REVIEW ARTICLE

Systematic review of the psychometric properties of disease-specific, quality-of-life questionnaires for patients with hepatobiliary or pancreatic cancers

Lang TIAN [1] and Xiao-Yi CAO[2]

[1]*Department of Hepatobiliary Surgery, Sichuan Cancer Hospital and* [2]*Department of Nephrology, Hemodialysis Center, West China Hospital, Sichuan University, Chengdu, China*

Abstract

Aim: To systematically review the quality of the psychometric properties of disease-specific quality-of-life questionnaires for patients with hepatobiliary or pancreatic cancers in order to help researchers and clinicians to select the most appropriate health-related quality-of-life (HRQoL) instruments.

Methods: MEDLINE from 1950, CINAHL from 1960, EMBASE from 1980, and PsycINFO from 1967, as well as additional sources were searched. The quality of the psychometric properties of the included instruments was evaluated by using the quality criteria for measurement properties of health status questionnaires.

Results: Ten studies that examined seven instruments were identified. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Liver Metastases of Colorectal Cancer, the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire, and the Quality of Life for Patients with Liver Cancer Instrument achieved satisfactory results in relation to the quality of their psychometric properties.

Conclusion: Several well-validated instruments exist to adequately assess disease-specific HRQoL in patients with hepatobiliary or pancreatic cancers. Further improvement of the already-existing, promising measures is recommended.

Key words: hepatobiliary neoplasms, literature review as a topic, pancreatic neoplasms, quality of life, surveys and questionnaires.

INTRODUCTION

Hepatobiliary cancers refer to primary malignancies that originate from the liver, gallbladder, and bile ducts and the most common malignancies are hepatocellular carcinoma, gallbladder cancer, and cholangiocarcinoma (Benson *et al.*, 2014). As the tumors that originate from the digestive system, although the hepatobiliary and pancreatic cancers are not the most common

Correspondence: Lang Tian, Department of Hepatobiliary Surgery, Sichuan Cancer Hospital, No. 55 South Renmin Road, Chengdu 610041, China.
Email: tian_lang1981@126.com

malignancies, they are regarded as a highly lethal group of cancers, with their incidence and death rates increasing significantly over the last decade (Benson *et al.* ; Siegel, Naishadham, & Jemal, 2012; Tempero, Arnoletti, Behrman, Ben-Josef, & Benson, 2012). Patients often are diagnosed at advanced stages due to the systemic and unspecific symptoms that are related to these cancers (Beazley & Cohn, 1995; Bruix & Sherman, 2011). Meanwhile, few effective treatment options exist, which can result in a poor prognosis with quite-low 1 year and 5 year survival rates (van Roest, van der Aa, van der Geest, & de Jong, 2016; Steel *et al.*, 2010). Therefore, palliative symptom management of these advanced cancers is of paramount importance.

Health-related quality of life (HRQoL) refers to an individual's subjective assessment of his or her health and well-being with multidimensional constructs, including physical, psychological, social, and symptomatic aspects (Carvert & Freemantle, 2003). The HRQoL is regarded as an important outcome for patients with hepatobiliary or pancreatic cancers in several previous studies. In addition to generic tools, such as the Short Form-36 Survey and EQ-5D, and cancer-specific questionnaires, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy generic questionnaires (FACT-G) to measure HRQoL, there have been considerable efforts made to develop disease-specific modules for different types of cancer due to their different etiologies, treatment, symptoms, and prognosis. The commonly used disease-specific HRQoL questionnaires for patients with hepatobiliary or pancreatic cancers comprise the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Module for Hepatocellular Carcinoma (EORTC QLQ-HCC18), the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer (EORTC QLQ-BIL21), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer (EORTC QLQ-PAN26) (Chie *et al.*, 2012; Fitzsimmons *et al.*, 1999; Friend *et al.*, 2011; Heffernan *et al.*, 2002).

Despite the availability of various disease-specific HRQoL instruments, an emerging issue that researchers and clinicians could encounter is that no commonly accepted tool has been recommended for the HRQoL appraisal of patients with hepatobiliary or pancreatic cancers. That may be ascribed to the lack of a systematic evaluation of the psychometric properties of the disease-specific tools using agreed quality criteria to enable a direct comparison between them (Terwee *et al.*, 2007). A comprehensive appraisal of the psychometric properties of the instruments involving their reliability and validity should be carried out in order to rate their quality by a systematic review. Therefore, the aim of this study was to carry out a systematic review of the quality of the psychometric properties of disease-specific HRQoL instruments in order to make recommendations on the most appropriate measurements to evaluate the disease-specific HRQoL of patients with hepatobiliary or pancreatic cancers through collecting evidence from previous studies.

METHODS

Selection criteria

The studies that met the following criteria were included: (i) recruited patients with hepatobiliary or pancreatic cancers (such as hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma, and pancreatic cancer) as samples; (ii) aim to develop and evaluate the psychometric properties of a self-reported instrument that was designed to assess disease-specific HRQoL; and (iii) have been published in the English language. Studies that aimed to develop questionnaires that evaluated generic or cancer-related HRQoL among these patients were excluded, as they cannot assess disease-specific characteristics.

Search strategy

An electronic search of MEDLINE from 1950, CINAHL from 1960, EMBASE from 1980, and PsycINFO from 1967 to October 30, 2016, was conducted in the systematic review. The search process was carried out by using the combination of medical subject headings and keywords. For instance, that terms referred to hepatocellular cancer (liver neoplasm* or liver cancer* or liver carcinoma* or liver tumor* or hepatic tumor* or hepatic carcinoma* or hepatic cancer* or hepatic neoplasm* or hepatocellular tumor* or hepatocellular neoplasm* or hepatocellular cancer* or hepatocellular tumor*, or hepatocellular carcinoma*) and terms that referred to HRQoL (quality of life* or health-related quality of life*) were combined with terms that referred to measurements (questionnaire* or instrument* or measure* or method* or assessment* or psychometric* or reliability or validity or responsiveness* or scale* or measurement* or evaluation*, or survey*) in order to search the literature related to disease-specific HRQoL tools for patients with hepatocellular cancer. The literature for other hepatobiliary cancers (gallbladder cancer and cholangiocarcinoma) and pancreatic cancer were searched similarly. Additional studies were extracted from reference lists or Google search engine.

Literature screening

Two raters conducted the literature selection process independently (L. T. and X-Y. C.). First, one rater (L. T.) evaluated article titles for their initial relevance and assessed abstracts and full-text articles for eligibility subsequently. Next, a second rater (X-Y. C.) verified the selection procedure. Disagreements were resolved by coordination from a third rater (X-L. F.) or consensus.

The articles that did not meet the eligibility criteria were firstly excluded according to their title or abstract. The abstracts that were identified as being potentially relevant were provisionally included and the final inclusion depended on retrieving the full texts.

Data extraction

Two raters extracted the data from the articles that met the eligibility criteria (L. T. and X-Y. C.). First, one rater (L. T.) recorded the study information by using a predesigned table, such as samples and settings, name of the instruments, language versions, total number of items, number of domains, and response options. Then, a second rater (X-Y. C.) checked the extracted information for accuracy. Discrepancies were resolved by consensus or by coordination from a third rater (X-L. F.).

Evaluation of the methodological quality of each study

The methodological quality of the studies on the psychometric properties of disease-specific HRQoL questionnaires was evaluated by the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist, which was designed originally to evaluate the methodological quality of studies of the measurement properties of health status measurement instruments (Mokkink *et al.*, 2012; Terwee *et al.*, 2012). According to the COSMIN taxonomy and definitions, the methodological quality of studies is assessed by nine measurement properties, composed of internal consistency, test-retest reliability, measurement error, content validity, criterion validity, structural validity, hypothesis testing, cross-cultural validity, and responsiveness (Mokkink *et al.*, 2010). The assessment of the methodological quality of the studies of each psychometric property comprises 5–18 items and each item is rated on a four-point rating scale: poor, fair, good, and excellent. The total score of the methodological quality of each study is determined by a measurement property and a methodological quality score of each measurement property can be obtained by taking the lowest score of any item in each measurement property (Terwee *et al.*, 2012). The methodological quality on criterion validity has not been examined in the review, as there is no gold standard in QoL measures.

Evaluation of the quality of the psychometric properties of the instruments

The quality of the psychometric properties of each disease-specific questionnaire was assessed using the quality criteria for measurement properties of health status questionnaires (Terwee *et al.*, 2007). The quality criteria is composed of eight measurement properties: internal consistency, content validity, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects and interpretability, with a four-point rating scale [positive (+), indeterminate (?), negative (–) or no information (0)]. For instance, internal consistency refers to the extent to which items in a scale or subscale are intercorrelated, thus measuring the same construct, a positive rating (+) is given if the Cronbach's alpha is calculated for each dimension and Cronbach's alpha ranges from 0.70 to 0.95; an indeterminate rating (?) is given in the case of doubtful design or method; a negative rating (–) is given for a Cronbach's alpha of <0.70 or >0.95, despite an adequate design and method; and a zero rating (0) is given if no information is obtained on this psychometric property (Terwee *et al.*, 2007). According to the quality assessment criteria, doubtful design or method is defined as lacking of a clear description of the design or methods of the study, sample size of <50 participants, or any important methodological weakness in the design or execution of the study (Terwee *et al.*, 2007). Moreover, in order to give a suggestion regarding the most proper instruments to select, Hamoen, De Rooij, Witjes, Barentsz, and Rovers (2015) developed a scoring model, in which each positive psychometric property was assigned 1 point, each doubtful property 0 points, and each negative property –1 point. No point was given if no information was obtained on a specific property, and an overall score was calculated based in the scoring model (Hamoen *et al.*). The criterion validity has not been evaluated as no gold standard in quality-of-life measures has been found.

Data synthesis

After data extraction and the quality assessment procedure, two raters (L. T. and X-Y. C.) analyzed and compared the extracted study information and conducted an iterative review until consensus was achieved. The direct content analysis method was used to describe the study information in the systematic review.

RESULTS

Study selection process

The literature review identified 823 potentially relevant studies primarily. At the end of the selection process,

10 studies that examined the psychometric properties of seven disease-specific HRQoL instruments for patients with hepatobiliary or pancreatic cancers were selected in the summary of evidence (Fig. 1).

Characteristics of the study population

Two studies recruited patients with cholangiocarcinoma and gallbladder cancers as samples (Friend *et al.*, 2011; Kaupp-Roberts *et al.*, 2016) and three studies recruited patients with hepatocellular cancer, with the number of samples ranging from 105 to 232 (Chie *et al.*, 2012; Mikoshiba *et al.*, 2012; Wan *et al.*, 2010). Furthermore, three studies recruited patients with hepatobiliary or pancreatic cancers (Butt *et al.*, 2012; Heffernan *et al.*, 2002; Yount *et al.*, 2002) and another two studies recruited patients with liver metastases from colorectal cancer (Blazeby *et al.*, 2009) and patients with metastatic pancreatic cancer (Cella *et al.*, 2013) as samples. The mean age of the samples varied from 47.5 to 68.1 years and only one study reported a disease duration of 39.6 ± 34.5 months among patients with hepatocellular cancers (Mikoshiba *et al.*). The treatment options for patients with hepatobiliary or pancreatic cancers across studies mainly comprised surgical treatment, chemotherapy, radiotherapy, and palliative care. Moreover, most of the studies were conducted in a clinical setting and some studies also were carried out in an outpatient clinic, community, or home setting. The included instruments have been assessed in patients from 12 countries or districts (Table 1).

Characteristics of the instruments

Of these disease-specific HRQoL questionnaires, the EORTC QLQ-BIL21 was a specific evaluation instrument for patients with cholangiocarcinoma and gallbladder cancers (Friend *et al.*, 2011; Kaupp-Roberts *et al.*, 2016) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Liver Metastases of Colorectal Cancer (EORTC QLQ-LMC21) performed as a HRQoL assessment tool that had been designed specifically for patients with liver metastases from colorectal cancer (Blazeby *et al.*, 2009). Both the EORTC QLQ-HCC18 and the Quality of Life for Patients with Liver Cancer Instrument (QOL-LC) were developed to evaluate disease-specific HRQoL among patients with
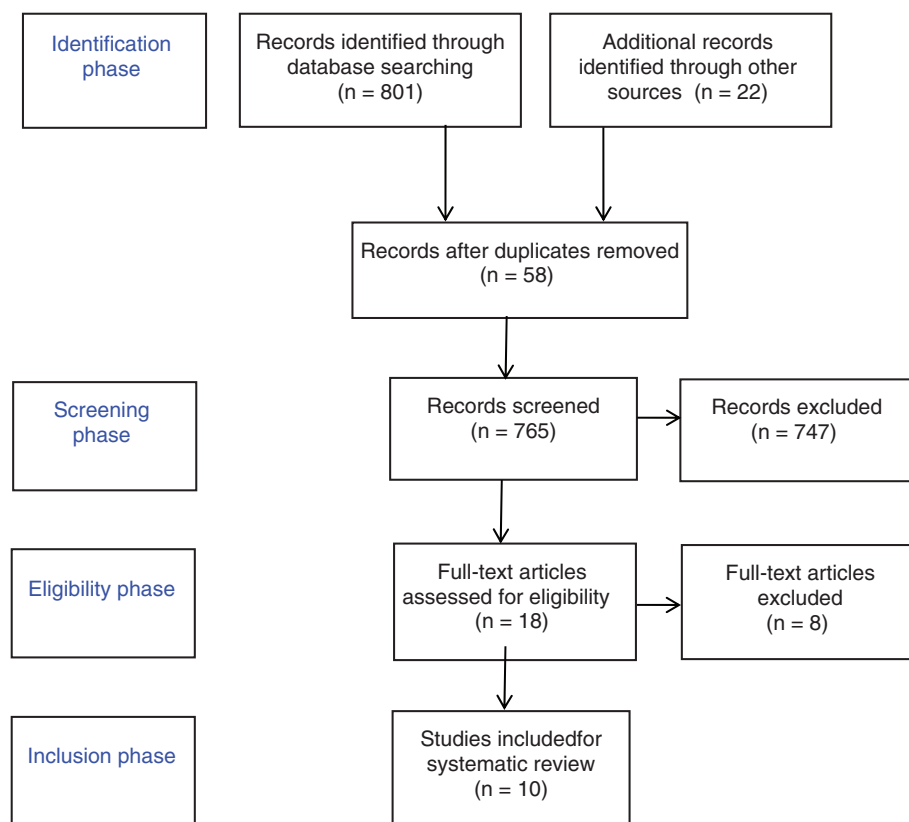

Figure 1 Flow chart of the study selection process.

Table 1 Characteristics of the study populations

Instrument	Author (year)	Patients (N)	Age (years)	Disease duration (months)	Treatment	Setting	Country
EORTC QLQ-BIL21	Kaupp-Roberts et al. (2016)	172 patients with cholangiocarcinoma and 91 patients with gallbladder cancer	Not reported	Not reported	Surgical treatment, chemotherapy/radiotherapy/photodynamic therapy/laser therapy, support care	Clinical, outpatient clinic, home	UK, Germany, Netherlands, Italy, Chile, India, China
EORTC QLQ-BIL21	Friend et al. (2011)	52 patients with cholangiocarcinoma or gallbladder cancer	67.0	Not reported	Surgery, chemotherapy, radiotherapy, supportive care	Clinical	UK, Italy, Taiwan, Germany
EORTC QLQ-HCC18	Chie et al. (2012)	232 patients with hepatocellular cancer	61.3	Not reported	Surgery, ablation, embolization, systemic therapy	Clinical	UK, France, Italy, Japan, Taiwan, Hong Kong
EORTC QLQ-HCC18	Mikoshiba et al. (2012)	192 patients with hepatocellular cancer	68.1	39.6	Hepatectomy, percutaneous ablation, chemoembolization, systemic therapy	Clinical	Japan
EORTC QLQ-LMC21	Blazeby et al. (2009)	356 patients with hepatic metastases from colorectal cancer	Hepatic resection: 63.3 palliative treatment: 65.6	Not reported	Hepatic resection or palliative treatment	Clinical	UK, France, Germany
FACT-Hep	Cella et al. (2013)	125 patients with metastatic pancreatic cancer	Not reported	Not reported	Chemotherapy	Clinical	USA
FACT-Hep	Heffernan et al. (2002)	54 patients with cancer of the liver (primary or metastatic), pancreas, gallbladder, or bile duct	61.5	Not reported	Surgery, chemotherapy, radiation, ablation, stent placement	Outpatient clinic	USA
FHSI-8	Yount et al. (2002)	51 patients with cancer of the liver (primary or metastatic), pancreas, gallbladder, or bile duct	61.5	Not reported	Not reported	Clinical	USA

Table 1 Continued

Instrument	Author (year)	Patients (N)	Age (years)	Disease duration (months)	Treatment	Setting	Country
FHSI-18	Butt et al. (2012)	50 patients with hepatobiliary or pancreatic cancer	60.5	Not reported	Chemotherapy	Clinical and community	USA
QOL-LC	Wan et al. (2010)	105 patients with liver cancer	47.5	Not reported	Not reported	Clinical	Mainland China

EORTC QLQ-BIL21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer; EORTC QLQ-HCC18, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Module for Hepatocellular Carcinoma; EORTC QLQ-LMC21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Liver Module-21; FACT-Hep, the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire; FHSI-8, the FACT-Hepatobiliary Symptom Index-8; QOL-LC, the Quality of Life for Patients with Liver Cancer Instrument.

hepatocellular cancer (Chie *et al.*, 2012; Wan *et al.*, 2010). Moreover, the FACT-Hep was adopted to test the HRQoL of patients with primary liver cancer, hepatobiliary–pancreatic cancers, or metastatic pancreatic cancer across studies (Cella *et al.*, 2013; Heffernan *et al.*, 2002) and the Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8 (FHSI-8) and Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-18 (FHSI-18) were designed to measure the HRQoL among patients with hepatobiliary–pancreatic cancers (Butt *et al.*, 2012; Yount *et al.*, 2002). Among these evaluated questionnaires, three instruments (the EORTC QLQ-HCC18, EORTC QLQ-BIL21, and EORTC QLQ-LMC21) were developed originally in European countries with various language versions, three (the FACT-Hep, FHSI-8, and FHSI-18) were developed in the USA, and only one (the QOL-LC) was developed in mainland China. In addition, most of the instruments adopted a four-point rating score or a five-point rating score for the response options, but only one instrument used a visual analog scale that ranged from 0 to 10 (Wan *et al.*). The response options of the included tools (the EORTC QLQ-HCC18, EORTC QLQ-BIL21, and EORTC QLQ-LMC21), which were developed by the Europe Quality of Life Group, were linearly transformed to a 0–100 score, with higher scores indicating a worse quality of life (Table 2).

The total number of items in each evaluated instrument ranged from eight to 45 items, with an average of 21.86 items. The majority of the evaluated questionnaires had multidimensional constructs that ranged from three-to-five domains and no dimensional information was available for the FHSI-8 (Yount *et al.*, 2002). As for the dimensional structure of the EORTC QLQ-HCC-18, Chie *et al.* (2012) proposed that this instrument comprised five subscales and four single items, whereas Mikoshiba *et al.* (2012) reported that it was a combination of four dimensions and six single items. With regard to the content of each measured instrument, the EORTC QLQ-HCC18, EORTC QLQ-BIL21, and EORTC QLQ-LMC21 performed as a disease-specific symptom assessment module in combination with the EORTC QLQ-C30 (Aaronson *et al.*, 1993) for the evaluation of disease-specific HRQoL. Both the FACT-Hep and the QOL-LC were comprehensive assessment tools, which comprised generic HRQoL dimensions (physical, psychological, social, and functional domains) and a specific symptom evaluation module for hepatocellular cancer. Furthermore, as symptom modules the FHSI-8 and the FHSI-18

Table 2 Characteristics of the instruments

Instrument	Author (year)	Language version	Target disease population	Response options	Scoring range
EORTC QLQ-BIL21	Kaupp-Roberts *et al.* (2016)	German, Dutch, Italian, Spanish, Mandarin Chinese, Hindi	Patients with cholangiocarcinoma and gallbladder cancer	Four-point scores	0–100
EORTC QLQ-BIL21	Friend *et al.* (2011)	English, Mandarin Chinese, Italian, German	Patients with cholangiocarcinoma and gallbladder cancer	Four-point scores	0–100
EORTC QLQ-HCC18	Chie *et al.* (2012)	English, Chinese, Japanese, Italian, French	Patients with hepatocellular cancer	Four-point scores	0–100
EORTC QLQ-HCC18	Mikoshiba *et al.* (2012)	Japanese	Patients with hepatocellular cancer	Four-point scores	0–100
EORTC QLQ-LMC21	Blazeby *et al.* (2009)	English, French, German	Patients with liver metastases from colorectal cancer	Four-point scores	0–100
FACT-Hep	Cella *et al.* (2013)	English	Patients with primary liver cancer, hepatobiliary–pancreatic cancers, or metastatic pancreatic cancer	Five-point scores	Sum scores
FACT-Hep	Heffernan *et al.* (2002)	English	Patients with primary liver cancer, hepatobiliary–pancreatic cancers, or metastatic pancreatic cancer	Five-point scores	Sum scores
FHSI-8	Yount *et al.* (2002)	English	Patients with hepatobiliary-pancreatic cancers	Five-point scores	0–100
FHSI-8	Butt *et al.* (2012)	English	Patients with hepatobiliary–pancreatic cancers	Five-point scores	Sum scores
QOL-LC	Wan *et al.* (2010)	Chinese	Patients with hepatocellular cancer	Visual analog scale	Sum scores

EORTC QLQ-BIL21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer; EORTC QLQ-HCC18, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Module for Hepatocellular Carcinoma; EORTC QLQ-LMC21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Liver Module-21; FACT-Hep, the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire; FHSI-8, the FACT-Hepatobiliary Symptom Index-8; QOL-LC, the Quality of Life for Patients with Liver Cancer Instrument.

frequently have been combined with the FACT-G (Cella *et al.*, 1993) in order to assess HRQoL, which patients with hepatobiliary cancer have perceived (Table 3).

Methodological quality of the studies

All the studies assessed the internal consistency, content validity, and hypothesis testing. Most of the studies evaluated reliability and responsiveness, whereas the structural validity and cross-cultural validity often were not evaluated. Moreover, none of the studies assessed measurement error. Among the measurement properties that were assessed, all the studies were rated as having "excellent" methodological quality regarding their content validity. Most of the studies were rated as having "good" methodological quality regarding their

reliability (3/5, 60%) and "fair" methodological quality in relation to their internal consistency (6/10, 60.0%). Half of the studies were rated as having "good" methodological quality in relation to their responsiveness (3/6, 50.0%) and "fair" methodological quality regarding hypothesis testing (5/10, 50.0%). In addition, one study that assessed its structural validity was rated as having a "poor" methodological quality and another study that evaluated cross-cultural validity also was rated as having a "poor" methodological quality (Table 4).

Quality of the psychometric properties of the instruments

In sum, as shown in Table 5, all the included instruments tested the content validity, internal consistency,

Table 3 Domains and items of the instruments

Instrument	Author (year)	Total number of items	Number of domains	Number of single items
EORTC QLQ-BIL21	Kaupp-Roberts *et al.* (2016)	21	Five: eating, jaundice, tiredness, pain, anxiety	Three: treatment side-effects, difficulties with drainage bags/tubes, concerns regarding weight loss
EORTC QLQ-BIL21	Friend *et al.* (2011)	21	Five: eating, jaundice, tiredness, pain, anxiety	Three: treatment side-effects, drainage tubes/bags, worries about losing weight
EORTC QLQ-HCC18	Chie *et al.* (2012)	18	Five: fatigue, jaundice, nutrition, pain, fever	Four: abdominal swelling, sexual interest, body image (two items)
EORTC QLQ-HCC18	Mikoshiba *et al.* (2012)	18	Four subscales: fatigue, nutrition, pain, fever	Six: jaundice (two items), abdominal swelling, sexual interest, body image (two items)
EORTC QLQ-LMC21	Blazeby *et al.* (2009)	21	Four: fatigue, nutrition, pain, emotional problems	Nine: problems with taste, tingling hands, sore mouth, dry mouth, problems with jaundice and weight loss, social, talking, and sexual problems
FACT-Hep	Cella *et al.* (2013)	45	Five: physical well-being, social/family well-being, emotional well-being, functional well-being, a disease-specific hepatobiliary cancer subscale	–
FACT-Hep	Heffernan *et al.* (2002)	45	Five: physical well-being, social/family well-being, emotional well-being, functional well-being, a disease-specific hepatobiliary cancer subscale	–
FHSI-8	Yount *et al.* (2002)	8	–	Eight: pain, lack of energy, feeling fatigued, weight loss, nausea, stomach pain/discomfort, jaundice, back pain
FHSI-8	Butt *et al.* (2012)	18	Three: disease-related symptoms, functional well-being, treatment side-effects	–
QOL-LC	Wan *et al.* (2010)	22	Four: physical well-being, psychological well-being, symptoms/side-effects, social well-being	–

–, no domains/no single items. EORTC QLQ-BIL21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer; EORTC QLQ-HCC18, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Module for Hepatocellular Carcinoma; EORTC QLQ-LMC21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Liver Module-21; FACT-Hep, the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire; FHSI-8, the FACT-Hepatobiliary Symptom Index-8; QOL-LC, the Quality of Life for Patients with Liver Cancer Instrument.

construct validity, and interpretability. The majority of the instruments evaluated reproducibility and responsiveness, whereas less than half of the instruments evaluated floor and ceiling effects. All the assessed instruments were rated positively regarding their content validity and an indeterminate rating was given in interpretability. Most of the instruments were rated as positive in internal consistency, except for the EORTC

Table 4 Methodological quality of the studies

Instrument	Author (year)	Internal consistency	Reliability	Measurement error	Content validity	Structural validity	Hypothesis testing	Responsiveness	Cross-cultural validity
EORTC QLQ-BIL21	Kaupp-Roberts et al. (2016)	Good	Good	0	Excellent	0	Poor	Fair	0
EORTC QLQ-BIL21	Friend et al. (2011)	Fair	0	0	Excellent	0	Poor	0	0
EORTC QLQ-HCC18	Chie et al. (2012)	Fair	Good	0	Excellent	0	Good	Good	0
EORTC QLQ-HCC18	Mikoshiba et al. (2012)	Good	Good	0	Excellent	0	Good	0	poor
EORTC QLQ-LMC21	Blazeby et al. (2009)	Good	0	0	Excellent	0	Good	Good	0
FACT-Hep	Cella et al. (2013)	Poor	0	0	Excellent	0	Fair	Fair	0
FACT-Hep	Heffernan et al. (2002)	Fair	Good	0	Excellent	0	Fair	Good	0
FHSI-8	Yount et al. (2002)	Fair	Fair	0	Excellent	0	Fair	0	0
FHSI-8	Butt et al. (2012)	Fair	0	0	Excellent	0	Fair	0	0
QOL-LC	Wan et al. (2010)	Fair	Fair	0	Excellent	Poor	Fair	Fair	0

EORTC QLQ-BIL21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer; EORTC QLQ-HCC18, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Module for Hepatocellular Carcinoma; EORTC QLQ-LMC21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Liver Module-21; FACT-Hep, the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire; FHSI-8, the FACT-Hepatobiliary Symptom Index-8; QOL-LC, the Quality of Life for Patients with Liver Cancer Instrument.

Table 5 Quality of the measurement properties of the instruments

Instrument	Author (year)	Content validity	Internal consistency	Construct validity	Reproducibility	Responsiveness	Floor and ceiling effects	Interpretability	Total score
EORTC QLQ-BIL21	Kaupp-Roberts et al. (2016)	Yes	Yes	Yes	Yes	Yes	0	Indeterminate	5
EORTC QLQ-BIL21	Friend et al. (2011)	Yes	Yes	Indeterminate	0	0	0	Indeterminate	2
EORTC QLQ-HCC18	Chie et al. (2012)	Yes	No	Yes	No	Indeterminate	Yes	Indeterminate	3
EORTC QLQ-HCC18	Mikoshiba et al. (2012)	Yes	No	Yes	No	0	0	Indeterminate	2
EORTC QLQ-LMC21	Blazeby et al. (2009)	Yes	Yes	Yes	0	Indeterminate	Yes	Indeterminate	4
FACT-Hep	Cella et al. (2013)	Yes	Yes	Indeterminate	0	Yes	0	Indeterminate	3
FACT-Hep	Heffernan et al. (2002)	Yes	Yes	Indeterminate	Yes	Yes	0	Indeterminate	4
FHSI-8	Yount et al. (2002)	Yes	Yes	Indeterminate	Indeterminate	0	0	Indeterminate	2
FHSI-8	Butt et al. (2012)	Yes	Yes	Yes	0	0	0	Indeterminate	3
QOL-LC	Wan et al. (2010)	Yes	Yes	Indeterminate	Yes	Yes	0	Indeterminate	4

EORTC QLQ-BIL21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Biliary Cancer; EORTC QLQ-HCC18, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Module for Hepatocellular Carcinoma; EORTC QLQ-LMC21, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Liver Module-21; FACT-Hep, the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire; FHSI-8, the FACT-Hepatobiliary Symptom Index-8; QOL-LC, the Quality of Life for Patients with Liver Cancer Instrument.

QLQ-HCC18 (Chie *et al.*, 2012; Mikoshiba *et al.*, 2012). Furthermore, among the assessed questionnaires, all the tools were rated as positive in their floor and ceiling effects (2/2, 100%) (Blazeby *et al.*, 2009; Chie *et al.*). In addition, half of the evaluated tools were rated as positive in their construct validity (5/10, 50.0%) and reproducibility (3/6, 50%) and most of the instruments were rated as positive in their responsiveness (4/6, 66.7%). Overall, the EORTC QLQ-BIL21, the EORTC QLQ-LMC21, the FACT-Hep, and the QOL-LC obtained the comparatively better ratings on all the psychometric properties (Blazeby *et al.*; Heffernan *et al.*, 2002; Kaupp-Roberts *et al.*, 2016; Wan *et al.*, 2010), which were recommended by the quality criteria for measurement properties of health status questionnaires (Terwee *et al.*, 2007).

Evaluation instrument for patients with cholangiocarcinoma and gallbladder cancers

The EORTC QLQ-BIL21 was evaluated in two studies and was rated positively regarding its content validity and internal consistency, but indeterminately in its interpretability. The quality assessment of the floor and ceiling effects was not conducted. Furthermore, this instrument that was assessed in the study by Kaupp-Roberts *et al.* (2016) achieved a positive rating in the construct validity, reproducibility, and responsiveness, results that were not similar to the ratings in the study by Friend *et al.* (2011).

Evaluation instrument for patients with liver metastases from colorectal cancer

The EORTC QLQ-LMC21 was rated positively in its internal consistency, content and construct validity, and floor and ceiling effects, but indeterminately in its responsiveness and interpretability. No reproducibility assessment was provided in the study (Blazeby *et al.*, 2009).

Evaluation instrument for patients with hepatocellular cancer

Three studies evaluated the HRQoL of patients with hepatocellular cancer. Among those, the QOL-LC was rated as positive in its internal consistency, content validity, responsiveness, and reproducibility, but indeterminately in its construct validity and interpretability. No information on the floor and ceiling effects was obtained in the study (Wan *et al.*, 2010). Moreover, the English and Japanese versions of the EORTC QLQ-HCC18 achieved a positive rating in their content and

construct validity, an indeterminate rating in their responsiveness and interpretability, and a negative rating in their internal consistency and reproducibility (Chie *et al.*, 2012; Mikoshiba *et al.*, 2012).

Evaluation instrument for patients with metastatic pancreatic cancer

The FACT-Hep was used to assess the HRQoL of patients with metastatic pancreatic cancer (Cella *et al.*, 2013). The scale was rated as positive in its internal consistency, content validity, and responsiveness, but indeterminately in its construct validity and interpretability. The psychometric property measurements on reproducibility and the floor and ceiling effects were not provided.

Evaluation instrument for patients with hepatobiliary–pancreatic cancers

Three questionnaires were used to test the HRQoL of patients with hepatobiliary–pancreatic cancers. Of these, the FACT-Hep was rated positively for its internal consistency, content validity, reproducibility, and responsiveness, but indeterminately for its construct validity and interpretability. The floor and ceiling effects were evaluated in the study (Heffernan *et al.*, 2002). Moreover, both the FHSI-8 and the FHSI-18 were rated positively regarding their internal consistency and content validity, but with an indeterminate rating in their interpretability. Their responsiveness and floor and ceiling effects were not evaluated in these two studies (Butt *et al.*, 2012; Yount *et al.*, 2002). In addition, the FHSI-8 was given an indeterminate rating in its construct validity and reproducibility (Yount *et al.*). However, the FHSI-18 was rated as positive in its construct validity but no evaluation was conducted on its reproducibility (Butt *et al.*).

DISCUSSION

To the authors' knowledge, this is the first study that systematically reviewed the psychometric properties of disease-specific HRQoL questionnaires for patients with hepatobiliary or pancreatic cancers that are used in research and clinical practice at the moment. Although a previous literature review focused on disease-specific HRQoL assessment tools for hepatocellular cancer (Gandhi, Khubchandani, & Iyer, 2014), no scoring system was adopted for the evaluation of the psychometric properties of these instruments. In addition, to date, no

systematic review on the disease-specific HRQoL instruments for patients with cholangiocarcinoma, gallbladder cancer, or pancreatic cancer has been carried out.

This systematic review has identified seven instruments that met the eligibility criteria. Among those, the EORTC QLQ-HCC18, EORTC QLQ-BIL21, and EORTC QLQ-LMC21 were disease-specific symptom modules in combination with the EORTC QLQ-C30 (Aaronson *et al.*, 1993) for disease-specific HRQoL evaluation. Meanwhile, the FHSI-8 and the FHSI-18, as symptom modules, also performed as supplements to the FACT-G (Cella *et al.*, 1993). In contrast, the FACT-Hep and the QOL-LC performed as comprehensive evaluation questionnaires, including generic HRQoL dimensions (physical, psychological, and social domains) and a specific symptom module. Although there were different types of each evaluated instrument (symptomatic or comprehensive tool), all the studies considered HRQoL as multidimensional in nature, which is consistent with the definition of HRQoL by Carvert and Freemantle (2003). A recognition of the multidimensional structure of HRQoL is beneficial to appraising the impact of the treatment options and to developing effective palliative management strategies.

Based on the COSMIN checklist, the current data indicated that the measurement error was not evaluated in any questionnaire in the review. Measurement error is defined as the systematic and random errors that are not ascribed to true changes (Mokkink *et al.*, 2010). It is regarded as adequate if the smallest important change reaches the limits of agreement or if the minimal detectable change is minimal, as compared to the minimal important change (Wong, Lang, & Lam, 2016). Therefore, it is better to incorporate measurement error as one of the psychometric properties of HRQoL measures in future studies. Moreover, cross-cultural validity refers to the degree to which the items in a translated version of an instrument represent those in its original version. Of these questionnaires, only the EORTC QLQ-HCC18 has been translated into Japanese (Mikoshiba *et al.*, 2012). Although this cross-cultural study adopted a rigorous research design and translation procedure, the methodological quality of cross-cultural validity was still poor in the translated version, which may be ascribed to the methodological deficiency of no confirmatory factor analysis having been carried out, which was recommended in the COSMIN checklist (Mokkink *et al.*, 2012).

Based on the quality criteria for measurement properties of health status questionnaires (Terwee *et al.*, 2007), the authors assessed the included HRQoL instruments for their reliability, validity, and responsiveness. Overall, the EORTC QLQ-BIL21, the EORTC QLQ-LMC21, the FACT-Hep, and the QOL-LC have obtained better ratings regarding the psychometric properties. Nevertheless, none of the evaluated questionnaires demonstrated satisfactory results on all the psychometric properties. Overall, among these assessed instruments, the EORTC QLQ-BIL21 that was tested in the study by Kaupp-Roberts *et al.* (2016) has obtained the highest total score in the evaluation of psychometric properties. It was rated positively for internal consistency, reproducibility, content validity, construct validity, and responsiveness, which demonstrated that it was a reliable and valid questionnaire for HRQoL evaluation in patients with cholangiocarcinoma and gallbladder cancers. Nevertheless, this tool was appraised in the study by Friend *et al.* (2011), who did not report its reproducibility and responsiveness in comparison to Kaupp-Roberts *et al.*, which may be ascribed to the fact that the former study was only a pilot study focusing on the instrument development procedure. An appraisal of instrument reliability and validity should be conducted in a large sample study in general.

With regard to the HRQoL instrument for patients with liver metastases from colorectal cancer, the EORTC QLQ-LMC21 has obtained the relatively satisfactory ratings regarding internal consistency, content and construct validity, and floor and ceiling effects (Blazeby *et al.*, 2009). However, no test–retest reliability information was obtained for the instrument. Test–retest reliability is regarded as one of the most important psychometric properties for the evaluation of stability with different time intervals, which should be included in the instrument development procedure.

Both the QOL-LC and the EORTC QLQ-HCC18 were specific HRQoL appraisal instruments for patients with hepatocellular cancer. Of those, the former was the most comprehensive assessment tool and it was rated positively in its internal consistency, content validity, responsiveness, and reproducibility, which demonstrated its satisfactory psychometric properties (Wan *et al.*, 2010). However, this tool was developed originally in mainland China; thus, cross-cultural studies should be conducted in order to assess its adaptability and feasibility among samples from different ethnic groups. Furthermore, although the EORTC QLQ-HCC18 is one of the commonly used HRQoL tools for hepatocellular cancer, its English and Japanese versions obtained lower scores in the methodological quality of the measurement properties (Chie *et al.*, 2012; Mikoshiba *et al.*, 2012). Both of the two instruments

were rated negatively in their internal consistency and reproducibility, which may be attributed to the lower Cronbach's alpha and intraclass correlation coefficient.

Moreover, regarding the HRQoL instrument for patients with metastatic pancreatic cancer, the FACT-Hep was rated positively in three psychometric properties (content validity, internal consistency, and responsiveness) (Cella *et al.*, 2013). The FACT-Hep is a comprehensive questionnaire that consists of a 27 item FACT-G and an 18 item Hepatobiliary subscale to evaluate disease-specific issues. Future studies should be carried out to examine its test–retest reliability.

In addition, three questionnaires (the FACT-Hep, FHSI-8, and FHSI-18) were used to test the HRQoL of patients with hepatobiliary–pancreatic cancers. Among these, the FACT-Hep obtained the highest total score for psychometric property evaluation. It was rated positively in its internal consistency, content validity, reproducibility, and responsiveness (Heffernan *et al.*, 2002). Moreover, both the FHSI-8 and the FHSI-18 were rated positively in their internal consistency and content validity, whereas their responsiveness was not evaluated in the two studies by Butt *et al.* (2012) and Yount *et al.* (2002). Responsiveness refers to the ability of a health-related, patient-reported outcome instrument to detect change over time in the construct to be measured. It is essential for researchers and clinicians to use a reliable and valid tool during and after treatment that is responsive to clinical changes. Measurements that can capture change over time are ideal and allow for comparisons between time points (Bryant, Walton, Shaw-Kokot, Mayer, & Reeve, 2016). In addition, with respect to the measurements of hepatobiliary–pancreatic cancers, it is important to note that all three questionnaires were validated in small samples ($n = 54$, $n = 51$, and $n = 50$, respectively). Therefore, these instruments might benefit from further validation in larger samples.

Several limitations have been noted. First, only studies that were published in English were recruited in the systematic review, which might have resulted in a selection bias. It is recommended that more papers in various languages should be included in future reviews. Second, some instruments were composed of subscales with low internal consistency. Therefore, further effort should be made to improve the psychometric property with additional reliability development work. Finally, although the EORTC QLQ-PAN26 was the most commonly used tool, in combination with the EORTC QLQ-C30, to measure the HRQoL of patients with pancreatic cancer, no information on the psychometric properties (reliability and validity) of this questionnaire

was found, which could have resulted in a selection bias of the systematic review. Therefore, another study is needed to examine the validity and reliability of the EORTC QLQ-PAN26 in future.

CONCLUSION

In summary, a considerable number of disease-specific HRQoL instruments with good psychometric properties have been identified. The EORTC QLQ-BIL21 and the EORTC QLQ-LMC21 were regarded as questionnaires with satisfactory reliability and validity for HRQoL evaluation in patients with cholangiocarcinoma and gallbladder cancers and for patients with liver metastases from colorectal cancer, respectively. The QOL-LC was a valid and reliable tool to measure the HRQoL of patients with hepatocellular cancer and the FACT-Hep was suggested to test the HRQoL of patients with hepatobiliary–pancreatic cancers. Further improvement of the already-existing, promising measurements is recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

X-Y. C. and L. T. designed the study, collected the data, carried out the analysis, and prepared the manuscript.

REFERENCES

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J. *et al.* (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of National Cancer Institute*, *85*, 365–376.

Beazley, R. M. & Cohn, I. (1995). Tumors of the pancreas, gallbladder, and extrahepatic bile ducts. In: G. P. Murphy, W. Lawrence & R. E. Lenhard (Eds), *Clinical oncology* (2nd edn, pp. 251–268). Atlanta, GA: The American Cancer Society.

Benson, A. B., D'Angelica, M. I., Abrams, T. A., Are, C., Bloomston, P. M., Chang, D. T. *et al.* (2014). Hepatobiliary cancers, version 2.2014. *Journal of the National Comprehensive Cancer Network*, *12*, 1152–1182.

Blazeby, J. M., Fayers, P., Conroy, T., Sezer, O., Ramage, J., Rees, M. et al. (2009). Validation of the European Organization for Research and Treatment of Cancer QLQ-LMC21 questionnaire for assessment of patient-reported outcomes during treatment of colorectal liver metastases. *British Journal of Surgery*, 96, 291–298.

Bruix, J. & Sherman, M. (2011). Management of hepatocellular carcinoma: An update. *Hepatology*, 53, 1020–1022.

Bryant, A. L., Walton, A., Shaw-Kokot, J., Mayer, D. K. & Reeve, B. B. (2016). A systematic review of psychometric properties of health-related quality-of-life and symptom instruments in adult acute leukemia survivors. *Cancer Nursing*, 39, 375–382.

Butt, Z., Parikh, N. D., Beaumont, J. L., Rosenbloom, S. K., Syrjala, K. L., Abernethy, A. P. et al. (2012). Development and validation of a symptom index for advanced hepatobiliary and pancreatic cancers: The National Comprehensive Cancer Network Functional Assessment of Cancer Therapy (NCCN-FACT) Hepatobiliary-Pancreatic Symptom Index (NFHSI). *Cancer*, 118, 5997–6004.

Carvert, M. J. & Freemantle, N. (2003). Use of health-related quality of life in prescribing research. Part 1: Why evaluate health-related quality of life? *Journal of Clinical Pharmacy and Therapeutics*, 28, 513–521.

Cella, D., Butt, Z., Kindler, H. L., Fuchs, C. S., Bray, S., Barlev, A. et al. (2013). Validity of the FACT Hepatobiliary (FACT-Hep) questionnaire for assessing disease-related symptoms and health-related quality of life in patients with metastatic pancreatic cancer. *Quality of Life Research*, 22, 1105–1112.

Cella, D. F., Tulsky, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A. et al. (1993). The functional assessment of cancer therapy scale: Development and validation of the general measure. *Journal of Clinical Oncology*, 11, 570–579.

Chie, W. C., Blazeby, J. M., Hsiao, C. F., Chiu, H. C., Poon, R. T., Mikoshiba, N. et al. (2012). International cross-cultural field validation of an European Organization for Research and Treatment of Cancer questionnaire module for patients with primary liver cancer, the European Organization for Research and Treatment of Cancer quality-of-life questionnaire HCC18. *Hepatology*, 55, 1122–1129.

Fitzsimmons, D., Johnson, C. D., George, S., Payne, S., Sandberg, A. A., Bassi, C. et al. (1999). Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *European Journal of Cancer*, 35, 939–941.

Friend, E., Yadegarfar, G., Byrne, C., Johnson, C. D., Sezer, O., Pucciarelli, S. et al. (2011). Development of a questionnaire (EORTC module) to measure quality of life in patients with cholangiocarcinoma and gallbladder cancer, the EORTC QLQ-BIL21. *British Journal of Cancer*, 104, 587–592.

Gandhi, S., Khubchandani, S. & Iyer, R. (2014). Quality of life and hepatocellular carcinoma. *Journal of Gastrointestinal Oncology*, 5, 296–317.

Hamoen, E. H., De Rooij, M., Witjes, J. A., Barentsz, J. O. & Rovers, M. M. (2015). Measuring health-related quality of life in men with prostate cancer: A systematic review of the most used questionnaires and their validity. *Urologic Oncology: Seminars and Original Investigations*, 33, e19–e28.

Heffernan, N., Cella, D., Webster, K., Odom, L., Martone, M., Passik, S. et al. (2002). Measuring health-related quality of life in patients with hepatobiliary cancers: The functional assessment of cancer therapy-hepatobiliary questionnaire. *Journal of Clinical Oncology*, 20, 2229–2239.

Kaupp-Roberts, S. D., Yadegarfar, G., Friend, E., O'Donnell, C. M., Valle, J. W., Byrne, C. et al. (2016). Validation of the EORTC QLQ-BIL21 questionnaire for measuring quality of life in patients with cholangiocarcinoma and cancer of the gallbladder. *British Journal of Cancer*, 115, 1032–1038.

Mikoshiba, N., Tateishi, R., Tanaka, M., Sakai, T., Blazeby, J. M., Kokudo, N. et al. (2012). Validation of the Japanese version of the EORTC hepatocellular carcinoma-specific quality of life questionnaire module (QLQ-HCC18). *Health and Quality of Life Outcomes*, 10, 58.

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L. et al. (2010). The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *Journal of Clinical Epidemiology*, 63, 737–745.

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L. et al. (2012). The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: An international Delphi study. *Quality of Life Research*, 19, 539–549.

van Roest, M. H., van der Aa, M. A., van der Geest, L. G. & de Jong, K. P. (2016). The impact of socioeconomic status, surgical resection and type of hospital on survival in patients with pancreatic cancer. A population-based study in the Netherlands. *PloS One*, 11, e0166449.

Siegel, R., Naishadham, D. & Jemal, A. (2012). Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*, 62, 10–29.

Steel, J. L., Kim, K. H., Dew, M. A., Unruh, M. L., Antoni, M. H., Olek, M. C. et al. (2010). Cancer-related symptom clusters, eosinophils, and survival in hepatobiliary cancer: An exploratory study. *Journal of Pain and Symptom Management*, 39, 859–871.

Tempero, M. A., Arnoletti, J. P., Behrman, S. W., Ben-Josef, E. & Benson, A. B. (2012). NCCN clinical practice guidelines in oncology: Pancreatic adenocarcinoma. [Cited 5 Feb 2012.] Available from URL: http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

Terwee, C. B., Bot, S. D., de Boer, M. R., van der Windt, D. A., Knol, D. L., Dekker, J. *et al.* (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology*, *60*, 34–42.

Terwee, C. B., Mokkink, L. B., Knol, D. L., Ostelo, R. W., Bouter, L. M. & de Vet, H. C. (2012). Rating the methodological quality in systematic reviews of studies on measurement properties: A scoring system for the COSMIN checklist. *Quality of Life Research*, *21*, 651–657.

Wan, C., Fang, J., Yang, Z., Zhang, C., Luo, J., Meng, Q. *et al.* (2010). Development and validation of a quality of life instrument for patients with liver cancer QOL-LC. *American Journal of Clinical Oncology*, *33*, 448–455.

Wong, C. K., Lang, B. H. & Lam, C. L. (2016). A systematic review of quality of thyroid-specific health-related quality-of-life instruments recommends ThyPRO for patients with benign thyroid diseases. *Journal of Clinical Epidemiology*, *78*, 63–72.

Yount, S., Cella, D., Webster, K., Heffernan, N., Chang, C., Odom, L. *et al.* (2002). Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: The FACT Hepatobiliary Symptom Index. *Journal of Pain and Symptom Management*, *24*, 32–44.