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Review

Methodological issues in assessing health-related quality of life of colorectal cancer patients in randomised controlled trials☆

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Abstract

Although health-related quality of life (HRQOL) is increasingly reported as an important endpoint in cancer clinical trials, questions still remain about the quality of its reporting. The aim of this study was to evaluate the level of reporting of HRQOL in randomised controlled trials (RCTs) of colorectal cancer (CRC). A systematic literature search from 1980 to March 2003 was undertaken on a number of databases. Identified eligible studies were selected and then evaluated on a broad set of HRQOL predetermined criteria by four reviewers. Thirty-one randomised controlled trials involving 9683 colorectal cancer patients were identified. Nearly all studies dealt with metastatic patients and principally compared different chemotherapy regimens. The HRQOL tool most often used was the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), which was used in 48% of the studies. Some methodological limitations were identified: 39% of the RCTs did not report HRQOL compliance at baseline and 52% did not give details on missing data. A rationale for using a specific HRQOL measure was given in only 10% of the studies. Whilst HRQOL assessment is a potential valuable source of information in understanding the impact of colorectal cancer, a number of methodological shortcomings have to be further addressed in future studies.

Keywords: Colorectal cancer; Quality of life; Randomised controlled trial; Systematic review

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the world and it is the second leading cause of cancer death in Western countries. Surgical resection of the primary tumour is attempted in up to 80% of patients and approximately half of these will be cured. Survival after surgery may be extended with postoperative chemotherapy and there is evidence that neoadjuvant radiotherapy reduces local recurrence after rectal excision [1]. Patients with metastatic CRC may be offered a variety of chemotherapies, although survival benefits are modest [2]. Hepatic resection of isolated liver metastases is increasing and there are a number of ablation techniques for local control of colorectal liver metastases. These treatments are traditionally evaluated with objective clinical endpoints, such as survival and operative morbidity and mortality. Such information is essential to inform decision-makers, but more and more studies in cancer clinical research report health-related quality of life (HRQOL) data [3]. This is important, particularly when survival gains are low.

There are several valid measures of HRQOL that are suitable to use in patients with CRC [4,5]. Although these instruments are widely available, there are many methodological issues that need to be addressed when HRQOL questionnaires are included in a clinical trial [6,7]. Consideration of the likely impact of the new treatment on HRQOL is required. Depending upon the research question, the mode of questionnaire administration may become an important issue, especially for large multicentre trials collecting sensitive data

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(e.g. sexual function after surgery). The timing of HRQOL measurements is also critical as some treatment symptoms may be missed with incorrect assessment points. Methods of HRQOL data analysis have different challenges often because of the repeated nature of multiple assessment points and concerns with missing data. When including HRQOL in clinical trials, measurement of HRQOL needs to be performed with a clinically appropriate questionnaire with good measurement properties. Unless standards for measuring HRQOL are adhered to in clinical trials, the data that are collected will be difficult to interpret and unlikely to make clinical sense. Despite a growing literature highlighting these principals, many studies in CRC do not address such concerns [8]. Previous review on randomised controlled clinical trials (RCTs) including an HRQOL evaluation in different cancer sites, such as prostate, brain, lung and breast, have shown overall a number of methodological shortcomings [9–13].

Although reviews exist on HRQOL aspects in CRC patients, to date, no detailed systematic reviews have been performed on HRQOL methodology used in RCTs. Furthermore, the issue of poor quality trials has been highlighted as a limiting factor for using HRQOL outcomes in the drugs approval process [14,15]. On these grounds, our aim was to systematically review the quality of HRQOL assessments used in RCTs of treatment for CRC patients.

2. Review methodology

A literature search was undertaken on the following databases: MedLine (1980–March 2003), the Cochrane Controlled Trials Register (Cochrane Library 2000, Issue 4) and the online National Cancer Institute database. Studies were selected based on the criteria cited below. In addition, significant articles listed as references were also included for possible selection. The search strategy for MedLine and Cochrane databases included the following words: *colon, colorectal, rectum,* and *cancer, carcinoma, hepatic metastases, liver metastases, neoplasm*. Alongside these, additional key words related to quality of life issues were added to the search: *quality of life, HRQOL, QoL, health related quality of life, health status, patient reported outcome*. The search was restricted to RCTs. There were no restrictions in the search-field description (for any of the key words used) or in the language of the article. The search on MedLine and the Cochrane controlled trials register yielded 116 and 158 candidate studies, respectively. The search on the online National Cancer Institute database was restricted to closed phase III trials for colon, rectal and anal cancer. This latter search yielded 168, 147 and four references, respectively. All candidate studies were checked for possible inclusion in the review. Overall, 593 candidate studies were retrieved and checked for possible inclusion. Unpublished studies were not taken into account.

3. Criteria for selecting studies

3.1. Types of participants

Participants were adult patients (aged 18 years and over) diagnosed with colon or rectal cancer as a primary site of disease regardless of the grade of the tumour stage. Patients undergoing screening procedures were not eligible.

3.2. Types of intervention

All RCTs comparing different medical treatment were eligible, regardless of the intervention type—surgical procedures, radiotherapy or chemotherapy. Any studies dealing with psychological intervention or any kind of intervention other than medical treatments were excluded (e.g. studies comparing home chemotherapy versus outpatient treatment or comparing any psychological intervention).

3.3. Types of outcome measures examined

Any studies including an HRQOL evaluation (either regarded as a primary or secondary endpoint) were considered. Only patient self-reported measures were considered, excluding studies exclusively assessing HRQOL by means of physician-assessed measures. This rationale is based on evidence showing considerable variability in results between clinician and cancer patient HRQOL reported outcomes [16–18]. Furthermore, there is a general consensus that patients are the most reliable source of information on their individual HRQOL, making a patient self-reported assessment desirable in clinical trials [19–21]. Patient-based HRQOL assessment offers the most direct means of evaluating the subjective morbidity associated with the disease and its treatment. Trials assessing unidimensional aspects of patient HRQOL, such as pain or other aspects related to quality of life were only taken into account when patient self-administered.

3.4. Types of studies

All published RCTs enrolling at least 50 patients (combined arms) published from 1980 to March 2003 were studied. The search was restricted to RCTs because they represent the *gold standard* by which health-care professionals make decisions about treatment effectiveness [22]. Publications meeting the above criteria, but involving a heterogeneous cancer patient

sample were excluded because of the possible difficulties in interpreting the HRQOL results relating specifically to CRC patients. Papers only reporting feasibility analyses, without giving any details on the results, were excluded. Because of their unreliability [23,24] and our aim to examine the quality of reporting, abstracts of conference proceedings were excluded.

4. Methods of evaluation of the studies

Four reviewers independently analysed all identified RCTs, unblinded for the authorship of the article. When disagreement about the analysis of a study occurred, all reviewers revised the paper to reconcile any differences. At the end of the process, all reviewers agreed upon the final classification. The selected trials were mainly evaluated on the level of HRQOL reporting and HRQOL methodology used rather than the overall quality of the trial as such.

In the absence of a *gold standard* for comparative HRQOL assessment methodology, authors based their evaluation on available literature regarding *good* practice for reporting HRQOL studies [6,7]. Thus, a predetermined scheme was developed and implemented, as previously reported in Refs. [9–12]. Four main categories were identified: demographics, trial design, HRQOL assessment methodology and methods of analysis (Tables 1–4). For HRQOL issues, attention focused primarily on the instrument type, rationale for instrument selection, covered domains, and presentation of psychometric details. Furthermore, we took note of the cross-cultural validity of the instrument. We did not evaluate the statistical appropriateness of the HRQOL analysis as, at present, there is no gold standard against which such an evaluation can be performed. When an article reported on a previously published HRQOL trial, it was deemed suitable for our review providing the reviewers agreed the original research contained insufficient HRQOL analysis. When more than one

Table 1
Demographics

Authors [Ref.]	Journal	Year of publication	Study location[a]	Industry funded[b]
Allen-Mersh and colleagues [50]	*Lancet*	1994	UK	Yes
Loprinzi and colleagues [51]	*J Clin Oncol*	1994	USA	No
Caudry and colleagues [52]	*Am J Clin Oncol*	1995	France	No
Cunningham and colleagues [53]	*Eur J Cancer*	1995	International	Yes
Hill and colleagues [54]	*J Clin Oncol*	1995	UK	Yes
Sullivan and colleagues [55]	*Pharmacotherapy*	1995	USA	Yes
Seymour and colleagues [56]	*J Clin Oncol*	1996	UK	Yes
Earlam and colleagues [57]	*J Clin Oncol*	1997	UK	No
Ross and colleagues [58]	*Ann Oncol*	1997	UK	No
Cocconi and colleagues [28]	J Clin Oncol	1998	International	Yes
Cunningham and colleagues [29]	*Lancet*	1998	International	Yes
Rougier and colleagues [30]	*Lancet*	1998	European	Yes
Schwenk and colleagues [31]	*Surg Endosc*	1998	Germany	No
Zaniboni and colleagues [32]	*Cancer*	1998	Italy	Yes
Comella and colleagues [33]	*Ann Oncol*	2000	Italy	Yes
De Gramont and colleagues [34]	*J Clin Oncol*	2000	International	Yes
Douillard and colleagues [35]	*Lancet*	2000	International	Yes
Saltz and colleagues [36]	*New Engl J Med*	2000	International	Yes
Sobrero and colleagues [37]	*Ann Oncol*	2000	Italy	No
Gray and colleagues [38]	*Ann Oncol*	2001	Australia	No
Unger and colleagues [39]	*Arzneimittelforschung*	2001	Germany	No
Blanke and colleagues [40]	*Ann Oncol*	2002	USA	Yes
Carmichael and colleagues [41]	*J Clin Oncol*	2002	International	Yes
Douillard and colleagues [42]	*J Clin Oncol*	2002	International	Yes
Furst and colleagues [43]	*Dis Colon Rectum*	2002	Germany	No
Ho and colleagues [44]	*Ann Surg*	2002	Singapore	No
Maughan and colleagues [45]	*Lancet*	2002	UK	Yes
Punt and colleagues [46]	*Ann Oncol*	2002	European	Yes
Sailer and colleagues [47]	*Br J Surgery*	2002	Germany	No
Weeks and colleagues [48]	*JAMA*	2002	USA	No
Fuchs and colleagues [49]	*J Clin Oncol*	2003	USA	Yes

UK, United Kingdom; USA, United States of America.

[a] A trial involving nations from more than one continent was defined as 'International'.

[b] Assessed if explicitly acknowledged in the paper. This evaluation is based solely on information extracted from the paper referenced in this table.

Table 2
Trial design

Authors [Ref.]	Method of randomisation stated	Informed consent reported	Trial inclusion and exclusion criteria reported	Number of patients[a]	Disease stage	Cancer site[b]	Mean age[c]	Type of intervention	HRQOL endpoint	HRQOL compliance mandatory	Hypothesis stated[d]
Allen-Mersh and colleagues [50]	Yes	Yes	Yes	100	Metastatic	C and R	57	Hepatic arterial floxuridine versus conventional symptom control	Primary	No	No
Loprinzi and colleagues [51]	No	Yes	Yes	128	Metastatic	C and R	na	Hydrazine sulphate versus placebo	Primary	Yes	No
Caudry and colleagues [52]	Yes	Yes	Yes	129	Metastatic and advanced recurrent	C and R	60	Fluorouracil and folinic acid versus infusional fluorouracil versus infusional fluorouracil and cyclophosphamide and mitomycin C	Secondary	No	No
Cunningham and colleagues [53]	Yes	Yes	Yes	439	Metastatic and advanced recurrent	C and R	61	Leucovorin and fluorouracil versus thymidylate synthase inhibitor	Primary	No	No
Hill and colleagues [54]	Yes	Yes	Yes	160	Metastatic	C and R	59	Infusional fluorouracil versus infusional fluorouracil and interferon alpha-2b	Secondary	No	No
Sullivan and colleagues [55]	Yes	Yes	Yes	218	Metastatic and locally advanced	C and R	na	Leucovorin and fluorouracil versus placebo and fluorouracil	Primary	No	No
Seymour and colleagues [56]	Yes	Yes	Yes	260	Metastatic and advanced recurrent	C and R	59	Leucovorin and fluorouracil versus leucovorin, fluorouracil and interferon alpha-2a	Secondary	No	Yes
Earlam and colleagues [57]	No	Yes	Yes	135	Metastatic	C and R	59	Systematic fluorouracil versus hepatic arterial fluorouracil versus symptom control	Primary	No	No
Ross and colleagues [58]	Yes	Yes	Yes	200	Metastatic and locally advanced	C and R	63	Infusional fluorouracil and mitomycin C versus infusional fluorouracil	Secondary	No	No
Cocconi and colleagues [28]	Yes	Yes	Yes	495	Metastatic and advanced recurrent	C and R	61	Raltitrexed versus leucovorin and fluorouracil	Secondary	No	No
Cunningham and colleagues [29]	Yes	Yes	Yes	279	Metastatic	C and R	60	Irinotecan and supportive care versus supportive care alone	Secondary	No	No
Rougier and colleagues [30]	Yes	Yes	Yes	267	Metastatic	C and R	58	Irinotecan versus infusional fluorouracil	Secondary	No	No
Schwenk and colleagues [31]	No	Yes	Yes	60	Uncertain	C and R excluding transverse colon and low rectal	65	Surgical trial: Laparoscopic or open resection	Primary	No	Yes
Zaniboni and colleagues [32]	Yes	Yes	Yes	888	Metastatic and locally advanced	C	62	Fluorouracil and folinic acid versus control	Primary	No	Yes
Comella and colleagues [33]	Yes	Yes	Yes	167	Locally advanced and metastatic	C and R	63	Irinotecan, leucovorin and fluorouracil or raltitrexed, leucovorin and fluorouracil versus methotrexate, leucovorin and fluorouracil	Secondary	No	No
De Gramont and colleagues [34]	Yes	Yes	Yes	420	Metastatic	C and R	63	Leucovorin and fluorouracil versus leucovorin, fluorouracil and irinotecan	Secondary	Yes	No
Douillard and colleagues [35]	Yes	Yes	Yes	387	Metastatic	C and R	61	Irinotecan, fluorouracil and calcium folinate versus fluorouracil and calcium folinate	Secondary	No	Yes

(*continued on next page*)

Table 2 (*continued*)

Authors [Ref.]	Method of randomisation stated	Informed consent reported	Trial inclusion and exclusion criteria reported	Number of patients[a]	Disease stage	Cancer site[b]	Mean age[c]	Type of intervention	HRQOL endpoint	HRQOL compliance mandatory	Hypothesis stated[d]
Saltz and colleagues [36]	No	Yes	Yes	683	Metastatic	C and R	61	Irinotecan, leucovorin and fluorouracil versus leucovorin and fluorouracil versus irinotecan	Secondary	No	No
Sobrero and colleagues [37]	Yes	Yes	Yes	214	Metastatic	C and R	62	Fluorouracil. Modulated bolus versus bolus or continuous	Secondary	No	No
Gray and colleagues [38]	Yes	Yes	Yes	74	Metastatic	C and R	60	Selective Internal Radiation Therapy and hepatic artery chemotherapy versus hepatic artery chemotherapy	Secondary	No	No
Unger and colleagues [39]	No	Yes	Yes	164	Metastatic and locally advanced	C and R	63	Fluorouracil and *E coli* extract versus fluorouracil and placebo	Secondary	No	No
Blanke and colleagues [40]	No	Yes	Yes	384	Metastatic and locally advanced	C and R	65	Leucovorin and fluorouracil versus leucovorin, fluorouracil and trimetrexate	Secondary	No	No
Carmichael and colleagues [41]	No	Yes	Yes	380	Metastatic	C and R	62	Leucovorin and fluorouracil versus leucovorin and uracil/tegafur	Secondary	No	No
Douillard and colleagues [42]	Yes	Yes	Yes	816	Metastatic	C and R	64	Leucovorin and fluorouracil versus leucovorin and uracil/tegafur	Secondary	No	No
Furst and colleagues [43]	Yes	Yes	Yes	74	Metastatic and local	R	60	Surgical trial: Pouch versus straight coloanal anastomosis	Primary	No	No
Ho and colleagues [44]	Yes	Yes	Yes	88	Metastatic and local	R	67	Surgical trial: J pouch and coloplasty after anterior resection	Secondary	No	No
Maughan and colleagues [45]	Yes	Yes	Yes	905	Metastatic, locally advanced and local	C and R	63	Fluorouracil and folinic acid versus infusional fluorouracil or raltitrexed	Secondary	Yes	Yes
Punt and colleagues [46]	No	Yes	Yes	365	Metastatic	C and R	62	Leucovorin and fluorouracil versus leucovorin, fluorouracil and trimetrexate	Secondary	No	No
Sailer and colleagues [47]	Yes	Yes	Yes	64	Metastatic and local	R	65	Surgical trial: Pouch colo-anal reconstruction versus straight reconstruction	Primary	Yes	Yes
Weeks and colleagues [48]	Yes	Yes	Yes	449	Metastatic and local	C	69	Surgical trial: Laparoscopic assisted versus open colectomy	Secondary	No	Yes
Fuchs and colleagues [49]	Yes	Yes	Yes	291	Metastatic	C and R	na	Irinotecan. Once a week for 4 weeks versus once every 3 weeks	Secondary	No	Yes

[a] Overall number of patients enrolled in the trial. When the number of patients registered was not available, the number of patients randomised was listed.

[b] C, colon; R, rectum.

[c] Mean age between treatment arms; na, not available.

[d] Assessed if authors stated a pretrial hypothesis on possible HRQOL changes.

Table 3
Health-related quality of life assessment methodology

Authors [Ref.]	Instrument used	Baseline compliance reported[a]	Psychometrics properties reported[b]	Cultural validity of translation verified[c]	Rationale for instrument(s)[d]	Adequacy of domains covered	Instrument administration reported[e]	Timing of assessments documented
Allen-Mersh and colleagues [50]	RSCL and HADS	Yes	Yes	N/A	No	Yes	No	Yes
Loprinzi and colleagues [51]	VAS	No	Yes	N/A	No	No	No	Yes
Caudry and colleagues [52]	VAS	No	Yes	Yes	No	Yes	No	Yes
Cunningham and colleagues [53]	EORTC QLQ-C30	Yes	Yes	Yes	No	Yes	No	Yes
Hill and colleagues [54]	EORTC QLQ-C30	Yes	Yes	N/A	No	Yes	No	Yes
Sullivan and colleagues [55]	FLIC	Yes	Yes	N/A	No	Yes	No	Yes
Seymour and colleagues [56]	HADS and RSCL	Yes	Yes	Yes	No	Yes	No	Yes
Earlam and colleagues [57]	HADS and RSCL and SIP	Yes	Yes	N/A	No	Yes	Yes	Yes
Ross and colleagues [58]	EORTC QLQ-C30	No	Yes	N/A	No	Yes	No	Yes
Cocconi and colleagues [28]	RSCL and EURO QoL and VAS	Yes	Yes	Yes	No	Yes	No	Yes
Cunningham and colleagues [29]	EORTC QLQ-C30	Yes	Yes	Yes	No	Yes	No	Yes
Rougier and colleagues [30]	EORTC QLQ-C30	Reported in Van Cutsem [65]	Yes	Yes	No	Yes	No	Yes
Schwenk and colleagues [31]	VAS	Yes	Yes	N/A	Yes	Yes	No	Yes
Zaniboni and colleagues [32]	GIVIO-SITAC Questionnaire	Yes	Yes	N/A	Yes	Yes	No	Yes
Comella and colleagues [33]	Amended RSCL	No	Yes	Yes	No	Yes	No	Yes
De Gramont and colleagues [34]	EORTC QLQ-C30	Yes	Yes	Yes	No	Yes	No	Yes
Douillard and colleagues [35]	EORTC QLQ-C30	No	Yes	Yes	No	Yes	No	Yes
Saltz and colleagues [36]	EORTC QLQ-C30	Yes	Yes	Yes	No	Yes	No	Yes
Sobrero and colleagues [37]	RSCL	No	Yes	Yes	No	Yes	No	Yes
Gray and colleagues [38]	VAS	No	Yes	N/A	No	No	No	Yes
Unger and colleagues [39]	EORTC QLQ-C30	No	Yes	Yes	No	Yes	No	Yes
Blanke and colleagues [40]	FACT-C	Yes	Yes	N/A	No	Yes	No	Yes
Carmichael and colleagues [41]	EORTC QLQ-C30	No	Yes	Yes	No	Yes	No	Yes
Douillard and colleagues [42]	FLIC	No	Yes	Yes	No	Yes	No	Yes
Furst and colleagues [43]	EORTC QLQ-C30 and Continence questionnaire	Yes	Yes	Yes	No	Yes	No	Yes
Ho and colleagues [44]	FIQL	No	Yes	No	No	Yes	No	Yes
Maughan and colleagues [45]	EORTC QLQ-C30 and HADS and six items *ad hoc*	Yes	Yes	N/A	No	Yes	Yes	Yes
Punt and colleagues [46]	EORTC QLQ-C30	Yes	Yes	Yes	No	Yes	No	Yes
Sailer and colleagues [47]	EORTC QLQ-C30 and EORTC QLQ-CR38 and GIQLI	Yes	Yes	Yes	Yes	Yes	No	Yes
Weeks and colleagues [48]	Symptom Distress Scale and QoL Index and a Global rating scale	Yes	Yes	N/A	No	Yes	Yes	Yes
Fuchs and colleagues [49]	EORTC QLQ-C30	No	Yes	Yes	No	Yes	No	Yes

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-C38, Quality of Life Questionnaire-ColoRectal 38; FACT-C, Functional Assessment of Cancer Therapy-Colorectal; FIQL, Fecal Incontinence Quality of Life Scale; FLIC, Functional Living Index for Cancer; GIQLI, Gastrointestinal Quality of Life Index; HADS, Hospital Anxiety and Depression Scale; RSCL, Rotterdam Symptom Checklist; SIP, Sickness Impact Profile; VAS, Visual Analogue Scale. Gruppo Interdisciplinare per la Valutazione degli Interventi in Oncologia - Studio Italiano Terapia Adiavante Colon (GIVIO-SITAC).

[a] Assessed if authors reported the number of patients providing a HRQOL assessment before the start of treatment.

[b] Assessed as 'Yes' if the psychometric properties were either reported or referenced in the paper.

[c] Refers to the international validation of the measure. We assessed as 'not applicable' (N/A) if the HRQOL instrument was validated in the same population (language) as the one of the trial.

[d] Rationale for instrument selection was assessed if authors justified or explained the choice processes in selecting the measure(s).

[e] Assessed if authors reported who and/or in which clinical setting the HRQOL instrument was administered.

paper reported HRQOL data of the same trial, information was pooled to be reported in the tables.

5. Results

According to the eligibility criteria, 31 RCTs assessing HRQOL by means of patient self-reported measures were identified between 1980 and March 2003 (Tables 1–4). Besides these, three other studies were also retrieved, but excluded from trial analyses (with the consensus of all authors). Two of these studies met our criteria, but did not report any details about the methodology used to assess HRQOL [25,26] and the remaining one was excluded because it was impossible to check for the HRQOL measure used [27].

5.1. Demographics and trial design

None of the studies retrieved was published before the 1990s. Whilst 22 studies (71%) were published over the last 6 years [28–49], only nine (29%) were published before 1998 [50–58]. Most of the studies 19 (61%) were industry-funded. Whereas 10 studies (32%) were carried out in a multinational context, the remaining ones were carried out within different nations: five (16%) in the USA, 14 (45%) in European countries and two (6%) in Australasian countries. Details are reported in Table 1.

All studies involved metastatic cancer patients and among these 11 RCTs (35%) also enrolled local or locally advanced patients. HRQOL was a primary endpoint in nine RCTs (29%). Whilst 26 studies (84%) compared different chemotherapy regimens, five (16%)

Table 4
Methods of health-related quality of life analysis and results

Authors [Ref.]	Test of statistical significance applied	Difference between treatment arms[a]	Clinical significance addressed[b]	Presentation of results[c]	Missing data documented[d]	Exploration of missing data
Allen-Mersh and colleagues [50]	Yes	No	No	Yes	No	N/A
Loprinzi and colleagues [51]	Yes	No	No	Yes	No	N/A
Caudry and colleagues [52]	Yes	Yes	No	Yes	Yes	No
Cunningham and colleagues [53]	Yes	No	No	Yes	Yes	No
Hill and colleagues [54]	Yes	Yes	No	Yes	Yes	No
Sullivan and colleagues [55]	Yes	No	Yes	Yes	Yes	No
Seymour and colleagues [56]	Yes	Yes	No	Yes	Yes	No
Earlam and colleagues [57]	Yes	Yes	No	Yes	Yes	No
Ross and colleagues [58]	Yes	Yes	No	Yes	No	N/A
Cocconi and colleagues [28]	Yes	Yes	No	Yes	Yes	No
Cunningham and colleagues [29]	Yes	Yes	No	Yes	No	N/A
Rougier and colleagues [30]	Yes	Yes	No	Yes	Reported in Van Cutsem [65]	No
Schwenk and colleagues [31]	Yes	Yes	No	Yes	Yes	No
Zaniboni and colleagues [32]	Yes	No	No	Yes	Yes	No
Comella and colleagues [33]	No	N/A	Yes	Yes	No	N/A
De Gramont and colleagues [34]	Yes	Yes	No	Yes	No	N/A
Douillard and colleagues [35]	Yes	Yes	No	Yes	Yes	No
Saltz and colleagues [36]	Yes	Yes	No	Yes	Yes	No
Sobrero and colleagues [37]	Yes	No	No	Yes	No	N/A
Gray and colleagues [38]	Yes	No	No	Yes	No	N/A
Unger and colleagues [39]	Yes	No	No	No	No	N/A
Blanke and colleagues [40]	Yes	No	No	Yes	No	N/A
Carmichael and colleagues [41]	Yes	Yes	No	Yes	No	N/A
Douillard and colleagues [42]	Yes	No	No	Yes	No	N/A
Furst and colleagues [43]	Yes	Yes	No	Yes	No	N/A
Ho and colleagues [44]	Yes	No	No	Yes	No	N/A
Maughan and colleagues [45]	Yes	Yes	No	Yes	Yes	No
Punt and colleagues [46]	Yes	No	No	No	No	N/A
Sailer and colleagues [47]	Yes	Yes	Yes	Yes	Yes	No
Weeks and colleagues [48]	Yes	Yes	Yes	Yes	Yes	Yes
Fuchs and colleagues [49]	Yes	No	No	Yes	No	N/A

[a] We applied 'Yes' if a trial showed at least a significant difference between treatment arms in one HRQOL domain at any time point assessment.
[b] This refers to the discussion of HRQOL data being clinically significant and not simply statistically significant.
[c] Any attempt to describe the HRQOL findings was accepted.
[d] Assessed as 'Yes' if authors provided some details of HRQOL missing data.

dealt with different surgical procedures [31,43,44,47,48]. Twenty-six RCTs (84%) dealt with both colon and rectal cancer and five only dealt with either colon [32,48] or rectal cancer [43,44,47]. The mean age of patients enrolled into these trials ranged from 57 to 69 years. The number of patients enrolled into the trials varied widely, from 60 [31] to 905 patients [45]. A major methodological drawback was a lack of *a priori* hypothesis about possible HRQOL changes before commencing the trial. Only eight RCTs (26%) explicitly stated an *a priori hypothesis* thus limiting spurious HRQOL results due to multiple significance testing. Further details are provided in Table 2.

5.2. HRQOL assessment methodology and methods of analysis

Our assessment revealed a lack of uniform approach to HRQOL assessment and, in general, poor reporting of details about the rationale for selecting a specific measure and instrument administration. Only three studies (10%) provided a rationale for selecting a HRQOL measure. Information about the administration of the HRQOL questionnaire was also only mentioned in three (10%) reports (e.g. administered by telephone, by computer touch-screen or by healthcare professionals in a specific context). Other possible limitations of the studies retrieved are the reporting of HRQOL baseline data and the documentation of missing data. Twelve RCTs (39%) did not provide the absolute number or the percentage of patients who completed the questionnaire before commencing the trial and 16 (52%) did not provide any details about HRQOL missing data during the course of the trial. The first possible bias associated with these aspects is the loss of ability to detect clinically meaningful differences as a result of a reduced number of observations. Furthermore, in those trials where an indication of HRQOL missing data was provided, only one trial [48] undertook a detailed statistical exploration of the biases due to missing data. The remaining studies did not investigate this issue.

However, all studies provided details about the timing of HRQOL assessment and 29 (94%) discussed somehow the HRQOL outcomes in the paper. All RCTs, with the exception of one [33], applied a statistical test for determining a HRQOL difference between treatment arms and most of these reported a difference. Seventeen studies (57% of the trials testing for difference), provided evidence of the impact of medical procedures on patients' HRQOL at least in one domain at any time-point assessment. Obtaining a statistical difference in terms of HRQOL outcome does not necessarily imply a clinically meaningful difference from a patients' perspective [59]. Whilst most of the studies found a difference between treatment arms, only four (13%) discussed the related HRQOL outcomes in terms of clinical significance from a patient's perspective. This issue is closely related to the difficulty in interpreting the HRQOL data from a given measure.

Different measures have been used to assess HRQOL in the selected studies but, overall, they cover at least the main HRQOL domains relevant for a generic cancer population. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was the most frequently used measure, being used in 15 RCTs (48%). Mostly it was used alone, although sometimes in conjunction with other measures [43,45,47]. Although the EORTC QLQ-C30 is a psychometrically robust HRQOL measure for a generic cancer population, it is not aimed at detecting specific HRQOL aspects related to CRC sufferers such as sexual functioning and body image. Hence, it may not be sensitive enough to detect specific HRQOL problems related to this kind of cancer population and may not provide a comprehensive overview of the impact of the new therapies on patients' HRQOL. Other generic cancer-specific measures were also used, such as the Rotterdam Symptom Checklist (RSCL) [28,33,37,50,56,57] administered in six studies (19%). Whilst most of the trials used a HRQOL measure validated on a generic cancer population, covering in this way at least the main HRQOL domains, just four RCTs (13%) also used questionnaires specifically validated on CRC patients thus increasing the sensitivity of the HRQOL measurement [40,43,44,47].

6. Conclusions

The assessment of HRQOL in cancer clinical trials is becoming more widespread and the proportion of studies including such an assessment is rapidly increasing. Nonetheless, previous reports have suggested that the level of HRQOL reporting in cancer clinical research is often poor thus hampering a clear understanding of such assessments for supporting clinical decision-making [9–13,60]. Hence, the main aim of this systematic review was to examine the reported quality of HRQOL trial methodology thus helping to identify some key aspects that need to be addressed when conducting and reporting HRQOL data in RCTs with CRC patients.

Using the stated selection and eligibility criteria, we found 31 RCTs of CRC patients with HRQOL assessment which included some 9683 patients. Although we searched studies published since 1980, it is worthy of note that most (71%) have been published since 1998, mainly in high Impact Factor journals (Table 1). Overall, a lack of uniform approach has been noted in terms of measurement and other related aspects of HRQOL design and analyses (Tables 2–4).

Fifty-two percent of trials failed to report on how they handled missing HRQOL data. The reasons why patients do not complete HRQOL questionnaires could provide important information. Are HRQOL data lost because the patient is too ill to fill out the questionnaire? Addressing such an issue may help to detect a possible selective loss of HRQOL information due to a patient's deteriorating health condition. The unreported details of missing data is a frequent problem in studies where HRQOL is measured [61] and previous works already proposed procedures to address this issue [8,62]. Reporting compliance at baseline has also been identified as a possible drawback. Thirty-nine percent of the RCTs failed to adequately address the issue by not reporting the number of patients who had completed the HRQOL questionnaire before commencing the trial. Without such an assessment, it is very difficult to interpret the related HRQOL outcomes and an attempt to draw any conclusions would be hazardous.

Another possible limitation of the identified studies is a lack of any significant effort to interpret the HRQOL measurement results. Statistical significance is useful in understanding whether data can be accounted for by chance fluctuations (e.g. patient selection bias), but fails to help in understanding clinical relevance from a patient's perspective in terms of HRQOL changes. In fact, especially when trials enroll a large number of patients, small differences in HRQOL may be statistically significant despite apparently small numerical differences in scores of the given questionnaire administered to the patient. An effort to determine if such small numerical differences have a clinical meaning from a patient's perspective has been highlighted as an important aspect for determining the impact of a given treatment [59,63]. However, we have noted that this concept is still relatively new in the clinical arena [9–12] and it is highly desirable that future studies should routinely address this issue to help evaluate the value of HRQOL results. In this review, we found that only 13% of studies addressed this issue.

A lack of an *a priori hypothesis* stated on possible HRQOL impact, and a lack of a rationale for selecting a specific HRQOL measure were also identified as possible design constraints. Twenty-six percent of the trials stated an *a priori hypothesis* and only 10% supported the choice of a specific HRQOL measure. These two issues are tightly interwoven, as the selection of a HRQOL tool should be based on the HRQOL hypothesis being tested. Hence, it should be verified that domains to be explored by an instrument reflect those which are expected to change in the trial. The issue of an *a priori* hypothesis should also be addressed as clinical trials could generate spurious HRQOL results due to multiple significance testing and differences between treatment groups might be exaggerated. A key consideration for future studies is the selection of a limited number of HRQOL indicators before commencing the trial, possibly basing this selection on previous related trials, or on a specific *a priori* research hypothesis about the impact of a given therapy. Whilst we identified the above reported methodological limitations, it was impressive that nearly all the studies used HRQOL valid measures covering at least the main HRQOL domains relevant for a generic cancer population and provided details on the HRQOL timing of assessment during the trial. Detailing the timing of such an assessment is an important aspect, especially in studies comparing different chemotherapy regimens and this was the case in most of the trials we reviewed.

It must be noted that the present paper has some limitations. It is possible that our review has not identified every trial with a HRQOL component. Another possible limitation lies in the exclusion of abstracts from conferences, as a result some studies where HRQOL results have been presented will have been missed. However, as our aim was to look at the quality of the reported trials, this might not be a significant limitation.

Measuring HRQOL in clinical trials requires making a number of decisions. These relate to several issues such as study design, the specific cancer population being evaluated, the most suitable measure to assess HRQOL for that given target population as well as the timing of measurements. Furthermore, specific information on the psychometric properties of the tool has to be taken into account when selecting a measure for a specific trial. All these aspects challenge researchers who are designing trials which include HRQOL as an endpoint. The present systematic review has helped to identify some key HRQOL aspects, in colorectal RCTs, which should be further addressed in future studies in order to have valuable outcomes and we encourage researchers to address such issues. The need to bridge the gap between HRQOL research and clinical practice has recently been highlighted [64] as an important challenge for the oncology community and such a goal is more likely to be achieved by robust HRQOL methodology.

In conclusion, we encourage researchers to address the methodological shortcomings highlighted in this paper. If HRQOL RCTs are to fulfill their potential of giving a comprehensive picture of a given treatment and also facilitate clinical decision-making, more robust design is necessary in future studies.

A recently published HRQOL checklist is likely to help researchers in designing future studies [66].

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