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Current Perspective

Quality of life in patients with advanced colorectal cancer: what has been learnt?

T. Conroy[a,*], H. Bleiberg[b], B. Glimelius[c]

[a]*Department of Medical Oncology, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France*
[b]*Gastrointestinal Unit, Institut Jules Bordet, Bruxelles, Belgium*
[c]*Department of Oncology/Radiology and Clinical Immunology, University Hospital, Uppsala and Radiumhemmet, Stockholm, Sweden*

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Abstract

Accurate assessment of health-related quality of life (HRQoL) in patients with advanced colorectal cancer is essential to improve our understanding of how cancer and chemotherapy influence patients' life and to adapt treatment strategies. Specific questionnaires have descriptive and predictive value and can be used to evaluate new therapies. Results from HRQoL assessments in randomised trials help patients and physicians to choose between treatment options. More than half of the patients treated with palliative chemotherapy have an improvement or at least a preservation of their HRQoL. However, several trials have found small differences in HRQoL between treatment groups. This may be due to the insufficient sensitivity of tools, low numbers of patients or missing data. An international consensus on the methods of measurement of HRQoL in oncology is warranted to enhance compliance, to better interpret results and to optimise the publication of precise HRQoL data.

Keywords: Colorectal cancer; Quality of life; Chemotherapy

1. Introduction

Colorectal cancer is common in Western societies, and more than 40% of patients will have metastases at some point during the course of the disease. Traditionally, objective end points such as response rate and survival have been used to evaluate the efficacy of chemotherapy in advanced colorectal cancer. In recent years, more and more trials have incorporated health-related quality of life (HRQoL) as a key endpoint and the American Society of Clinical Oncology [1] claims that *patient outcomes* (toxicity, survival and HRQoL) are more important than *cancer outcomes* (response rate, duration of response). HRQoL data provide direct measures of benefit as perceived by the patient. Accurate HRQoL measurements, therefore, using valid, standardised, relevant questionnaires are essential to ensure that data are of clinical value. Unfortunately, reviewing trials comparing palliative chemotherapy with supportive care [2], the Colorectal Cancer Collaborative Group concluded that data on the effect of palliative chemotherapy on HRQoL were insufficient to draw firm conclusions. Reasons for this severe judgement included a lack of unified HRQoL instruments, use of non-validated tools, and weak data analysis. However, several trials comparing different regimens have included accurate HRQoL assessments. In the present article, we review the studies in advanced colorectal cancer that have incorporated well-validated instruments.

2. The instruments

Multitudes of HRQoL instruments have been described providing adequate coverage of the basic HRQoL domains (i.e. physical, functional, social and emotional function). There is no consensus as to which instruments are more appropriate. These instruments can be classified in three main categories: generic instruments, cancer-specific instruments and symptom-focused questionnaires.

* Corresponding author. Fax: +33-383-598359.
E-mail address: t.conroy@nancy.fnclcc.fr (T. Conroy).

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2.1. Generic instruments

Generic instruments are multi-item scales designed to be used across a wide range of chronic disease populations. Examples of well-validated generic instruments include the Sickness Impact Profile (SIP), the Nottingham Health Profile (NHP), and the medical outcomes studies Short Form health survey (SF-36). These instruments allow for comparisons of results across different health conditions, but they are relatively insensitive for a specific intervention.

2.2. Cancer-specific instruments

Cancer-specific instruments address problems specific to a given cancer patient population. The Spitzer QoL index (QLI) is a five-item instrument that asks the physicians to rate the well-being of the patients in the areas of activity, daily living, health, support and outlook as either 0, 1 or 2 for each item, producing a total score from 0 to 10 [3]. The QLI was compared with a visual-analogue scale, a 10-cm line with anchors referring from 'perfect health' to 'worst imaginable health', in 128 patients with chemoresistant colorectal cancer [4]. Evidence of a ceiling effect for the QLI appeared with a high proportion of unconfirmed best scores. When rated by the physician, the scores of the visual-analogue scale were 12% lower than the patients' ratings ($P < 0.0001$). This confirmed other reports showing a poor correlation between doctors' and patients' HRQoL assessment. The Functional Living Index-Cancer (FLIC) is a well-validated 22-item questionnaire [5] which provides a total score.

The European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire (QLQ-C30) is a 30-item cancer-specific questionnaire designed for use in clinical trials [6]. It includes five functional scales, three symptoms scales and one global scale (Global Health Status/QoL). Five single items assess additional symptoms including appetite loss and diarrhoea.

Psychometric properties of the QLQ-C30 in metastatic colorectal cancer have been verified in a study including 351 patients [7]. The clinical significance of changes in scores has been assessed [8]. Patients with a mean change in scores of 5–10 points (on the 0–100 range) reported 'a little' change in HRQoL. A 'moderate change', in HRQoL was reflected in scores changing by 10–20 points; and patients that reported 'very much' change in HRQoL, had mean scores that changed by greater than 20. So a 10% improvement in a HRQoL score, maintained over two consecutive measurements 4 weeks apart, qualifies for a HRQoL response, and the number of patients reporting 'a response' can then potentially be documented. No clinical trial in colorectal cancer has, however, used this categorisation.

The Functional Assessment of Cancer Therapy-General version (FACT-G) consists of four domains: physical well-being, social and family well-being, emotional well-being and functional well-being [9]. As well as the QLQ-C30, a longitudinal change of 5% in FACT-G is considered as a clinically meaningful change [10]. Items are written as statements. FACT-G, EORTC QLQ-C30 and FLIC have been compared in a study of 310 French patients including 60 patients with colorectal cancer [11]. The acceptability of EORTC QLQ-C30 and FLIC was better than that of FACT-G, due to a significantly lower rate of missing, confusing or upsetting items.

2.3. Symptom-focused questionnaires

The Rotterdam Symptom Checklist (RSCL) consists of 38 items and an overall HRQoL question [12]. This well-validated HRQoL questionnaire is frequently used with the Hospital Anxiety and Depression Scale (HADS) [13].

The Anorectal Sphincter-Conservative Treatment (ASCT) questionnaire is an anorectal cancer specific symptom scale [14]. It contains 18 questions related to bowel habit.

The modular approach of HRQoL assessment combines the administration of a 'core' questionnaire, supplemented by a specific 'module' assessing specific issues, not sufficiently covered by the core instrument. The use of a module increases the specificity and the sensitivity to detect small, but clinically important, differences in HRQoL. EORTC QLQ-C30 and FACT-G are such core instruments, which can be supplemented by colorectal cancer-specific modules.

The EORTC colorectal questionnaire (QLQ-CR38) is developed to be used in conjunction with the QLQ-C30 [15]. An international validation study is required to further establish the acceptability, cross-cultural validity and responsiveness of this questionnaire. The preferential use of this module seems to be surgical and adjuvant treatment trials, and not trials in advanced disease. The EORTC QoL group is now developing a module for liver metastases from colorectal cancer.

The FACT-Colorectal (FACT-C) instrument combines the FACT-G with a nine-item colorectal cancer subscale [16]. In contrast to EORTC QLQ-C30, the FACT-C has a total score resulting from all items.

For instrument selection for the research setting, the most important considerations are the extent to which the selected instrument adequately covers the research question, has adequate psychometric properties (especially responsiveness), and whether it is feasible for use. It is often recommended to use both a general and a disease-specific instrument. In studies among colorectal cancer patients, the FLIC, the RSCL and the EORTC QLQ-C30 have been the most widely used.

3. HRQoL assessment in clinical studies in advanced colorectal cancer

Results from HRQoL measurement in advanced colorectal cancer patients have given useful information summarised below.

3.1. The predictive value of HRQoL data

Baseline HRQoL in patients enrolled in clinical trials is a major prognostic factor in numerous trials [4,17–24]. This was assessed in multivariate analysis in six studies [17,19–22,24]. The global scale of the QLQ-C30 was an independent predictor of survival in the three larger studies [19,22,24]. HRQoL appears to be a stronger predictor of overall survival than performance status measured by the clinician [20,24]. So HRQoL measurement results can help to stratify patients in clinical trials and its use would facilitate comparisons between studies.

3.2. The descriptive value of HRQoL scores

Results from HRQoL questionnaires help develop an improved understanding of cancer-related and treatment-related symptoms. It counterbalances insufficiencies in clinical judgement. For example, in the Nordic multicentre study in asymptomatic patients [25], 44% of the patients had symptoms that could have been related to their disease. This may due to the fact that patients report symptoms only when they are severe [26]. HRQoL studies can also add to information from toxicity scales. Patients often report adverse effects more often than physicians [27]. In a randomised study comparing raltitrexed to fluorouracil (5-FU) plus leucovorin, the investigators reported no significant difference in the rate of grade 3-4 nausea/vomiting and yet the patients reported significantly higher rates of nausea/vomiting in the raltitrexed arm using a HRQoL questionnaire [28]. Other papers also suggest a consistent bias with physicians underestimating the severity of patients' symptoms.

3.3. Chemotherapy versus best supportive care

HRQoL instruments have suggested that first-line chemotherapy not only has a survival advantage over supportive care, but can also improve or stabilise the HRQoL [29–31]. However, these studies have some limitations: in the Austrian study comparing 5-FU/leucovorin and cisplatin with supportive care, only 26 of the 50 patients included filled in the two FLIC questionnaires. Global HRQoL and specific domain scores did not differ between the two groups [29]. In the Nordic study [31], 183 asymptomatic patients were randomised between immediate 5-FU-based chemotherapy versus primary expectancy with chemotherapy not considered until symptoms appeared. Survival was statistically significantly longer for patients randomised to receive the initial chemotherapy. HRQoL study was performed in only one institution where 43 patients were randomised; 36 of which were interviewed with a questionnaire specific to the study. Patients randomised to initial chemotherapy maintained a good HRQoL, especially for the physical and emotional domains [25]. A more recent pooled analysis of two randomised studies in asymptomatic patients, compared initial chemotherapy with primary expectancy where chemotherapy was given only after the appearance of symptoms was performed. 63% of the patients filled the EORTC QLQ-C30. The percentage of high global QoL did not differ between the two groups [32]. Allen-Mersch and colleagues [30] compared floxuridine hepatic-artery infusion in patients with colorectal liver metastases with supportive care. HRQoL was measured with RSCL and HADS. No significant difference in HRQoL was found between the treatment and control groups. However, a significant prolongation in survival without physical symptoms, anxiety and depression was described.

3.4. Impact of chemotherapy response

In symptomatic patients, palliative chemotherapy improves the HRQoL of 25–33% of patients and maintenance of a good HRQoL for at least 4 months is obtained in another 25% of patients [18,27]. In a trial using 5-FU-based treatments, more than 50% of patients were scored as cases or borderline for anxiety and/or depression at baseline according to the HADS questionnaire. A steady improvement during treatment was observed with a 50% reduction in the number of patients with borderline or case anxiety and depression 3 months later [33]. Conversely, an ineffective drug, tauromustine, given as first-line treatment, is associated with a reduced HRQoL [17].

HRQoL changes appeared different in patients with or without symptoms at diagnosis. Symptomatic patients who respond to chemotherapy have less severe symptoms and better physical function compared with non-responders [19,20,27,34]. Non-responders have significantly higher depression, pain and physical symptom score compared with responders [20]. In asymptomatic patients, response to chemotherapy does not significantly influence patients' HRQoL [35]. In another trial, the investigators reported that patients with good HRQoL score at baseline were more likely to deteriorate than patients with a poor HRQoL score at baseline, but the latter were more likely to have an improvement in their scores [28].

3.5. Effects of toxicities

The expected, positive effects of new treatments must be weighed against the perception of side-effects and

results from HRQoL measurement contributes to the more accurate evaluation of the balance between morbidity and therapeutic benefit. For example, a comparison of 3-weekly infusional 5-FU schedules in patients with a good performance status, showed a significant deterioration in physical and global HRQoL during 6 months in two arms [36]. These results are likely due to the side-effects of treatment. The EORTC QLQ-C30 asks patients about the previous week and patients receiving weekly treatment are more likely to report symptoms and toxicities. Interferon α, a potential, but ineffective, modulator of 5-FU, was associated with a decreased HRQoL assessed by the HADS and RSCL questionnaires [33]. A Medical Research Council (MRC) trial addressed the question of any differences between protracted 5-FU infusion (Lokich regimen), LV5FU2 (De Gramont regimen) and raltitrexed [23]. HRQoL was measured using EORTC QLQ-C30 and HADS. 84% of the patients completed baseline HRQoL measures and only 43% the three assessments. Raltitrexed was inferior to protracted 5-FU infusion and LV5FU2, particularly for emotional and social functioning. Palliation of key symptoms (fatigue, pain, insomnia, appetite loss) was less frequent with raltitrexed. These results are partly due to toxicity with worse nausea/vomiting scores in the raltitrexed arm.

3.6. First-line combinations

In a randomised trial of LV5FU2 with or without oxaliplatin [35], emotional functioning improved in both arms, but HRQoL was not different between the two arms, despite differences in the response rate. It was suggested that the QLQ-C30 has a poor sensitivity for side-effects such as diarrhoea, mucositis or neurological toxicity, which differed significantly in the two arms. Again, the time-frame of the QLQ-C30 instrument and the infrequent HRQoL assessments (every fourth treatment cycle) probably explained the lack of differences. Moreover, the QLQ-C30 may not have detected mucositis and neurological toxicity because it does not contain these items. A site-specific or chemotherapy-specific module would then be required. Lastly, compliance (defined as the proportion of HRQoL forms returned out of those anticipated) was good at inclusion (84%), but rapidly decreased to 56% at 4 months and 38% at 8 months [7].

Other trials have compared 5-FU-based polychemotherapy including mitomycin C or irinotecan to 5-FU/leucovorin alone [37–39]. In these trials, a significantly higher response rate did not correlate with a higher HRQoL. These results are disappointing because a higher HRQoL was predicted with the significant increase in the response rate. This may be due to different causes:

- compliance was poor (59–62% in the Douillard trial). Patients with the lower HRQoL may not have completed the questionnaires [40].
- 90% of the patients were asymptomatic and likely had a high HRQoL at inclusion. However, this hypothesis cannot be confirmed because the scores at inclusion are not described in the final papers.
- EORTC QLQ-C30 may have an insufficient sensitivity to detect changes and a chemotherapy-specific module may increase responsiveness.
- HRQoL measurement was stopped when patients failed. In many cases, progressive disease at the end of first-line treatment is not associated with symptoms reducing HRQoL (but the information of no response may well be).
- Changes in patients' internal standards due to adaptation processes may be responsible for a minimisation of the perception of the consequences due to the disease or the treatment. This phenomenon, also described as a 'response-shift', has also been described in patients with colon cancer undergoing radical resection [41].

We have no method of identifying which of the above mentioned explanations prevailed.

3.7. Optimal duration of first-line chemotherapy

There is no standard scientific attitude on the optimal duration of first-line chemotherapy. Only one trial assessed the HRQoL of patients with stable or responding disease after 12 weeks of initial treatment. Patients were randomised to receive 12 additional weeks of chemotherapy versus no further treatment [42]. There was no statistically significant difference in progression-free or overall survival. Patients randomised to continue chemotherapy reported significantly more serious toxicities and significantly worse HRQoL using EORTC QLQ-C30 and HADS.

3.8. Second-line treatment

Because second-line chemotherapy has modest effects on survival, achieving an improvement or a maintenance in HRQoL could be an important benefit to patients. It is particularly necessary to be certain that the benefits of improved HRQoL in some domains are not offset by a deterioration in others as a result of the side-effects of treatment.

Few randomised studies are available. Hydrazine, an agent intended to stimulate appetite, was compared with placebo in patients with advanced colorectal cancer who were resistant to 5-FU. More rapidly deteriorating HRQoL scores were recorded in the hydrazine sulphate patients, but these were not significantly different [43]. Irinotecan as a second-line treatment was compared

with supportive care alone after 5-FU failure [44]. 71% of the patients filled two EORTC questionnaires. The diarrhoea score was significantly better (lower) in the supportive-care group ($P=0.02$). Scores were greater for all the HRQoL function scales (except emotional) and global HRQoL in the irinotecan arm. Patients also reported fewer tumour-related symptoms including fatigue and pain, when treated with irinotecan. The HRQoL analysis indicated that the side-effects of chemotherapy were favourably balanced by fewer tumour-related events. A problem is the time-frame of QLQ-C30 being 1 week, since the interval between irinotecan infusions was 3 weeks. However, compared with infusional 5-FU, second-line irinotecan did not improve HRQoL [45]. In 5-FU-progressive patients, those who were stabilised by chemotherapy have a HRQoL profile comparable to that of responders, as opposed to patients with progressive disease [46].

3.9. Use in routine clinical practice

Probably due to time and resource constraints, HRQoL is not yet assessed in everyday clinical practice. The introduction of an individual HRQoL assessment into the daily routine was assessed in a few trials. To our knowledge, only one trial dealing specifically with cancer patients is available [47]. 450 patients completed the EORTC QLQ-C30 and Beck Depression Inventory. After randomisation, results were reported (intervention arm) or not reported (control arm) to the health care team. Six months after randomisation, no significant differences appeared between the two arms. However, for the subgroup of patients who were depressed at baseline, there was a significant reduction in depression for the intervention arm ($P=0.001$). Another trial including 2704 patients [48], using a similar design, demonstrated an increased satisfaction with care in several dimensions, probably due to an improved doctor–patient communication. There is a clear need for further research on the possible benefits of HRQoL measurement as an intervention in itself before its use in clinical routine practice would be recommended.

If a therapeutic individual benefit is further demonstrated with HRQoL assessments, the data collection should be simplified in the future. Electronic methods of data collection (palmtop, or touch-screen personal computer) look promising for implementation in clinical practice [49].

4. Drawbacks and methodological issues

4.1. Missing data and practical issues

The occurrence of missing data is a frequent problem in studies in which HRQoL is being measured [50], leading to serious problems in the analysis and interpretation. Useful HRQoL data can be lost because some patients may be too ill to complete the questionnaire or because of insufficient organisation in some centres. This creates a pattern of loss of information that is selective. Statistical methods for analysing data with a non-random dropout are being developed, but no gold standard has emerged. Missing data could be patient-related, but the concept of HRQoL endpoints is usually well accepted by patients and even patients in palliative care are willing to complete HRQoL measures [51,52]. Procedures to reduce to a minimum missing data have been implemented in clinical research groups [53]. A review of methods to reduce missing data can be found in a special issue of Statistics in Medicine [54]. Examples of important practical issues are listed in Table 1.

Maintenance of HRQoL measurement after treatment failure should be considered in phase III trials. This may increase the differences between arms. To stop asking patients about their well-being, especially when the disease is progressing and patients are withdrawn from trials, may also have a negative psychological impact [55].

Timing in HRQoL assessment in relation to the administration of chemotherapy causes problems. All patients should have a baseline assessment before randomisation, because knowledge of their group assignment may influence their answers to the questionnaires. Exact timing is also difficult to choose when two regimens differ in their time intervals. For example, in a trial comparing raltitrexed used at 3-week intervals with 5-FU/leucovorin every 4 weeks [56], HRQoL was assessed with EuroQoL and RSCL. A statistically significant benefit in favour of raltitrexed at 2 weeks in

Table 1
Strategies to minimise missing data

- HRQoL needs only be measured if it is clinically relevant.
- HRQoL assessment should be an integral part of the trial and not an option.
- Completion of the baseline questionnaire should be an eligibility criterion.
- Questionnaires with complicated formats should be avoided or minimised.
- A background section of the protocol should explain the rationale for collecting HRQoL data and methods and guidelines should be explicitly stated.
- Importance of HRQoL assessment should be explained in the consent form.
- The importance of HRQoL assessment and how to complete the questionnaires should be explained to the patient.
- One named and motivated member of staff should be made responsible for the administration of the HRQoL questionnaire in each centre.
- If an assessment is missing because of organisational problems, the patient should be contacted and asked to complete and return the mailed questionnaire.

several domains and overall HRQoL was described. In a similar trial, EORTC QLQ-C30 was completed by patients at baseline and every 12 weeks thereafter. No differences in HRQoL was observed, except a higher rate of perceived nausea/vomiting in the raltitrexed-treated group [28]. These differences between these two similar trials are probably due to the timing of HRQoL distribution in relation to the administration of treatment and expression of toxicities.

4.2. Data analysis

The inclusion of HRQoL endpoints in clinical trials requires the same methodological rigour as other endpoints. Due to the number of domains and potential statistical tests, it is important to prevent artifacts from multiple significance testing when no *a priori* hypothesis is defined. Specific hypotheses for HRQoL endpoints should be predefined in each study. Investigators can decide to limit the number of HRQoL domains that would be examined by significance testing. The absence of an inbalance between HRQoL scores at inclusion should be checked. Due to the multiplicity of HRQoL data, adjustments to the P values should be performed to account for multiple statistical comparisons.

Statistical methodology for analysing HRQoL data has developed rapidly over the past few years. However, there is no consensus on the most relevant way to analyse longitudinal studies, and the interpretation should be made with caution, especially in cases of non-random drop-out. In advanced colorectal cancer trials, changes in HRQoL scores between groups have been analysed using simple t-tests or Mann–Whitney tests [20,23]. Others used sophisticated statistical methods for the analysis of repeated measurement data such as analysis of variance for repeated measures [18,20,30,38,39,44] or generalised estimating equations [28,43]. In some papers, methods of analysis were not described [33,35]. In most trials, very few details are given and the clinical significance of HRQoL results is not addressed. None of the published trials presented the distribution of HRQoL scores at baseline. These methodological limitations hinder the interpretation of the results. Therefore, an international consensus on methods of measurement of HRQoL in oncology is warranted to enhance compliance, to better interpret the HRQoL results and to optimise publication of precise HRQoL data.

A useful way of presenting trial results would be to describe the distribution of changes: how many patients benefit? how many show no change? and how many worsen? Another method should be to define the palliative response as a predefined improvement in a selected primary HRQoL scale that should be maintained for at least two months or more, in analogy with the objective response evaluations based upon repeated imaging techniques. Alternative methods of analysing HRQoL data using independent raters blinded to trial data and clinical information have been proposed [57].

5. Conclusion

The interpretation of HRQoL data is more difficult than that of data on traditional endpoints. Missing data are among the number of serious methodological problems. Despite these difficulties, HRQoL analysis have provided new insights into the advantages and disadvantages of various chemotherapy combinations that are not provided by traditional endpoints. Assessment of HRQoL is clearly in need of further methodological refinement before this parameter can be regarded as being fully established with respect to its ability to provide useful data unequivocally. Use of an advanced colorectal or a chemotherapy module will probably increase the sensitivity to changes of core questionnaires such as EORTC QLQ-C30.

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