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Contents

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AIM AND SCOPE

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REVIEW

Value of quality of life analysis in liver cancer: A clinician's perspective

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Abstract

Health related quality of life (HRQOL) is increasingly recognized as an important clinical parameter and research endpoint in patients with hepatocellular carcinoma (HCC). HRQOL in HCC patients is multifaceted and affected by medical factor which encompasses HCC and its complications, oncological and palliative treatment for HCC, underlying liver disease, as well as the psychological, social or spiritual reaction to the disease. Many patients presented late with advanced disease and limited survival, plagued with multiple symptoms, rendering QOL a very important aspect in their general well being. Various instruments have been developed and validated to measure and report HRQOL in HCC patients, these included general HRQOL instruments, *e.g.*, Short form (SF)-36, SF-12, EuroQoL-5D, World Health Organization Quality of Life Assessment 100 (WHOQOL-100), World Health Organization Quality of Life Assessment abbreviated version; general cancer HRQOL instruments, *e.g.*, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Functional Assessment of Cancer Therapy (FACT)-General, Spitzer Quality of Life Index; and liver-cancer specific HRQOL instruments, *e.g.*, EORTC QLQ-HCC18, FACT-Hepatobiliary (FACT-Hep), FACT-Hep Symptom Index, Trial Outcome Index. Important utilization of HRQOL in HCC patients included description of symptomatology and HRQOL of patients, treatment endpoint in clinical trial, prognostication of survival, benchmarking of palliative care service and health care valuation. In this review, difficulties regarding the use of HRQOL data in research and clinical practice, including choosing a suitable instrument, problems of missing data, data interpretation, analysis and presentation are examined. Potential solutions are also discussed.

Key words: Hepatocellular carcinoma; Health related quality of life; Palliative care; Prognosis; Survival; The European Organisation for Research and Treatment of Cancer QLQ-C30; QLQ-HCC18; Index score; Functional Assessment of Cancer Therapy; EQ-5D; Spitzer; Short form 36; FHSI-8; World Health Organization Quality of Life Assessment

Core tip: Health related quality of life (HRQOL) is an important clinical parameter and research endpoint in hepatocellular carcinoma (HCC) patients. Instruments discussed are short form (SF)-36, SF-12, EQ-5D, World Health Organization Quality of Life Assessment (WHOQOL) 100, WHOQOL-BREF, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Functional Assessment of Cancer Therapy (FACT)-G, Spitzer QoL index, EORTC QLQ-HCC18, FACT-Hep, FHSI-8, TOI. Important utilization of HRQOL included measurement and monitoring of HRQOL, treatment endpoint in clinical trial, prognostication of survival, benchmarking of palliative care service and health care valuation. Various difficulties in using HRQOL data in research and clinical practice, including choosing a suitable instrument, missing data, data interpretation, analysis and presentation are explained. Potential solutions are also discussed.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common and aggressive cancer that arises usually in a cirrhotic liver. Etiological pattern differs between Caucasians (mostly alcoholic liver disease and hepatitis C viral infection) and Asians (predominantly chronic hepatitis B)[1,2]. HCC carries high morbidity and mortality, since many patients present only when symptomatic. Patients with early disease are typically asymptomatic and their diseases are usually detected by regular HCC screening or incidental finding during investigation for other diseases[3]. Advanced disease at presentation is common and patients suffer from symptoms resulting from large space occupying lesion(s) in the liver or associated hepatic dysfunction/failure.

Early diseases are potentially curable by complete surgical extirpation[4,5]. Local tumor ablation, for example radiofrequency ablation (RFA), is a reasonable alternative to partial hepatectomy for small HCC[6,7]. Liver transplantation is considered if the disease falls within the Milan criteria but the anticipated residual liver function is not adequate[8]. Liver directed therapies, such as transarterial chemoembolisation (TACE) and selective internal radiation therapy (SIRT), are palliative treatment for patients with higher tumor burden that is confined to the liver[9-11]. For patients with advanced disease palliative treatment with systemic targeted agents, namely sorafenib and regorafenib, were demonstrated to improve their overall survival (OS)[12-14]. However, in the two phase Ⅲ trials of first-line sorafenib in advanced HCC patients, the improvement in median OS was modest at 2-3 mo[12,13] when compared to placebo. Similar magnitude of benefit was observed in the second-line setting using regorafenib when compared to placebo[14].

In most clinical trials on patients with advanced HCC, the endpoints of interest are disease-free survival (DFS), progression-free survival (PFS) and OS. However in this poor prognostic group, treatment is mainly palliative and the survival benefit is modest. Hence, apart from survival improvement, health related quality of life (HRQOL) becomes very relevant. Thus, increasing number of phase Ⅲ HCC trials have adopted QOL as additional study endpoints. HRQOL therefore has become an important monitoring parameter and treatment goal in clinical research and practice.

HRQOL in HCC patients is a complicated and multidimensional issue that involves medical, psychological, social and spiritual factors. Apart from symptoms arising from HCC and its complications, underlying liver disease and oncological treatment are intertwined with other factors including palliative care service, social and spiritual support, individual's coping skill, patients' function and general well being as well as cultural background, educational level and health literacy.

Therefore HRQOL intrinsically is a multifaceted and complex assessment of human life. Assessment of HRQOL should be comprehensive. Various instruments have been developed to measure and report HRQOL in these patients, they also serve as a means to communicate and reflect on patient's overall well being.

HRQOL INSTRUMENTS UTILIZED TO ASSESS HCC PATIENTS

HRQOL assessment using general tools

HRQOL in HCC patients could be measured using general cancer QOL instruments, *e.g.*, the European Organization for Research and Treatment of Cancer QLQ-C30[15], Functional Assessment of Cancer Therapy - General[16], Spitzer Quality of Life Index[17]; as well as general disease QOL instruments, *e.g.*, Short Form 36[18], short form (SF) 12[19], World Health Organization Quality of Life Assessment 100[20], World Health Organization Quality of Life Assessment abbreviated version[21], EuroQoL-5D[22,23]. These are described in Table 1.

HRQOL assessment using liver-cancer specific tools

Since HCC patients commonly have symptoms related to concomitant underlying liver disease in addition to the tumor(s) within the liver, liver-cancer specific HRQOL instruments have been developed to address symptoms in relation to the malignancy as well as chronic liver disease. These include the European Organization for Research and Treatment of Cancer QLQ-HCC18[24], Functional Assessment of Cancer Therapy-Hepatobiliary[25], Functional Assessment of

Table 1 Health related quality of life instruments commonly used in hepatocellular carcinoma studies

General instruments	
European Organization for Research and Treatment of Cancer QLQ-C30	EORTC QLQ-C30 is a general cancer instrument containing multiple items, measured in multiple-point Likert scales, that reflect the multidimensionality of HRQOL construct[15]. It includes five functional domains (physical, role, cognitive, emotional and social), three symptom domains (fatigue, pain, nausea/vomiting), and a global health and QOL domain. Six single items assess common symptoms in cancer patients (dyspnea, appetite loss, sleep disturbance, constipation and diarrhea) and financial problem. All scales and domains are transformed to scores ranging from 0 to 100. A lower score for a functional or global QOL scale reflects a relatively poorer functioning level or global QOL, a higher score for a symptom/problem scale reflects a more disturbing symptom/problem
Functional Assessment of Cancer Therapy - General	The FACT-G questionnaire is a commonly used tool for HRQOL assessment in general cancer patients[16]. It consists of 27 items for assessment of symptoms and four domains of HRQOL: (1) physical well being (PWB) containing seven items with a subscale score ranging from 0 to 28 points; (2) socio-family well being (SFWB) containing seven items with a subscale score of 0-28 points; (3) emotional well being (EWB) containing six items with a subscale score of 0-24 points; and (4) functional well being (FWB) containing seven items with a subscale score of 0-28 points. Patients were asked to score each item according to how true each statement was to them during the past week on a 5-point ordinal scale, from 0 indicating "not at all" to 4 indicating "very much". The FACT-G total score is the summation of the four subscales (PWB, FWB, SFWB and EWB) scores and can range from 0 to 108. Higher scores reflect better HRQOL
Spitzer Quality of Life Index (Spitzer QoL index)	Spitzer QoL index is a general cancer HRQOL measurement[17]. A score of 0 (worst QOL) to 10 (best QoL) was calculated after the patient answered five items of the questionnaire in the areas of activity, daily life, health perceptions, social support and behavior. Each item is rated on a 3-point Likert scale
Short form 36	SF-36 is a general disease questionnaire to measure the following 8 domains of health: General health, bodily pain, social functioning, role-physical, physical functioning, vitality, role-emotional and mental health[18]. The raw scores of each subscale are converted to scores that range from 0 to 100, with higher scores indicating higher levels of functioning or well being. Scores representing overall physical functioning and mental functioning were calculated from the subscales and are grouped as the physical component summary scale and mental component summary scale
Short form 12	SF-12 is a shortened version of SF-36. It contains a 12-item generic measure of health status developed from SF-36[19]. It also yields scores for eight domains: Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. It likewise provides overall summaries of the physical and mental components
World Health Organization Quality of Life Assessment 100	The WHOQOL-100 questionnaire comprises of 100 items grouped into 25 facets[20]. One of the facets measures overall quality of life/health. The remaining 24 facets are organized in 6 domains: (1) physical health; (2) psychological health; (3) level of independence; (4) social relationships; (5) environment; and (6) spirituality/religion/personal beliefs. Each facet includes four items, rated on a 5-point Likert scale, with higher scores indicating more positive evaluations. Domain and facet raw scores can also be transformed onto a 0 to 100 scale. Higher scores denote higher HRQOL
World Health Organization Quality of Life Assessment abbreviated version	The original 6-domain structure of WHOQOL-100 was subsequently reduced into 4 comprehensive domains by the WHOQOL Group, comprising: (1) physical health (merging the level of independence domain); (2) psychological health (merging the spirituality/religion/personal beliefs domain); (3) social relationships; and (4) environment[21]. It contains a total of 26 questions. Attributes incorporated within the physical health domain of the WHOQOL-BREF include: activities of daily living, dependence on medicines or medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest and work capacity. Attributes incorporated within the psychological health domain are: body image and appearance, negative and positive feelings, self-esteem, spirituality, religion and personal beliefs, thinking, learning, memory and concentration. Measurements of social health domain include personal relationships, social support and sexual activity. Features incorporated in the environmental health domain are: Financial resources, freedom, physical safety and security, health and social care, home environment, opportunities for acquiring the new information and skills, participation in and opportunities for recreation, physical environment and transportation. Higher scores denote higher HRQOL
EuroQoL-5D	EQ-5D is a general disease instrument for describing and valuing HRQOL developed by the EuroQoL Group[22,23]. The questionnaire consists of 2 sections: The EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system contains one question in each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). In the 3-point Likert version (EQ-5D-3L), each question has three levels of response: No problems, some problems or extreme problems. A specific value (weight) is attached to each response of each question according to that country's specific value sets. Studies have been conducted to elicit preferences from general population samples to derive these value sets. A summary score is calculated by deducting all values of the 5 responses from the full mark of 1. A summary score of 1 represents perfect health, 0 represents death, below 0 represents a state being worse than dead. This summary score could be used for quality adjusted life-year (QALY) calculations. Thus EQ-5D is an important tool for economic valuation. The EQ VAS lets the respondent place an "x" on a vertical VAS to reflect his/her self rated health. The endpoints are labeled "best imaginable health state" at 100 and "worst imaginable health state" at 0

Liver-cancer specific instruments	
European Organization for Research and Treatment of Cancer QLQ-HCC18	EORTC QLQ-HCC18 includes eighteen multiple item scales organized into six domains (fatigue, body image, jaundice, nutrition, pain and fever) and two items (abdominal swelling and sex life)[24]. All scales are grouped and transformed to score ranging from 0 to 100. A lower score represents a less severe symptom/problem. EORTC QLQ-HCC18 is used together with EORTC QLQ-C30
Functional Assessment of Cancer Therapy-Hepatobiliary	The FACT-Hep questionnaire is a 45-item instrument for measuring HRQOL in patients with hepatobiliary cancers (liver, bile duct and pancreas)[25]. FACT-Hep is used together with FACT-G. It consists of the 27 items (PWB, FWB, SFWB and EWB domains) in FACT-G together with an 18-item disease-specific hepatobiliary cancer subscale (HepCS) which address specific symptoms of hepatobiliary carcinoma, such as back/stomach pain, gastrointestinal symptoms, anorexia, weight loss, jaundice, as well as side-effects of treatment. An aggregate HepCS score could be obtained. The FACT-G and HepCS scores are summed to form the FACT-Hep total score. Higher scores on all scales of the FACT-Hep reflect better HRQOL or fewer symptoms
Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index	FHSI-8 is a subset of FACT-Hep. It includes eight items from the FACT-Hep that measure specific symptoms of patient priority concern and side effects of hepatobiliary carcinoma[26]. Higher scores on all items of the FHSI-8 reflect fewer symptoms
Trial Outcome Index	TOI is also a subset of FACT-Hep. It consists of the summation of the PWB, FWB and HepCS subscales[25]. Higher scores reflect better HRQOL and fewer symptoms

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer QLQ-C30; FACT-G: Functional Assessment of Cancer Therapy - General; QoL: Quality of Life; SF-36: Short form 36; SF-12: Short form 12; WHOQOL-100: World Health Organization Quality of Life Assessment 100; FACT-Hep: Functional Assessment of Cancer Therapy-Hepatobiliary; FHSI-8: Functional Assessment of Cancer Therapy - Hepatobiliary Symptom Index; TOI: Trial Outcome Index; HCC: Hepatocellular carcinoma; HRQOL: Health related quality of life.

Cancer Therapy-Hepatobiliary Symptom Index[26] and Trial Outcome Index[25]. Liver specific tools are used together with their general counterparts. See Table 1 for description of each instrument.

Validation of HRQOL instruments

All the above instruments were validated, many were widely validated in patients of different languages and cultural backgrounds[15-17,19-21,25-30].

Validation of an HRQOL instrument encompasses reliability and validity analyses. Internal consistency reliability determines if there is satisfactory correlation between items within the same multi-item scale. Test-retest reliability assesses if there is good correlation between measurements of the same patient at 2 closely separated time points when major QOL discrepancy is not expected. Convergent validity tests for adequate correlation between conceptually related scales within the same instrument or a different validated instrument. Discriminant validity evaluates the ability to differentiate between patients of different clinical statuses. Responsiveness to change looks for significant change in score corresponding to patient's improvement or deterioration in condition with time. Good convergence and discrimination are required for scaling success to support the hypothesized scale structure. These are the essential statistical analyses to validate QOL instruments.

UTILIZATION OF HRQOL INSTRUMENTS

HRQOL assessments have been conducted in HCC patients in different settings, and these are listed in Table 2.

To describe symptomatology and HRQOL of HCC patients

Baseline QOL at HCC diagnosis: HRQOL instruments were frequently used in HCC studies to assess baseline symptomatology and QOL of patients at presentation (Table 2). For instance, a case-control study compared baseline HRQOL of HCC patients at diagnosis with that of normal population[31]. HCC patients had significantly worse physical domain QOL but better environmental QOL of WHOQOL-BREF compared to healthy controls. Another case-control study reported bodily pain, role limitation-physical and physical component summary of SF-36 were significantly worse in HCC patients compared to matched cirrhotic control[32]. Similarly, another report found significantly worse physical, functional, emotional, social-family well-being and overall QOL of FACT-Hep in HCC patients when compared to general population; it also found significantly worse functional well-being and overall QOL in HCC patients when compared to controls with chronic liver disease[33].

Observational studies with QOL assessment during treatment: Many case series on HCC patients underdoing surgical resection, liver transplantation, local ablation, SIRT or transarterial chemoembolisation (TACE) for HCC also reported patients' QOL.

HCC patients after curative intent treatment, for example partial hepatectomy, typically had transient deterioration in QOL followed by improvement of QOL. For long term survivors, their QOL could be comparable to that of control cirrhotic patients but worse than that of general population[34-37]. Patients with recurrent disease after curative treatment had deterioration in QOL[34].

In a prospective cohort study, 388 patients with solitary HCC of $\leqslant$ 3 cm were treated with either surgical resection or percutaneous RFA, there was no difference in DFS or OS between the 2 groups. However, FACT-Hep total scores at 3, 6, 12, 24, 36 mo post treatment were significantly better in percutaneous RFA group compared to resection group[38].

Table 2 Clinical studies in hepatocellular carcinoma that involved health related quality of life assessment

Ref.	Year	Study type	*n*	HCC status	Intervention(s)	HRQOL instruments used	HRQOL assessment time point(s)	Remarks
Poon *et al*[34]	2001	Cohort	76	Resectable and unresectable	Resection (66) *vs* TACE (10)	FACT-G	Baseline, 3, 6, 7, 12, 18 and 24 mo	Observational study with QOL assessment during treatment
Brans *et al*[40]	2002	Cohort	26	Unresectable	SIRT (14) *vs* TACE (14)	EORTC QLQ-C30	Baseline, 1 and 3 mo	Observational study with QOL assessment during treatment
Bianchi *et al*[32]	2002	Case-control	101	Any stage	NA	SF-36	Baseline	To describe symptomatology and/or HRQOL of HCC patients -HRQOL of HCC patients compared to 202 matched cirrhotic patients
Chow *et al*[59]	2002	Phase Ⅲ trial	329	Unresectable	Tamoxifen 120 mg/d (121) *vs* tamoxifen 60 mg/d (76) *vs* placebo (132)	Global QOL domain of EORTC QLQ-C30	Baseline, then every 1 mo	Phase III trial with HRQOL endpoint
Steel *et al*[46]	2004	Cohort	28	Allocated to SIRT or TACE	SIRT (14) *vs* TACE (14)	FACT-Hep, HepCS, TOI, FHSI8	Baseline, 3, 6 and 12 mo	Observational study with QOL assessment during treatment. Included in[97]
Poon *et al*[47]	2004	Randomized phase Ⅱ trial	88	Allocated to TACE	Branched chained amino acid *vs* control	FACT-G	Baseline, 3, 6, 9 and 12 mo	Phase Ⅱ trial with HRQOL endpoint
Steel *et al*[84]	2005	Cohort	82	Any stage	Various treatments	FACT-Hep, HepCS, TOI, FHSI8	Baseline, 3 and 6 mo	To describe symptomatology and/or HRQOL of HCC patients -Compared HRQOL between patients and proxy-raters. Included in[97]
Steel *et al*[96]	2005	Case-control	21	TNM stage Ⅲ or Ⅳ	NA	FACT-Hep, Sexual History Questionnaire	Baseline	To describe symptomatology and/or HRQOL of HCC patients - Included 23 patients with chronic liver disease
Barbare *et al*[58]	2005	Phase Ⅲ trial	420	Not eligible for resection or local treatment	Tamoxifen (210) *vs* control (210)	Spitzer QoL index	Baseline, then every 3 mo	Phase Ⅲ trial with HRQOL endpoint
Kirchhoff *et al*[48]	2005	Randomized phase Ⅱ trial	70	Eligible for TACE	TACE with microspheres (35) *vs* TACE (35)	Global QOL of EORTC QLQ-C30	Baseline, then every 6 mo	Phase Ⅱ trial with HRQOL endpoint
Steel *et al*[97]	2006	Combined analysis of 3 studies	157	Mixed patient populations from 3 studies	Various treatments	FACT-Hep, HepCS, TOI, FHSI8	Baseline, 3 and 6 mo	Observational study with QOL assessment during treatment - evaluates minimally important difference in HRQOL
Eid *et al*[36]	2006	Cohort	7	Allocated to hepatic ablation or resection	Hepatic ablation (3) *vs* resection (4)	EORTC QLQ-C30, FACT-Hep, FHSI8, Profile of Mood States (POMS)	Baseline, postoperative visit, 1.5, 3 and 6 mo	Observational study with QOL assessment during treatment. Study included other liver tumor types (33 patients)
Yeo *et al*[65]	2006	Combined analysis of 2 phase Ⅲ trials	233	Unresectable or metastatic	Chemotherapy, hormonal therapy	EORTC QLQ-C30	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC
Wang *et al*[98]	2006	Cohort	83	Non-metastatic, 3 nodules or less	TACE + RFA (43) *vs* TACE (40)	FACT-G	Baseline, 3 mo	Observational study with QOL assessment during treatment
Cebon *et al*[49]	2006	Phase Ⅰ/Ⅱ trial	63	Not eligible for standard therapies	Octreotide long acting release	FACT-Hep, patient disease and treatment assessment form (Pt DATA form), patient benefit form	Baseline, then every 1 mo	Phase Ⅰ/Ⅱ trial with HRQOL endpoint

Llovet *et al*[12]	2006	Phase Ⅲ trial	602	Not eligible for local treatment or had disease progression after surgery or local treatment	Sorafenib (299) *vs* placebo (303)	FHSI-8	Baseline then every 3 wk	Phase Ⅲ trial with HRQOL endpoint
Lee *et al*[31]	2007	Case control	161	Any stage	Surgical, TACE, percutaneous ethanol injection, supportive care	EORTC QLQ-C30, WHOQOL-BREF	Cross sectional one-time assessment	To describe symptomatology and/or HRQOL of HCC patients - compared with national matched healthy controls
Kondo *et al*[37]	2007	Case-control	97	Non-metastatic, 3 nodules or less	Percutaneous ablation	SF-36	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL compared to 97 matched chronic liver disease controls, and normal population values
Steel *et al*[33]	2007	Case-control	83	Any stage	NA	FACT-Hep	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL compared to 51 matched chronic liver disease controls, and 138 controls from general population
Martin *et al*[35]	2007	Cohort	4	Resectable	Resection	EORTC QLQ-C30, FACT-Hep, FHSI-8	Baseline, discharge, postoperative visit, 1.5, 3, 6 and 12 mo	Observational study with QOL assessment during treatment. Included 28 patients with other liver tumors
Becker *et al*[50]	2007	Randomized phase Ⅱ trial	120	Not eligible for resection or local treatment	Octreotide (61) *vs* placebo (59)	EORTC QLQ-C30	Baseline, 1, 3 mo, then every 3 mo	Phase Ⅱ trial with HRQOL endpoint
Dimitroulopoulos *et al*[51]	2007	Randomized phase Ⅱ trial	127	Advanced stage. Somatostatin receptor overexpression for randomisation	Octreotide (31) *vs* placebo (30) observation (66)	EORTC QLQ-C30	Baseline then every 1 mo	Phase Ⅱ trial with HRQOL endpoint
Sun *et al*[99]	2008	Cohort	22	Mainly advanced disease	Various treatments	FACT-Hep, Functional assessment of chronic illness therapy spirituality subscale (FACIT-Sp-12)	Baseline, 1, 2 and 3 mo	Observational study with QOL assessment during treatment. Included 23 patients with pancreatic cancer
Méndez Romero *et al*[52]	2008	Phase Ⅰ / Ⅱ trial	9	Not eligible for other local treatments	SBRT	EORTC QLQ-C30 EQ-5D VAS	Baseline, 1, 3 and 6 mo	Observational study with QOL assessment during treatment. Included 19 patients with liver metastases. Phase Ⅰ / Ⅱ trial with HRQOL endpoint
Bonnetain *et al*[66]	2008	Combined analysis of 2 phase Ⅲ trials[59,101]	538	Not eligible for resection, transplantation or percutaneous ablation	Tamoxifen *vs* supportive care; TACE + tamoxifen *vs* tamoxifen	Spitzer QoL index	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC
Doffoël *et al*[100]	2008	Phase Ⅲ trial	138	Eligible for TACE	TACE + tamoxifen (70) *vs* tamoxifen (68)	Spitzer QoL index	Baseline, then every 2 mo during treatment, every 3 mo after treatment	Phase Ⅲ trial with HRQOL endpoint
Barbare *et al*[60]	2009	Phase Ⅲ trial	272	Not eligible for curative treatment	Octreotide (135) *vs* placebo (137)	EORTC QLQ-C30	Baseline, then every 1 mo during treatment, every 3 mo after treatment	Phase Ⅲ trial with HRQOL endpoint
Cheng *et al*[13]	2009	Phase Ⅲ trial	271	Unresectable or metastatic, no prior systemic therapy	Sorafenib (150) *vs* placebo (76)	FHSI-8. Physical well being domain of FACT-Hep	Baseline then every 3 wk	Phase Ⅲ trial with HRQOL endpoint
Wible *et al*[44]	2010	Cohort	73	Allocated to TACE	TACE	SF-36	Baseline, 4, 8 and 12 mo	Observational study with QOL assessment during treatment

Dollinger *et al*[101]	2010	Phase Ⅲ trial	135	Locally advanced or metastatic	Thymostimulin (67) *vs* placebo (68)	FACT = Hep	Baseline then every 3 mo	Phase Ⅲ trial with HRQOL endpoint
Chow *et al*[61]	2011	Phase Ⅲ trial	204	Advanced disease, not eligible for standard therapies	Megestrol acetate (195) *vs* placebo (69)	EORTC QLQ-C30	Baseline, then every 1 mo during treatment, then every 3 mo after treatment completed	Phase Ⅲ trial with HRQOL endpoint
Shun *et al*[102]	2012	Cohort	89	Allocated to TACE	TACE	SF-12, Symptom Distress Scale, Hospital Anxiety and Depression Scale	3 d before discharge, 1 and 2 mo	Observational study with QOL assessment during treatment
Qiao *et al*[103]	2012	Observational	140	Any stage	NANANAdadsdfsaNA	FACT-epHHep	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL worsens with advancing stage
Eltawil *et al*[45]	2012	Cohort	48	Allocated to TACE	TACE	WHOQOL-BREF	Baseline then every 3-4 mo	Observational study with QOL assessment during treatment
Fan *et al*[104]	2012	Cross sectional	286	Any stage		EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL compared with population norms. Correlation between HRQOL and coping and illness perception
Diouf *et al*[67]	2013	Reanalysis of a phase Ⅲ trial[61]	215	Not eligible for curative treatment, baseline HRQOL data available	Octreotide *vs* placebo	EORTC QLQ-C30	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC. HRQOL data may improve existing staging systems
Soliman *et al*[53]	2013	Phase Ⅱ trial	21	Not eligible for or refractory to standard therapies, symptomatic	Liver radiotherapy	EORTC QLQ-C30, FACT-Hep, HepCS, TOI, FACT-G	Baseline, 1, 3 and 6 mo	Phase II trial with HRQOL endpoint. Included 20 patients with liver metastasis
Salem *et al*[41]	2013	Cohort	56	Allocated to SIRT or TACE	SIRT (29), TACE (27)	FACT-Hep	Baseline, 2 and 4 wk	Observational study with QOL assessment during treatment
Brunocilla *et al*[105]	2013	Cohort	36	Allocated to sorafenib	Sorafenib	FACT-Hep, FHSI-8, FACT-G	Baseline, 1 wk, 1 and 2 mo	Observational study with QOL assessment during treatment
Johnson *et al*[62]	2013	Phase Ⅲ trial	1150	Not eligible for resection or local treatment, no prior systemic treatment	Brivanib (577) *vs* sorafenib (578)	Physical function and role function of EORTC QLQ-C30	Baseline then every 6 wk	Phase Ⅲ trial with HRQOL endpoint
Meyer *et al*[63]	2013	Phase Ⅱ / Ⅲ trial	86	Unresectable, non-metastatic	TACE *vs* TAE	EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline, 1.5, 3 and 6 mo	Phase Ⅱ trial with HRQOL endpoint
Mise *et al*[106]	2014	Cohort	69	Allocated to resection	Resection	SF-36	Baseline then every 3 mo	Observational study with QOL assessment during treatment
Huang *et al*[38]	2014	Cohort	388	Solitary HCC ⩽ 3 cm	Resection, radiofrequency ablation	FACT-Hep, HepCS, TOI, FACT-G	Baseline, 3, 6, 12, 24 and 36 mo	Observational study with QOL assessment during treatment
Zhu *et al*[64]	2014	Phase Ⅲ trial	564	Progressive disease during or after sorafenib	Everolimus (362) *vs* placebo (184)	Global QOL and physical function of EORTC QLQ-C30	Baseline, then multiple reassessments	Phase Ⅲ trial with HRQOL endpoint
Palmieri *et al*[107]	2015	Case control	24	Any stage	NA	SF-36	Baseline	To describe symptomatology and/or HRQOL of HCC patients - evaluates relationship between psychological profile and HRQOL in HCC. Included 22 cirrhotic patients without HCC, 20 control subjects
Chie *et al*[108]	2015	Cohort	171	Allocated to respective treatments	Surgery (53), ablation (53), TACE (65)	EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline, then 4-6 wk for post-ablation/post-TACE, 12-15 wk post-operation	Observational study with QOL assessment during treatment

Heits *et al*[109]	2015	Cross sectional	173	Allocated to liver transplanation	liver transplantation	EORTC QLQ-C30	At one variable time point post-transplantion	To describe symptomatology and/or HRQOL of HCC patients
Xie *et al*[110]	2015	Cohort	102	Allocated to resection or TACE	resection (58), TACE (44)	SF-36	Baseline, 1, 3, 6, 12 and 24 mo	Observational study with QOL assessment during treatment
Xing *et al*[111]	2015	Cohort	118	Allocated to TACE	TACE with doxorubicin eluted beads	SF-36	Baseline, 1-3, 6 and 12 mo	Observational study with QOL assessment during treatment
Kolligs *et al*[54]	2015	Randomized phase II trial	28	Allocated to SIRT or TACE	SIRT (13), TACE (15)	FACT-Hep	Baseline, then every 6 wk	Phase II trial with HRQOL endpoint
Klein *et al*[42]	2015	Combined analysis of prior phase I/II trials	98	Allocated to SBRT	SBRT	EORTC QL-C30, FACT-Hep	Baseline, 1, 3, 6 and 12 mo	Phase I/II trial with HRQOL endpoint
Kensinger *et al*[48]	2016	Case-control	139	Allocated to priority liver transplantation	Liver transplantation	SF-36	Baseline, post transplantation	Observational study with QOL assessment during treatment - included 362 subjects without HCC
Lei *et al*[39]	2016	Cohort	205	Allocated to resection or transplantation	Liver transplantation (110), resection (95)	SF-36	Baseline, then every 1-2 mo for the first 6 mo, then every 2-3 mo for the next 6 mo, then every 6 mo	Observational study with QOL assessment during treatment
Yang *et al*[112]	2016	Cohort	17	Portal vein thrombosis	TACE and transarterial ethanol ablation	EORTC QLQ-C30	Baseline then every 1 mo	Observational study with QOL assessment during treatment
Anota *et al*[55]	2016	Phase I trial	21	Not eligible for curative treatment	TACE with idaurubicin eluted beads	EORTC QLQ-C30	Baseline, 15, 30 and 60 d	Phase I trial with HRQOL endpoint
Chie *et al*[88]	2016	Case-control	227	Any stage	Various treatments	EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline, post-treatment	Observational study with QOL assessment during treatment - Compared HRQOL between Asian and European HCC patients
Lv *et al*[56]	2016	Randomized phase II trial	120	Allocated to TACE	COX2 inhibitor (60) *vs* placebo (60)	Locally developed questionnaire	Baseline, 24 and 48 h	Phase II trial with HRQOL endpoint
Koeberle *et al*[57]	2016	Randomized phase II trial	106	Unresectable or metastatic	Sorafenib + everolimus (60) *vs* sorafenib (46)	FACT-HepCS, EQ-VAS	Baseline, then every 2 wk until week 12	Phase II trial with HRQOL endpoint
Shomura *et al*[113]	2016	Cohort	54	TNM stage IV	Sorafenib	SF-36	Baseline, then every 3 mo	Observational study with QOL assessment during treatment
Bruix *et al*[14]	2016	Phase III trial	573	Progressive disease during sorafenib	Regorafenib (379) *vs* placebo (193)	FACT-Hep, TOI, FACT-G, EQ-5D, EQ-VAS	Baseline, then multiple reassessments	Phase III trial with HRQOL endpoint
Li *et al*[69]	2017	Cohort	472	Any stage	Various treatments	EORTC QLQ-C30, EORTC QLQ-HCC18, C30 index score, HCC18 index score	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC. QOL derived scoring system resembles a staging system

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: EuroQoL-5D; FACT-G: Functional Assessment of Cancer Therapy - General; FACT-Hep: Functional Assessment of Cancer Therapy - Hepatobiliary; FHSI-8: Functional Assessment of Cancer Therapy - Hepatobiliary Symptom Index; HCC: Hepatocellular carcinoma; HepCS: Hepatobiliary cancer subscale; HRQOL: Health related quality of life; *n*: Sample size; NA: Not applicable; RFA: Radiofrequency ablation; SBRT: Stereotactic body radiation therapy; SF-12: Short Form 12; SF-36: Short Form 36; SIRT: Selective internal radiation therapy; Spitzer QoL Index: Spitzer Quality of Life Index; TACE: Transarterial chemoembolization; TOI: Trial Outcome Index; VAS: Visual analogue scale; WHOQOL-BREF: World Health Organization Quality of Life Assessment abbreviated version.

A surgical series compared post operative QOL using SF-36 between liver transplantation (*n* = 95) and resection (*n* = 110) in HCC patients fulfilling Milan's criteria. It reported no significant difference in all domains, physical component summary scale and mental component summary scale between these 2 cohorts. However it did not correlate with survival outcomes[39].

Patients received palliative locoregional therapies, *e.g.*, TACE, SIRT, stereotactic body radiation therapy (SBRT) commonly reported early deterioration of HRQOL, which could be attributable to treatment toxicity[40-43].

A case series reported HRQOL (SF-36) of HCC patients who received TACE[44]. Overall patients' mental component summary scale improved at 4 mo after TACE. For patients received more than 2 cycles of TACE, their mental component summary scale improved after the initial 2 cycles of TACE, and their bodily pain score also improved. Another TACE series observed deterioration of physical health domain of WHOQOL-BREF that coincided with HCC progression[45]. A cohort study using FACT-Hep reported better functional well-being and overall QOL in HCC patients after treatment with SIRT when compared to TACE[46].

As clinical trials endpoint

HRQOL has been increasingly used as secondary endpoint in HCC clinical trials. Phase Ⅰ/Ⅱ trials put emphasis on treatment tolerability or toxicity, and thus QOL impact is a logical endpoint of interest. Quite a number of phase Ⅰ/Ⅱ HCC trials have QOL as secondary endpoints[47-57] (Table 2).

QOL analysis in phase Ⅰ/Ⅱ clinical trials: A phase Ⅰ/Ⅱ trial assessed the use of octreotide in 63 untreatable HCC patients[49]. Grade 3/4 toxicities were uncommon and responses were rare. QOL assessment using FACT-Hep was performed at baseline and every 1 mo afterwards. There was no significant change in reassessment QOL compared to baseline.

A combined analysis of 3 phase Ⅰ/Ⅱ trials of SBRT addressed the QOL of 98 HCC, 86 liver metastasis and 21 intrahepatic cholangiocarcinoma patients[42]. EORTC QLQ-C30 and FACT-Hep were used for QOL assessment, which was scheduled at baseline, 1, 3, 6 and 12 mo. Overall the QOL deteriorated at 1 mo after SBRT, then recovered at 3 mo. Patients with liver metastasis had significantly better QOL at 1 and 6 mo than patients with primary liver cancer.

A randomized phase Ⅱ trial evaluated TACE with microspheres *vs* TACE in 70 HCC patients[48]. G4 toxicities were rare in both arms. Global QOL domain of EORTC QLQ-C30 was used for QOL monitoring, which was measured at baseline and every 3 mo afterwards. There was no significant difference in QOL in both arms.

QOL analysis in phase Ⅲ clinical trials: Although phase Ⅲ trials focus on evaluation of treatment efficacy, there is an increasing trend for these phase Ⅲ clinical trials to incorporate HRQOL as a study endpoint. Effective treatment could improve QOL, whereas treatment-related toxicity, disease progression with ineffective treatment could worsen QOL. Thus it is important to investigate whether a treatment could provide a net QOL benefit. Capturing HRQOL data in clinical trials could provide valuable information to guide clinicians in treatment decision. Commonly used tools included EORTC QLQ-C30, EORTC QLQ-HCC18, Spitzer QoL index, FACT-G, FACT-Hep, FHSI-8[12-14,58-64] (Table 2). Some trials defined *a priori* 1-2 scales of interest within an HRQOL instrument as study endpoint, *e.g.*, global QOL or physical functioning domain of EORTC QLQ-C30[59,60,64].

A phase Ⅲ trial comparing first-line tamoxifen *vs* best supportive care alone in advanced HCC patients found no significant difference in OS in both arms. HRQOL, measured using Spitzer QoL index, decreased in both groups of patients with time[58].

A phase Ⅲ trial compared first-line megestrol acetate *vs* placebo in advanced HCC patients[61]. There was no significant impact on OS with megestrol acetate. However, patients received megestrol acetate had significantly better scores in EORTC QLQ-C30 appetite loss, nausea/vomiting and emotional functioning scales compared to placebo. Such prospective randomized HRQOL data might provide rationale in using megestrol acetate for palliative symptom relief in advanced HCC patients.

The SHARP study and the phase Ⅲ trial reported by Cheng *et al*[13] were pivotal trials demonstrating PFS and OS benefits of first-line sorafenib in advanced HCC patients compared to placebo[12]. Drug related serious adverse events were more frequent in sorafenib arm than placebo arm in both studies. Both trials employed deterioration in FHSI-8 score as one of the definitions of symptomatic progression. In both trials, median time to symptomatic progression was not significantly different between sorafenib and placebo arms.

The phase Ⅲ BRISK-FL study randomized 1150 advanced HCC patients to first-line brivanib or sorafenib[62]. There was no significant difference in OS, time to tumor progression or response rate between the 2 arms. The overall incidence of serious adverse events was 56% for brivanib arm and 48% for sorafenib arm. The study used EORTC QLQ-C30 physical and role functioning domains as HRQOL endpoint. There was no significant difference in HRQOL at baseline between the 2 arms. The mean scores for physical and role functions declined at 12 wk in both brivanib and sorafenib patients, but the deterioration was significantly worse in brivanib arm. The objective of non-inferiority in OS was not met for brivanib. Should the onjective be met, the available QOL could potentially be a key in guiding clinicians on the use of a more tolerable agent (in this case sorafenib) which has less impairment in QOL.

From these first-line trials on tyrosine kinase inhibitors, it appear that the toxicity profile of brivanib was worse than sorafenib, while that of sorafenib was worse than placebo. The deterioration in QOL may be due to treatment-related toxicities, which can be offset by improvement in QOL due to disease control by a more effective treatment. This postulation could

Table 3 Algorithm of C30 and HCC18 index scores

QOL Index scores for survival prognostication	
C30 index score	∑ [(100-Physical functioning), (100-Role functioning), (100-Emotional functioning), (100-Cognitive functioning), (100-Social functioning), (100-global QOL), scores of Fatigue, Nausea/vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial Difficulty]/15
HCC18 index score	∑(scores of Fatigue, Body Image, Jaundice, Nutrition, Pain, Fever, Sex life, Abdominal distension)/8

QOL: Quality of life.

theoretically be explored in a meta-analysis of these studies, however, the usage of different HRQOL instruments across studies precluded such an attempt.

In the EVOLVE-1 trial, HCC patients who failed sorafenib were treated with everolimus or placebo[64]. Disease control rate was significantly better in the everolimus arm, but there was no significant difference in PFS or OS between the 2 arms. On the other hand, the time to definitive deterioration in EORTC QLQ-C30 physical functioning was significantly shorter in the everolimus arm. This might be related to the significantly increased incidence in grade 3/4 adverse events in the everolimus arm compared to the placebo arm. This study again exemplified the importance in inclusion of HRQOL assessment in clinical trial because the intervention itself could have negative effect on QOL.

The phase Ⅲ RESORCE trial evaluated second-line regorafenib *vs* placebo in advanced HCC patients with prior sorafenib. Compared to placebo arm, patients randomized to regorafenib had significantly longer OS and PFS (using modified Response Evaluation Criteria in Solid Tumors for HCC), and reported more drug related adverse events. HRQOL was assessed using FACT-G, FACT-Hep, TOI, EQ-5D and EQ-VAS. The FACT-Hep total score and TOI were significantly lower in regorafenib arm than placebo arm, while FACT-G, EQ-5D and EQ-VAS were not significantly different[14]. Cost-effectiveness analysis of this expensive intervention is essential in parts of the world where medical resources are particularly limited, the use of EQ-5D will allow such analysis to be conducted.

As prognostic tools for overall survival

One interesting use of HRQOL data in HCC patients is prognostication for OS. Three studies showed that in advanced HCC patients, baseline HRQOL at diagnosis was prognostic for OS[65-67]. Our group reported the prognostic significance of EORTC QLQ-C30 in advanced HCC patients, where worse scores in appetite loss, physical function and role function domains were independent risk factors for shorter OS[65]. In another study using EORTC QLQ-C30, better baseline role function score was found to be a significant prognostic factor for longer OS in advanced HCC patients[67]. Baseline Spitzer QoL index was also reported to be prognostic of survival in 538 advanced HCC patients, where higher baseline Spitzer QoL index score was associated with longer OS[66]. However, a study recruiting HCC patients of all stages reported FACT-G was not prognostic of overall survival[68].

Our group subsequently evaluated the prognostic value of baseline EORTC QLQ-C30 and QLQ-HCC18 in a cohort of newly diagnosed HCC patients including all stages and found both were significant prognostic factors for OS irrespective of stage of disease[69]. Better scores in QLQ-C30 pain, QLQ-C30 physical functioning, QLQ-HCC18 pain, QLQ-HCC18 fatigue scales at diagnosis were significant independent prognostic factors for longer OS. In order to enhance the user-friendliness of these instruments, two summative scoring systems, the C30 index score and HCC18 index score, were derived. See Table 3 for the formulae.

Both of these scores were found to be highly significant factors for OS and their prognostic values resemble that of a staging system.

For C30 index score of 0-20, 21-40, 41-60, 61-100, the median OS were 16.4, 7.3, 3.1, 1.8 mo respectively ($P < 0.0001$). For HCC18 index score of 0-20, 21-40, 41-60, 61-100, the median OS were 16.4, 6.0, 2.8, 1.8 mo respectively ($P < 0.0001$).

Attempts have been made to enhance existing staging systems with HRQOL data[66,67]. Addition of EORTC QLQ-C30 data has been shown to improve the performance of the Cancer of the Liver Italian Program (CLIP)[70,71], the Barcelona Clinic Liver Cancer system[72], the Groupe d'Étude et de Traitement du Carcinome Hépatocellulaire system[73]. Spitzer QoL index could improve the prognostic value of CLIP[66].

Valuation of health care service

Cost-effectiveness studies analyze the cost per outcome (effectiveness) of health care interventions, and compare this with reference to the country's willingness to pay threshold. In cancer setting, this outcome is commonly QALY. HRQOL measurement allows valuation of HRQOL specific to the population. When this is combined with time, QALY could be calculated[74]. A popular instrument for this purpose is EQ-5D.

Certain treatments for HCC, such as liver transplantation and tyrosine kinase inhibitors, carry significant economic burden due to high utility and cost, particularly in areas with endemic hepatitis B viral infection. Cost-effectiveness analysis is therefore important to assist societal economic consideration by policy makers in health care service. A number of cost-effectiveness analyses in HCC have been carried out in this regard[75-80].

Palliative care service benchmark

HRQOL is an important benchmark for palliative care service and clinical trial[81]. Palliative care in cancer setting aims to improve QOL of cancer patients. It involves prevention, early identification and relief of sufferings (physical, psychological, social and spiritual) of cancer patients during the whole course of their illnesses. Therefore effective palliative care could be reflected in improvement in QOL.

Palliative care trials commonly recruit patients with a wide range of malignant diseases, including HCC. A prospective study conducted in Germany assessed the change in HRQOL using EORTC QLQ-C30 in cancer patients admitted to a hospital unit or palliative home care service where palliative treatment was given for symptoms relief[82]. Of all the patients who received palliative service for 7 d, 57% had a better rating in symptom domains and 42% had a better rating in functional domains when compared to their rating before receiving the service.

DIFFICULTIES IN UTILIZATION OF HRQOL IN CLINICAL TRIAL AND PRACTICE

Prospective study design

Although retrospective analysis of QOL can be conducted, HRQOL data have to be prospectively collected to be usable. Unless an institute has routine HRQOL assessment for all patients, a retrospective study is impossible to have HRQOL as a parameter.

Choosing a suitable tool

Choosing a suitable HRQOL instrument for a study could be challenging. Although the majority of the mentioned instruments were extensively validated, which instrument prevails over another is largely unknown. The aim of a study and the characteristics of individual HRQOL instruments should be considered. If the symptom aspect of HRQOL was of interest, one may favor an instrument housing more liver-cancer related symptoms, for example, EORTC QLQ-C30 plus QLQ-HCC18, or FACT-Hep. One should also take into account the instrument's responsiveness to change with clinical condition in order to accurately capture significant HRQOL deterioration or improvement in subsequent reassessment time points. If follow-up cost-effectiveness analysis of an intervention is anticipated, the study needs to include an instrument with QOL valuation ability, for example, EQ-5D.

Missing data

Missing data is common in HRQOL studies, and inadequate reporting and handling of missing data are also common[83]. Analysis of incomplete data could give biased results. Therefore missing data should be prevented, identified and handled appropriately.

Prevention of missing data should be planned before a study begins. As opposed to survival data that could be captured even when patients have succumbed, follow-up QOL assessment relies mainly on active participation of patients. They need to have adequate physical and cognitive function and motivation to answer relevant questionnaires. This could be demanding to patients with deteriorated clinical status. This proves particularly challenging in clinical trial involving advanced HCC patients because their PFS generally is short and the clinical downhill course can be rapid. More frequent HRQOL reassessment may maximize the capture of HRQOL data before significant clinical deterioration occurs. Proxy (treating clinicians or patients' care-giver) filled questionnaires could be a reasonable substitute[84] but still creates significant bias because HRQOL is a personal and subjective measurement. Computerized questionnaire during follow up visit could be programmed to forbid submission of incomplete questionnaire. Patients may forget to return reassessment questionnaires by mail if such system is utilized. Some studies employed reminder system to reduce this non-compliance.

When missing data occurred, it is essential to identify the mechanism of missing data and tackle it accordingly. There are 3 mechanisms of missing data: (1) missing completely at random (MCAR): MCAR is said to occur if the reason of missing data is unrelated to any variable of the study. For example, an on-site hand-held device for HRQOL assessment broke down for a certain period of time; (2) missing at random (MAR): If the reason of missing data was related to non-QOL data, MAR is present. For example, elderly patients are more prone to forget returning the reassessment questionnaire by mail than younger patients; and (3) missing not at random (MNAR): MNAR is assumed when the reason of missing data is related to the QOL data. For example, severely ill patients with the worse QOL may feel too weak to complete reassessment questionnaires.

MCAR and MAR are categorized as ignorable missingness. Whereas MNAR is categorized as non-ignorable missingness, because the observed (available) QOL data are typically biased. Therefore it is important to investigate the mechanism of missing data in order to employ specific method of handling. Various statistical methods have been established to investigate the mechanism of missing data[85]. Nevertheless, confirmation of the underlying mechanism may not be possible. Once assumption of the mechanism is made, appropriate method to deal with missing data follows[86].

The following are the methods to handle missing data: (1) complete case analysis: Patients with missing data are excluded from the analysis; (2) single imputation: Single imputation replaces a missing value by a single value and analysis is carried out as if all data are observed. The replacement value could be the mean or mode of observed data, last observed value carried forward, baseline observed value carried forward, or predicted value from a regression equation based on information from observed data. Single imputation

may have a higher risk of biasing the analysis because the uncertainty of imputed values was not addressed; (3) multiple imputation: Multiple imputation generates multiple copies of the original dataset by replacing missing values using a specified regression model. Analysis is then performed for each dataset and the results are pooled into one estimate with standard error taking into account the uncertainty of the imputation process; and (4) statistical models: Mixed models and generalized estimating equations could be used to allow for missing data without imputation, making assumptions about their relationships with the observed data.

Option (1) will only be unbiased in case of MCAR or MAR. For MNAR, options (2-4) are more appropriate. Sensitivity analysis is then carried out. It involves separate analysis of every dataset generated by various imputation methods and comparison of the results. Sensitivity analysis reflects whether an analysis is robust (insignificant distortion of conclusion) after handling of missing data[87]. These are the key steps to minimize the detrimental effect of missing data on the results of QOL studies.

Population related difference in HRQOL

HRQOL changes significantly across different diseases, cultures and ethnicities. For example, in Chinese culture people take endurance as a merit, they often minimize the verbalization or expression of discomfort, thus symptoms scales might underestimate their symptomatology. Oriental culture tends not to discuss sex issue openly, therefore missing data rate in the sexual problem scale could be particularly high. Different languages and dialects could also affect patient's interpretation of the intended questions. Therefore HRQOL instruments need validation in different countries, since HRQOL data from one country may not be applicable to another.

This is evident in a study that compared HRQOL between Asian and European HCC patients[88]. It reported significantly better scores in emotional functioning and insomnia (based on EORTC QLQ-C30) and sexual interest (based on EORTC QLQ-HCC18) in Asian when compared to European patients, after adjusting for demographic and clinical variables.

Data interpretation

Most HRQOL instruments consist of a collection of scores in various domains. How can one define a domain score being significantly good or bad? How can one define a clinically significant change in a domain score? Attempts have been made to evaluate minimally important differences in HRQOL measurements by comparing the scores among different patient groups stratified according to various clinical anchors, for example, stage of disease, performance status, *etc*[89-92]. This permits meaningful interpretation of HRQOL data. Studies sometimes employed these findings to define their HRQOL endpoints. However caution has to be exercised as these cutoffs or thresholds might be population- or disease-specific and might not be applicable to all.

Data analysis

Raw HRQOL ordinal data are commonly used as continuous variables in data analysis. Analysis is usually in the form of comparison of mean domain score between 2 patient groups or 2 time points within the same group. The situation is complicated by the fact that when all domain scores are included in a multivariate analysis model, the numerous raw HRQOL data could cause excessive multiple comparisons and instability of model[93,94].

Studies using limited number of domains within an HRQOL instrument may have avoided such problem, but may sacrifice potentially significant HRQOL variables.

Diouf *et al*[67] dichotomized all EORTC QLQ-C30 scale scores using 50 as an empirical cut-off for analysis. This may prevent overfitting and multi-collinearity and allows clinicians to understand HRQOL data in a simpler manner. As these cut-offs were supposed to be population-specific, another analysis was performed and reported the real cut-off for various scales[95].

Another way of HRQOL data analysis while avoiding multi-collinearity, yet without sacrificing any QOL data, is to use 1 score to represent all scales in the whole instrument. As discussed earlier, by transforming the EORTC QLQ-C30 into C30 index score, and EORTC QLQ-HCC18 into HCC18 index score for data analysis, our group has shown that these index scores were the most significant independent factors for OS among all the individual HRQOL variables, whether continuous or dichotomized[69].

Different studies used different HRQOL instruments. QOL data, unlike survival data or response assessment, are not unified to allow cross trial communication. Cross study comparison of HRQOL result is not usually possible. Performing meta-analysis on HRQOL studies is therefore difficult.

Limitation for use in clinical practice

Measurement of HRQOL in clinical practice is desirable. QOL changes over time in HCC patients when their diseases improve or progress, or when treatment complications arise. Deterioration in QOL reflects the need for palliative care intervention. However routine capturing of QOL data is difficult. Filling in the instruments, calculating all domain and total scores could be cumbersome in the clinical setting. Difficulty in interpretation of a collection of numerical scores also deters a clinician from welcoming it. Modern handheld device might help patients to self-administer the questionnaires during waiting time, it can help generate all domain and total scores automatically, as well as support interpretation of individual score according to published local reference values.

CONCLUSION

Quality of life could be as important as survival in HCC patients because majority of them have advanced disease and limited survival. QOL measurement provides valuable information in clinical practice and research. Future research into utilization in clinical trials as well as routine clinical practice are warranted.

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