systemic chemotherapy	0 (0)	4 (3)
Chemoembolisation alone	14 (44)	27 (17)
Chemoembolisation and percutaneous ablation	0 (0)	2 (1)
Chemoembolisation and systemic chemotherapy	0 (0)	5 (3)
Lipiodol embolisation alone	0 (0)	8 (5)
Radiofrequency ablation (RFA)	1 (3)	15 (10)
Transplant	0 (0)	14 (9)
Systemic chemotherapy alone	4 (13)	12 (8)
Ethanol injection alone	0 (0)	5 (3)
Best supportive care alone	2 (6)	10 (6)
<i>Co-morbid disease (%)</i>		
Hepatitis B	7 (22)	98 (62)
Hepatitis C	3 (9)	16 (10)
Hepatitis B and/or C and/or alcoholic disease	1 (3)	15 (10)
Alcoholic liver disease	1 (3)	9 (6)
Haemochromatosis	5 (16)	1 (1)
Other or unknown	15 (47)	19 (12)
<i>Child-Pugh grade (%)</i>		
A	26 (81)	124 (79)
B	3 (9)	22 (14)
C	3 (9)	9 (6)
Unknown	0 (0)	3 (2)

UK, United Kingdom.

contain scales addressing fatigue (3 items), body image (2 items), jaundice (2 items), nutrition (5 items), pain (2 items) and fevers (2 items) and two single items addressing sexual interest and abdominal swelling. The module development committee of the EORTC QoL group has approved the module and developmental process.

4. Discussion

The EORTC QLQ-HCC18 has been methodologically developed using standard guidelines. It is designed for use with the QLQ-C30 core instrument to assess all major dimensions of health-related QoL in patients with HCC. The content of the questionnaire has been derived not only from the published literature, but also from health professionals dealing with these patients and, most importantly, from the patients themselves. Testing the QLQ-HCC18 in 158 patients from the UK, Taiwan and Hong Kong confirms that the items are understood, relevant and acceptable to patients with different cultural backgrounds and with differing HCC aetiology. The hypothesised scale structure and single items, address aspects of chronic liver disease (nutrition, jaundice, fevers, abdominal swelling), as well as QoL issues specific to the primary tumour and its treatment (fatigue, body image, pain). The fourth phase of questionnaire development is currently in preparation and will provide essential information on the psychometric properties of the module.

There are two published questionnaires for HCC with supporting psychometric data, the FACT-Hep and The Liver Cancer QoL Scale [13,21]. The FACT-Hep includes problems related to pancreatic cancer and colorectal liver metastases (such as back pain and gastrointestinal symptoms). It may therefore lack specificity for patients with HCC. One study in 20 patients with HCC used the FACT Hep [23]. Significant changes in generic aspects of QoL were reported, but HCC symptoms or treatment-related symptoms did not demonstrate major changes after treatment. A prospective study after resection of HCC used the generic FACT questionnaire to measure QoL [24]. Significant changes in QoL were reported in several of the core scales, but no disease-specific items were used in this study. The Liver Cancer QoL Scale was developed in Chinese patients and has not been widely used elsewhere. Although the EORTC QLQ-HCC18 has only been developed within two language subgroups, it is the first questionnaire to include patients from the East and West in development and therefore has the potential for use in international trials in HCC.

The development of the EORTC QLQ-HCC18 has primarily involved patients from the UK, Taiwan and China and is currently available in Arabic, Chinese (Cantonese), English and Taiwanese (Mandarin).

Although most EORTC questionnaire modules are developed in more European countries, half of the world's total patients with HCC are Chinese because of the chronic hepatitis B carrier rate (in excess of 10%). This questionnaire was therefore deliberately developed in a relevant population in which it will mainly be used in the future. The Phase 4 part of questionnaire development (reliability and validity testing) will partly incorporate a UK randomised study, centres from Hong Kong and Taiwan and other centres from across Europe will be invited to participate. This multi-lingual approach is essential to examine the cross-cultural validity of the module. The EORTC QLQ-HCC18 is therefore suitable for use in clinical trials of HCC. Further international testing will be performed to confirm the clinical and psychometric validity of the questionnaire.

Conflict of Interest Statement

None declared.

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