Quality of life assessment and reporting in colorectal cancer: A systematic review of phase III trials published between 2012 and 2018

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Abstract: In this study, our aim was to describe QoL prevalence and heterogeneity in QoL reporting in colorectal cancer phase III trials.
We included all phase III trials evaluating anticancer drugs in colorectal cancer patients published between 2012 and 2018 by 11 major journals.
Out of the 67 publications identified, in 41 (61.2%) QoL was not listed among endpoints. Out of 26 primary publications of trials including QoL among endpoints, QoL results were not reported in 10 (38.5%). Overall, no QoL data were available in 51/67 (76.1%) primary publications. In particular, in the metastatic setting, QoL data were not available in 12/18 (66.7%) trials with primary endpoint overall survival, and in 20/29 (69.0%) trials with other primary endpoints.
QoL was absent in a high proportion of recently published phase III trials in colorectal cancer, even in trials of second or further lines, where attention to QoL should be particularly high.

FUNDING

This work received no funding.

DISCLOSURE

Massimo Aglietta had roles as consultant or advisor for Roche, Bristol Myers Squibb, Merck and Co.; Giorgio Vittorio Scagliotti received honoraria, research funding and had roles as consultant or advisor for Roche, Pfizer, AstraZeneca, Lilly Pharma and MSD; Francesco Perrone received honoraria for regulatory or educational advisory board from AstraZeneca, Bayer, Celgene, Incyte, Janssen-Cilag, Pierre Fabre, Sandoz and received research funding from AstraZeneca, Baxter, Bayer, Incyte, Merck, Pfizer, Roche and Tesaro; Massimo Di Maio received honoraria and had roles as consultant or advisor for AstraZeneca, Lilly Pharma, Bristol Myers Squibb, MSD and Janssen. All remaining authors declared no conflicts of interest.

***Cover Letter**

Torino, July 21th, 2019

Dear Editor,

On behalf of my colleagues, I am submitting the manuscript: "**Quality of life (QoL) assessment and reporting in colorectal cancer: a systematic review of phase III trials published between 2012 and 2018."** for consideration for publication in *Critical Reviews in Oncology/Hematology*.

This work follows our previous publication in Annals of Oncology (*Marandino L. et al. Deficiencies in health-related quality-of-life assessment and reporting: a systematic review of oncology randomized phase III trials published between 2012 and 2016. Ann Oncol. 2018 Dec 1;29(12):2288-2295.*). Compared to the Annals of Oncology work, the manuscript has updated including also the trials published in 2017 and 2018 and we focused on colorectal cancer patients.

The analysis is based on 67 publications. Overall, due to absent endpoint or unpublished results, QoL data were absent in 51 (76.1%) primary publications (95.0% in adjuvant/neoadjuvant setting, 69.2% in first line, and 66.7% in second and further lines). Interestingly, this data doesn't change over time: QoL was not reported in 74.4% publications between 2012 and 2015 vs. 79.2% between 2016 and 2018.

Furthermore, in metastatic patients where attention to QoL could be essential, QoL data were not available in 66.7% trials with primary endpoint overall survival and in 69.0% trials with other primary endpoints.

We hope that this analysis can be interesting and stimulating, challenging the research community to adopt more QOL outcomes in trials, and the scientific community to give the adequate focus on QoL when reading results of cancer studies. We hope that this topic can be of interest for the readers of *Critical Reviews in Oncology/Hematology*.

As corresponding author, I declare that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the manuscript. This manuscript is not under consideration elsewhere.

No funding was received for this study, and we specified it in the Funding section.

Potential conflicts of interest have been reported in the Disclosure section.

I am looking forward to hearing from you.

Yours sincerely,

Massimo Di Maio

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***Detailed Response to Reviewers**

Reviewers' comments:

Reviewer #1: In this paper, the authors provide a comprehensive review of quality of life (QoL) data from recent phase III clinical trials conducted in colorectal cancer patients. First demonstration: few studies included QoL results. Furthermore, the authors show great heterogeneity in QoL methods of analysis and presentation of results. The rigourous and scientific approach gives important information and nicely describe the current status of knolwdge on the topic. The topic of QoL assesment is quite hot, especially in advanced setting, when benefits and side effects should be well balanced in clinical decision making.
Some points could be improved:
1) Methods: how the authors selected the 11 journals for their review? It is not clear and should be specified in the text.

We thank the reviewer for the comment. We have included in this work all the journals considered in our previously published systematic review (Marandino et al, Annals of oncology, 2018 Dec, PMID: 30304498). Despite we have focused the analysis on colorectal cancer, we limited the update to the same 11 journals included in the previous analysis because they represent, in our opinion, the highest impact factor journals where large oncology randomized clinical trials are usually published.

We acknowledge that this limitation could have excluded some randomized trials published in other journals in the period included in the analysis. We have modified the paragraph in the Methods section, to better clarify this aspect.

2) Results: no data are reported on correlation between gain or loss in QoL and trials results (positive vs negative): did the authors analyzed this aspect? Do they think that this could influence QoL reporting?

We thank the reviewer for the comment. We think that is a very interesting point but it is inherently difficult to verify. Indeed, we were able to verify the direction of QoL results only when these are published in a primary publication or in a secondary one.

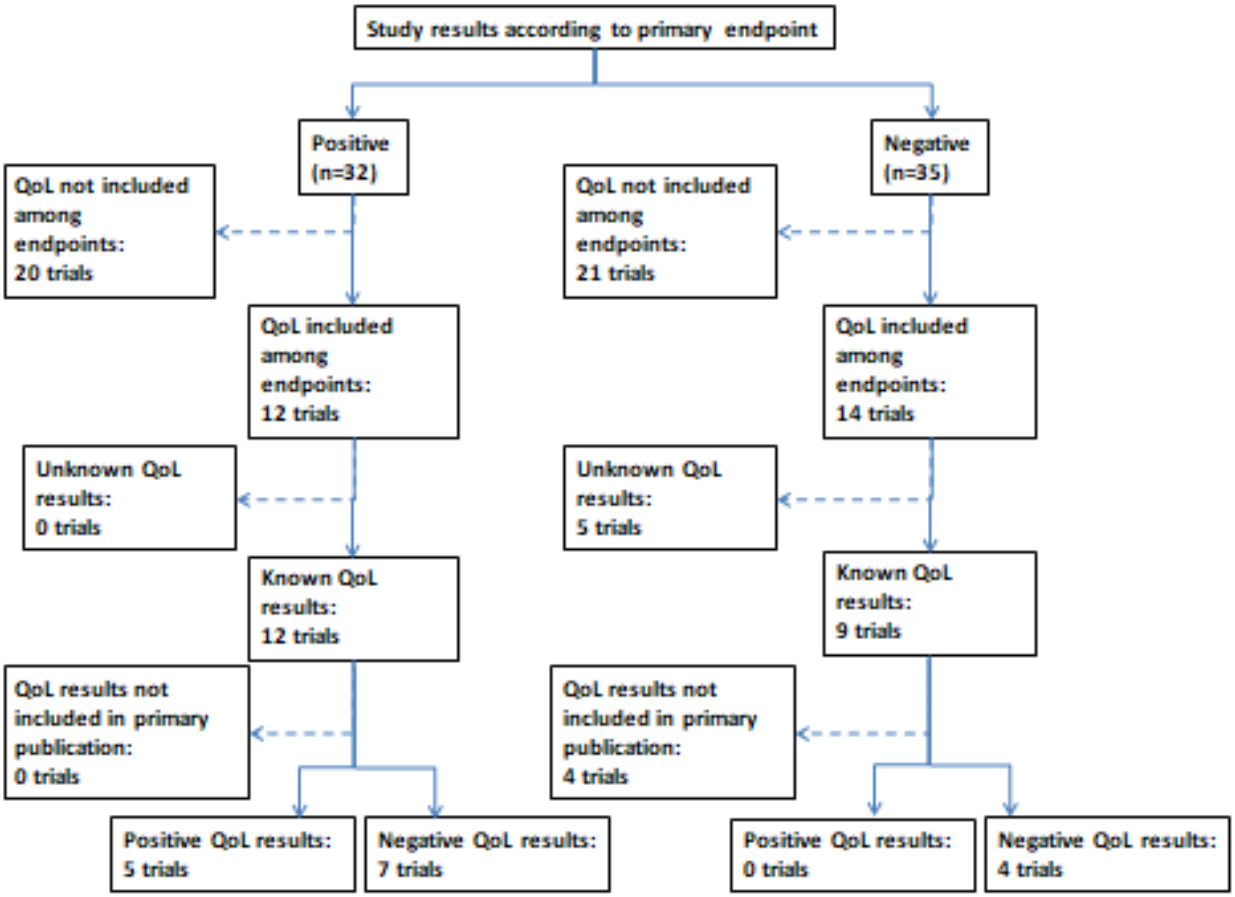
A bias favoring the publication of positive results is reasonable, and we could have in literature a higher percentage QoL data for positive studies. However, this remains a limited observation, because we would need to verify the direction of all the QoL results, even when not published.

However, we acknowledge that this comment is very useful, and we added to Table 2, Table 3 and Table 4 (reporting the details of each study included in the analysis) the details of QoL results (positive or negative) when available.

Indeed, among 32 trials with positive results, all the 12 trials including QoL among study endpoints (37.5%) reported QoL results in the primary publication: 5 trials reported a positive QoL result, while 7 trials reported negative QoL results.

On the contrary, among 35 trials with negative results, despite 14 of these trials included QoL among endpoints, only 4 (11.4%) include QoL results in the primary publication: all these trials reported a negative QoL result. In 5 cases we have only a secondary publication: also in this case, all trials reported negative QoL results. In the remaining 5 trials including QoL as an endpoint, results have not been published.

These data are summarized in the graph below (that we report for Reviewer only):



In summary, these data show that the chance of publication of QoL results is higher in trials that are positive for the primary endpoint compared to trials that are negative for the primary endpoint. However, within positive trials, QoL results are not necessarily in the same direction (being negative in more than half of the 12 positive trials with available QoL results) and their inclusion in the publication is useful for a more complete and balanced evaluation of treatment value.

4) Few grammatical and typing errors are present. Check carefully.

Thanks for the suggestions. We reviewed and corrected grammar errors and typos.

Quality of life (QoL) assessment and reporting in colorectal cancer: a systematic review of phase III trials published between 2012 and 2018.

Short title: QoL in CRC phase III trials

ABSTRACT

Background: In this study, our aim was to describe QoL prevalence and heterogeneity in QoL reporting in colorectal cancer phase III trials.

Methods: We included all phase III trials evaluating anticancer drugs in colorectal cancer patients published between 2012 and 2018 by 11 major journals.

Results: Out of the 67 publications identified, in 41 (61.2%) QoL was not listed among endpoints. Out of 26 primary publications of trials including QoL among endpoints, QoL results were not reported in 10 (38.5%). Overall, no QoL data were available in 51/67 (76.1%) primary publications. In particular, in the metastatic setting, QoL data were not available in 12/18 (66.7%) trials with primary endpoint overall survival, and in 20/29 (69.0%) trials with other primary endpoints.

Conclusions: QoL was absent in a high proportion of recently published phase III trials in colorectal cancer, even in trials of second or further lines, where attention to QoL should be particularly high.

Keywords: health-related quality of life; colorectal cancer; endpoints; patient-reported outcomes; randomized controlled trials

1. INTRODUCTION

Colorectal cancer (CRC) represents the third most common cancer affecting both men and women worldwide[1]. Although metastatic CRC (mCRC) remains a highly lethal disease, recent advances in the outcome of these patients have been achieved. This prognostic improvement could be attributed to several factors, including the availability of new drugs and/or new combinations, with a median overall survival (mOS) considerably increased from 12 months in the 5-fluorouracil (5-FU)-based chemotherapy era to approximately 30 months observed in recent clinical trials[2,3].

Notwithstanding the increased anti-tumoral activity and efficacy of systemic treatments, the impact of drug toxicity, that could negatively affect patients' quality of life (QoL), should not be forgotten, particularly in those clinical settings characterized by a limited life expectancy and a more delicate balance between benefits and harms of treatment. In the latter settings, uncertainty could remain concerning the net clinical benefit, especially for patients with chemo-refractory mCRC treated in and beyond third-line setting. In these patients, several drugs recently approved for use in clinical practice, like regorafenib and TAS-102, produce a modest survival benefit, with not negligible toxicity issues[4,5]. Therefore, particularly in this scenario, an integrated analysis of "cost-benefit" ratio for the patient should become mandatory[6], as well as the evaluation of patients' experience with patient reported outcomes (PROs).

PROs, which are outcomes assessed directly by the patient[7], may produce a different patients' perspective on the disease and treatment received, complementing the conventional reporting of anti-tumor efficacy data and the physician-based description of adverse events [8]. Health-related quality of life (HRQoL) is a specific type of PRO which evaluates the patient's perspective *"of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being*"[7]. In dedicated documents, European Medicines Agency (EMA) and Food and Drug Administration (FDA) emphasized the importance of the impact of treatments on health-related quality of life in everyday life[7,9]. These aspects are crucial for the evaluation of the clinical benefits of new drugs. Indeed, PROs provide data on patient's QoL, symptoms, treatment adherence or satisfaction with care by including any information directly reported by the patient himself/herself on his/her perception of the disease and its treatment. PROs try to capture a personal perspective, that

may vary from person to person, using well-established methods. PROs should be more widely used to complement the range of traditional indicators of efficacy in oncology and provide information regarding both positive and negative patient experiences. Moreover, in 2015, both American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) proposed frameworks to quantify the benefit of oncology medications, and QoL is included in both instruments[10,11].

In a previous systematic review, not specifically focused on CRC, we showed that QoL was not included among endpoints in a high proportion (210 of the 446 publications analyzed, 47%) of oncology phase III randomized trials published by major journals between 2012 and 2016. In addition, even when QoL was included among study endpoints, we found that QoL results were significantly underreported and often affected by a significant delay in publication[12].

Aim of this systematic review is to describe QoL prevalence as an endpoint in randomized phase III trials testing anticancer drugs in colorectal cancer patients, published between 2012 and 2018. In addition, we described the underreporting of QoL results and critical methodological issues of QoL assessment.

2. METHODS

Articles published by 11 major scientific journals, already selected for our original analysis in all solid tumors as the journals where oncology randomized controlled trials are usually published [12], were retrieved for this update spcecifically focused on colorectal cancer trials. Namely, our search included 3 general medical journals (*New England Journal of Medicine, Lancet, JAMA*) and 8 oncology journals (*Lancet Oncology, Journal of Clinical Oncology, JAMA Oncology, Journal of the National Cancer Institute, Annals of Oncology, European Journal of Cancer, British Journal of Cancer, Cancer*). With the aim to identify primary publications of randomized phase III trials testing anticancer drugs in patients with solid tumors, all issues of the mentioned journals published between January 2012 and December 2018 were hand-searched. The original analysis[12], limited to papers published between 2012 and 2016, has been updated for the present analysis, with the addition of articles on CRC published in 2017 and 2018.

Trials testing non-pharmacologic interventions were excluded from the analysis. Both trials conducted in early stages of disease (e.g., adjuvant chemotherapy, neo-adjuvant chemo-radiotherapy) and trials conducted in advanced / metastatic setting were included, while trials testing prevention strategies were excluded.

To collect data from each selected paper, the same dedicated case report form used for the previous analysis[12] was adopted, and the electronic database, with one record for each paper, was updated. For each trial, information about publication (journal, year, first author, date of definitive issue and ahead-of-print publication, availability of online supplemental material and/or study protocol) was collected. Impact factor (IF), corresponding to the year of each publication, was retrieved from the Journal of Citation Reports, and publications were divided into 3 categories according to IF: low (<15), intermediate (15-30), high (>30). Information recorded about the clinical trial included: sponsorship (for-profit vs. non-profit), study design (open-label vs. blinded; superiority vs. non-inferiority), details of treatment of both experimental and control arms, disease setting. Articles were divided in 3 categories: (i) adjuvant or neoadjuvant treatment in early stages; (ii) first-line treatment for metastatic disease; (iii) second and/or further lines of treatment for metastatic disease. Similarly to our previous analysis, trials were classified as for-profit when sponsored by the drug company and as non-profit when sponsored by an academic institution or a cooperative group, even if receiving drug supply and/or economic support from one or more drug

companies (when not explicated in the publication, details about the study sponsorship were retrieved from ClinicalTrials.gov study record, if available). Experimental treatments were classified into 2 main groups (that were not mutually exclusive): chemotherapy +/- other drugs; targeted agents +/- other drugs. According to study results in terms of primary endpoint, clinical trials were classified into positive or negative.

Information about study endpoints (both primary and secondary, tertiary or exploratory) was derived from the Methods section of the publication and/or from the study protocol (when available as online supplementary material). When QoL was not listed among endpoints in the paper and study protocol was not available, QoL was considered as "apparently absent", except when QoL results were actually presented in the Results section or in a secondary publication: in the latter case, QoL was included *de facto* among endpoints. For all records, secondary QoL publications were searched in PubMed, by using the name of the drug(s) and/or the name of authors of the primary publication and/or the study acronym / code, when available. Time to secondary QoL publication was calculated according to Kaplan-Meier method, from the date of primary definitive publication to the date of secondary QoL definitive publication, if existing, or to the date of last PubMed check (February 15th, 2019).

Details of QoL methodology (type of QoL tools adopted, type of statistical analysis and presentation of results) were collected. As for type of statistical analysis, several non-mutually exclusive categories were identified: mean scores at different time points, mean changes from baseline, proportion of responding patients, time to deterioration. Among details of QoL methodology, we verified whether statistical approaches for dealing with missing data were explicitly stated in the paper and whether data about compliance to QoL questionnaires were reported in the publication.

All analyses were performed with SPSS for Windows, version 25.0.

3. RESULTS

3.1 Study characteristics

Overall, 67 eligible publications were identified. The main characteristics of the eligible publications are reported in **Table 1** (the complete list is reported in the table 2 - 4).

The three most represented journals were Lancet Oncology (20 papers, 29.9%), Annals of Oncology (18 papers, 26.9%) and Journal of Clinical Oncology (14 papers, 20.9%).

Median IF of the eligible publications was 18.038 (interquartile range 11.612—26.303, range 4.819—59.558).

The majority of trials (47, 70.1%) were conducted in patients with advanced/metastatic disease, but studies are well distributed among the 3 setting categories that we defined for classification: adjuvant/neoadjuvant setting (20, 29.9%), first-line or maintenance setting (26, 38.8%) and second and further lines setting (21, 31.3%). Experimental treatment was chemotherapy ± other drugs in 52 trials (77,6%) and targeted therapy ± other drugs in 40 trials (59,7%). More than one-third of the trials (26, 38.8%) were sponsored by a drug company, while the remaining (41, 61.2%) were promoted by an academic institution or a cooperative group.

The details of each eligible publication are reported in **Table 2** (studies conducted in early stages), in **Table 3** (studies conducted in the first-line or maintenance setting) and in **Table 4** (studies conducted in second- and further lines setting), respectively.

3.2 Inclusion of QoL among study endpoints

The inclusion of QoL among endpoints according to study characteristics is detailed in **Table 5**. In the whole series, QoL was a primary endpoint in 1 trial (1.5%), a secondary / exploratory endpoint in 21 trials (21.3%), while in the remaining 41 (61.2%) QoL was not listed at all among study endpoints. The proportion of trials without QoL as an endpoint was 69%, 54.8% and 57.1% among papers published in journals with low, intermediate and high IF, respectively. QoL was not included among endpoints in a relevant proportion both in for-profit trials (53.8%) and even more in non-profit trials (65.8%).

QoL was not listed among endpoints in 17 trials (85.0%) in adjuvant/neoadjuvant setting, in 13 trials (50.0%) in first line, and 11 trials (52.4%) in second and further lines. Proportion of trials not including QoL among endpoints was similar over time: QoL was not listed in 26 trials (60.5%) publications between 2012 and 2015 vs. 15 trials (62.5%) between 2016 and 2018.

3.3 Presence of QoL results in the primary publication

The presence of QoL results according to study characteristics is detailed in **Table 6**. Out of 26 primary publications of trials including QoL among endpoints, QoL results were not reported in 10 (38.5%). Due to the absence among study endpoints or to the lack of results in the publication, QoL results were available in 16 publications (23.9%), while QoL results were absent in the remaining 51 (76.1%): namely, 19 trials out of 20 (95.0%) in adjuvant/neoadjuvant setting, 18 trials out of 26 (69.2%) in first line and 14 trials out of 21 (66.7%) in second and further lines.

The proportion of publications without QoL results, due to absent endpoint or unpublished results, was 86.2%, 67.7% and 71.4% among papers published in journals with low, intermediate and high IF, respectively. QoL results were lacking in a relevant proportion both in publications of for-profit trials (73.1%) and non-profit trials (78.1%).

Proportion of trials without available QoL results in primary publication was similar over time: QoL was lacking in 32 (74.4%) publications between 2012 and 2015 vs. 19 (79.2%) publications between 2016 and 2018.

3.4 QoL secondary publications

Overall, with a median follow-up of 45.3 months, 7 secondary QoL publications were found (the complete list of secondary publications is available in the **Table 2 - 4**). Median IF of the secondary QoL publications was 6.029 (interquartile range 5.548– 9.523, range 2.806 – 36.421), compared to 18.038 (interquartile range 14.907—21.023, range 9.269—26.509) of the respective primary publication. For the 10 trials including QoL as an endpoint, but without any QoL result in the primary publication, probability of secondary publication was 0%, 33.3% and 50.0% after 1, 3 and 5 years respectively. (**Figure 1**).

3.5 QoL reporting according to study primary endpoint and study results

21 trials (31.3%) had overall survival as primary endpoint, while the remaining 46 (68.7%) had endpoints other than overall survival. Among the latter 46 trials, 30 (65.2%) did not include QoL as an endpoint, and among 16 trials including QoL as an endpoint, 6 did not report QoL results in primary publication. Overall, due to the absence of endpoint or unpublished results, QoL results were not reported in 36 (78.3%) publications of trials with a primary endpoint other than overall survival.

According to authors' conclusions, studies were divided into positive (32, 47.8%) and negative (35, 52.2%). Among 32 trials with positive results, 20 (62.5%) did not include QoL as an endpoint. Despite all trials with positive results including QoL as an endpoint reported QoL results in the primary publication (12 / 12, 100%), overall, due to absent endpoint, the majority of trials with positive results were lacking QoL results (20 / 32, 62.5%). Out of the 12 trials including QoL results, 5 trials reported a positive QoL result, while 7 trials reported negative QoL results.

On the other hand, among 35 trials with negative results, 21 (60%) did not include QoL as an endpoint. Out of 14 negative trials including QoL among endpoints, 4 (28.6%) included QoL results in the primary publication and 5 (35.7%) reported QoL in a secondary publication: all these trials reported a negative QoL result. In the remaining 5 (35.7%) negative trials including QoL as an endpoint, results have not been published.

In the investigated period, we identified 5 trials which prompted authorization for use in clinical practice by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), all of which were done in the setting of advanced disease. Three of these trials did not include QoL among endpoints.

3.6 QoL methodology

In 21 trials with available QoL results (including secondary publications), most common QoL tools were EORTC QLQ-C30 (14, 66.7%); EORTC colorectal cancer module (3, 14.3%); EQ5D (8, 38.1%); FACT-C (3, 14.3%) and other FACT tools (4, 19.0%).

Common methods of analysis were mean scores over time (10, 47.6%), mean changes (6, 28.6%), time to deterioration (5, 23.8%) and proportion of responders or worsening patients (4, 19.0%).

Out of 26 trials with QoL as endpoint, 9 (34.6%) trials did not report details about compliance to QoL questionnaires, and 21 (80.7%) did not include any explicit statement about statistical approaches adopted for dealing with missing QoL data.

4. DISCUSSION

This review of recently published randomized phase III trials conducted in CRC patients shows that QoL results are lacking, due to exclusion from study endpoints or absence of results, in a high proportion of publications. This deficiency is particularly relevant in trials of advanced disease, where attention to QoL should be necessarily higher. Of note, we found that QoL data were not available in 66.7% of the publications regarding second or further lines of treatment. Furthermore, our data show that methodology of QoL analysis is quite heterogeneous in terms of type of instruments, analysis and presentation of results. These results underline that, although QoL assessment in clinical trials is unanimously considered relevant, this principle is often not respected when clinical trials are designed and when results are analyzed and published.

Similarly to our previous analyses, conducted in all solid tumors[12] and in prostate cancer trials[13], we collected the information about the presence of QoL among endpoints from the manuscript of the publication and from the study protocol, when the latter was available. However, we did not have access to study protocol for all the publications included in the analysis and, in some cases, we might have considered QoL apparently absent although it was actually included among endpoints. Consequently, the real prevalence of QoL could be higher than reported in our analysis. However, this limitation may reinforce our disappointing conclusions, because if a study included QoL among endpoints but this was completely neglected in the study publication, the importance attributed to QoL by the authors was *de facto* really marginal.

Recent years have been characterized by the conduction and publication of many pivotal trials of new drugs and/or new combinations in CRC. However, inclusion of QoL among study endpoints results quite low (38.8% of publications considered) and this is reflected in the even lower proportion of trials with available QoL results (23.9% of primary publications), with a stable trend over the time period considered in the analysis (25.6% between 2012 and 2015 vs. 20.8% between 2016 and 2018). As a matter of fact, the high proportion of absent QoL results in the adjuvant setting could be not surprising, considering that the negative treatment impact - hopefully temporary - on QoL could be considered a “justified” risk, to obtain an improvement in the chance of a definitive cure. This could justify,

at least in part, the lower attention to QoL evaluation in early setting: nearly all trials (95%) we analyzed did not include QoL among the endpoints, and this proportion in CRC is even higher than the result observed in all solid tumors[12]. However, absence of QoL is particularly relevant in the setting of metastatic patients, where only 31.9% of primary publications reported QoL results. Differently from trials conducted in early stages, the palliative setting is characterized by a relevant proportion of symptomatic patients and many treatments are characterized by a modest benefit in terms of PFS and OS. For these reasons, a complete evaluation of the balance between benefits and harms of treatments should necessarily include QoL evaluation. Furthermore, knowledge of QoL data could improve the information to patients, and facilitate clinical choice between alternative treatments, particularly if they show similar survival outcomes.

For instance, in recent years, two different new drugs, namely regorafenib and trifluridine/tipiracil [4,5], have been tested in the third-line setting, showing a modest survival benefit, that led to approval by regulatory agencies and inclusion in clinical practice guidelines. However, while in the CORRECT study, testing the efficacy of regorafenib, a formal assessment of QoL was performed, in the RECOURSE study, testing TAS-102, QoL was not among study endpoints. In the latter case, the absence of QoL assessment has led study investigators to perform an indirect assessment of patients' QoL, that is encumbered by several limitations, first of all the use of a non-validated instrument not based on patient-reported outcomes[14].

Our literature research found that QoL results were presented in a secondary publication for seven trials. Although we recognize that splitting up QoL data in a separate publication from survival results seems to be an opportunity for a comprehensive way of reporting, probability of a secondary publication was only 50.0% even 5 years after first publication. Moreover, separate reporting of QoL results may reduce their value in clinical decision making, as clinicians less likely read or could be not aware of the successive papers[15]. Our findings corroborate previous observations, according to which most drugs enter the market without explicit evidence of benefit on QoL[16].

We also investigated the impact of QoL assessment in studies promoted by academic researchers and/or independent cooperative groups vs for-profit studies. Concordantly with

our previous results in all solid tumors, both for-profit and, even more, non-profit trials did not include QoL among endpoints in a considerable percentage (73.1% for profit- trials and 78.1% in non-profit trials). In our view, this result is particularly disappointing, considering that academic trials, if really aiming to optimize treatment choices in clinical practice, should be characterized by higher attention to QoL.

Several methodological issues can be associated with the adoption of QoL among the endpoints of a clinical trial. For example, the choice of the correct QoL questionnaire and of the proper timing of questionnaires administration, the method of analysis and description of results, and the statistical management of missing data may be particularly challenging. CRC, especially in patients who have already received multiple lines of treatment, is exposed to a non-negligible proportion of early deterioration and treatment withdrawal compared to other tumors characterized by a better prognosis (e.g. breast cancer or prostate cancer). In these clinically challenging scenarios, missing data can represent a methodological problem, and we suppose that many researchers could consider this issue as a barrier to adoption of QoL questionnaires. While data missing at baseline are substantially related to defects in the quality of study procedures, missing data at later time points may be frequently related to treatment toxicities, tumor progression and/or symptomatic worsening, with difficulty in completing questionnaires. This aspect could introduce possible selection bias (patients who complete questionnaires feel better than those who do not complete) and could lead to misleading results regarding QoL, which is particularly relevant in patients with advanced and progressive disease. Unfortunately, we found that only a minority of publications clarified methods of management of missing data in QoL analysis.

As well as for other solid tumors, several validated QoL tools are currently available for trials conducted in CRC cancer, each one with its strengths and weaknesses. As expected, we found differences in their adoption among trials. The most common instrument used for QoL assessment was the EORTC Quality of Life Questionnaire C30 (66.7% of trials with available QoL details), supplemented in few cases by the CRC-specific module. However, some studies used other types of QoL assessments.

Not surprisingly, similarly to what we described in other settings[13], we found a significant heterogeneity in the methods used for the analysis and presentation of QoL

results. As expected, we found that description of mean scores or mean changes from baseline at different time points was commonly used to summarize QoL results (47.6% and 28.6% of trials with available QoL results, respectively). This method allows a simple graphical and numerical representation of results, it is familiar to most readers and it is widely accepted to compare QoL trajectory among different study arms. However, this method is weak in capturing a potentially relevant heterogeneity in the QoL response experienced by individual patients[17]. From this point of view, analysis of responders (proportion of subjects with improved or stable or worse score, compared to baseline) in each specific QoL domain gives a useful complementary information, but our analysis showed that it is adopted only in a minority of studies (19%). In addition, many studies describe QoL results with a particular emphasis on the early phase of treatment (that is of course useful to reassure about the absence of a negative impact of treatment toxicity on patients' status), but only a minority of studies focus on QoL description at the time of instrumental progression and treatment failure. Curves describing the time to deterioration of global QoL or specific symptoms are particularly useful in describing the real efficacy of experimental treatment in delaying symptomatic worsening of disease. Unfortunately, we found this kind of analysis only in 23.8% of the trials analyzed.

Of course, no single method of analysis and presentation can assure an exhaustive description of QoL results. Moreover, even in those cases where more methods are planned in the study protocol, the presentation of results is often suboptimal, as the space dedicated to QoL is often marginal[12].This appears rather surprising, because the limitations in article length could be easily exceeded by the possibility to integrate the main article with online supplement and appendix materials.

In conclusion, our review of trials conducted in colorectal cancer and published in recent years shows that the inclusion of QoL among study endpoints and the timely and complete reporting of QoL results are definitely suboptimal. The heterogeneity in the choice of instruments, timing, modality and presentation of analysis and presentation of results make more difficult the interpretation of results.

Figures and tables

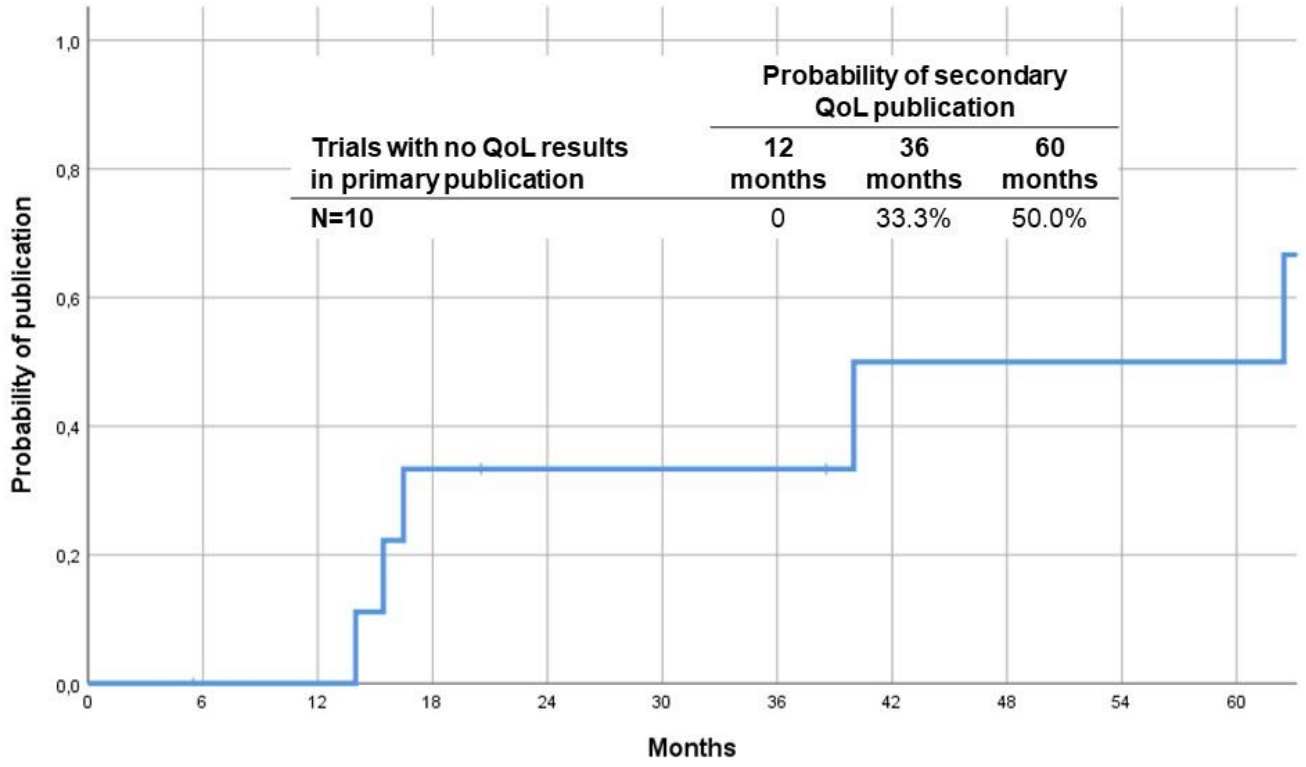


Figure 1. Kaplan-Meier curves of time to secondary publication with quality of life (QoL) results, for trials including QoL as a secondary / exploratory endpoint, but without any QoL result in the primary publication.

Table 1. Characteristics of the 67 primary publications included in the analysis.

	Number of publications	(%)
Year of primary manuscript		
2012	9	13,4%
2013	11	16,4%
2014	7	10,5%
2015	16	23,9%
2016	9	13,4%
2017	4	6,0%
2018	11	16,4%
Primary manuscript journal		
Annals of Oncology	18	26,8%
British Journal of Cancer	2	3,0%
European Journal of Cancer	4	6,0%
JAMA	3	4,5%
Journal of Clinical Oncology	14	20,9%
Journal of National Cancer Institute	2	3,0%
Lancet	2	3,0%
Lancet Oncology	20	29,8%
New England Journal of Medicine	2	3,0%
Sources of funding		
Profit	26	38,8%
Non-profit	41	61,2%
Setting of disease		
Adjuvant/neoadjuvant setting	20	29,9%
First-line or maintenance setting	26	38,8%
Second and further lines	21	31,3%
Study design		
Superiority	53	79,1%
Non-inferiority	14	20,9%
Masking		
Open label	52	77,6%
Blinded	15	22,4%
Countries involved		
Single country	33	49,3%
2 or more countries	34	50,7%
Type of experimental therapy*		
Chemotherapy +/- other	52	77,6%
Targeted therapy +/- other	40	59,7%
Primary endpoint		
Overall survival	21	31,3%
Other	46	68,7%
Study result		
Positive	32	47,8%
Negative	35	52,2%

*Categories are not mutually exclusive

Table 2: Studies in adjuvant/neoadjuvant setting

Study	Setting	Experimental arm	Control arm	Primary endpoint	Study result	QoL endpoint	QoL results	Method of analysis	Tools	QoL present in study	Focus items QoL	Timing QoL	Missing data	Compliance
Alberts SR et al, 2012[18]	Adjuvant	Cetuximab - FOLFOX	FOLFOX	DFS	Negative	Absent	-	-	-	-	-	-	-	-
de Gramont A et al, 2012[19]	Adjuvant	Bevacizumab + FOLFOX or CAPOX	FOLFOX	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Ngan SY et al, 2012[20]	Neoadjuvant	Short Course-RT followed by surgery and 5FU+Leucovorin as adjuvant therapy	Long Course-RT with 5FU followed by surgery and 5FU+Leucovorin as adjuvant therapy	Local recurrence	Negative	Secondary	Negative (secondary publication)	Mean changes / AUC	EORTC QLQ C30 / CR38	Absent – Secondary publication	Global, functioning and symptom scales	During treatment and up to 12 months	Imputation with proxy measurement by physicians	Yes
Hofheinz RD et al, 2012[21]	Neoadjuvant	Capecitabine + CRT (Capecitabine)	5 FU + CRT (5FU)	OS	Positive	Absent	-	-	-	-	-	-	-	-
Köhne	Adjuv	High-	Standard	RFS;	Negativ	Abse	-	-	-	-	-	-	-	-

CH et al, 2013[22]	ant	dose 5-flurouracil ± Leucovorin	bolus 5-FU regimen with leucovorin	OS.	e	nt								
Glynne-Jones R et al, 2014[23]	Adjuvant	CAPOX	FUP only	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Taieb J et al, 2014[24]	Adjuvant	Cetuximab - FOLFOX	FOLFOX	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Yoshida M et al, 2014[25]	Adjuvant	S1	Tegafur-uracil + leucovorin	DFS	Positive	Absent	-	-	-	-	-	-	-	-
Allegra CJ et al, 2015[26]	Neoadjuvant	Factorial (2x2) design:		Local recurrence	Positive (Capecitabine) Negative (Oxaliplatin)	Absent	-	-	-	-	-	-	-	-
		RT + Capecitabine (+/- oxaliplatin)	RT + 5FU (+/- oxaliplatin)											
		RT + Fluoropyrimidine (Capecitabine or FU) + Oxaliplatin	RT + Fluoropyrimidine (Capecitabine or FU)											
Breugo	Adjuv	CT or CRT	FUP only	OS	Negativ	Abse	-	-	-	-	-	-	-	-

m AJ et al, 2015[27]	ant	(5FU-Leucovorin or Capecitabine)			e	nt								
Hebbar M et al, 2015[28]	Neoadjuvant, Adjuvant	6 cycles of FOLFOX 7 followed by 6 cycles of FOLFIRI	12 cycles of FOLFOX 4	DFS	Negative	Secondary	Negative (secondary publication)	Time to deterioration	EORTC QLQ-C30	Absent – Secondary publication	Global, functioning and symptom scales	All course of treatment	Included in the definition of analysis. Imputation analysis	Yes
Rödel C et al, 2015[29]	Neoadjuvant, Adjuvant	Preoperative CRT (5FU+Oxaliplatin) followed by 5FU-Leucovorin-Oxaliplatin as adjuvant therapy	Preoperative CRT (5FU) followed by 5FU as adjuvant therapy	DFS	Positive	Absent	-	-	-	-	-	-	-	-
Sadahiro S et al, 2015[30]	Adjuvant	Consecutive 5 days per week for	Tegafur-uracil + leucovorin for 28	DFS	Negative	Absent	-	-	-	-	-	-	-	-

		18 months of Tegafur-uracil + leucovorin	of 35 days for 6 months											
Bujko K et al, 2016[31]	Adjuvant	SC-RT followed by FOLFOX 4	Long-course chemoradiation (5FU, Leucovorin, Oxaliplatin)	R0 resection rate	Negative	Absent	-	-	-	-	-	-	-	-
Kerr RS et al, 2016[32]	Adjuvant	Bevacizumab + Capecitabine	Capecitabine	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Oki E et al, 2016[33]	Adjuvant	S-1	Tegafur-uracil	RFS	Positive	Absent	-	-	-	-	-	-	-	-
André T et al, 2018[34]	Adjuvant	CAPOX or FOLFOX for three months	CAPOX FOLFOX for six months	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Iveson TJ et al, 2018[35]	Adjuvant	CAPOX or FOLFOX for three months	CAPOX FOLFOX for six months	DFS	Positive	Secondary	Positive	Mean scores, AUC	EORTC QLQ-CR30, CR2	Present	Global, functioning and sympt	All courses of treatment and	Multiple imputation analysis	Yes

									9, EQ5D, FACT-GOG/Ntx		om scales	follow-up		
Matsuda C et al, 2018[36]	Adjuvant	Tegafur-uracil	FUP alone	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Sobrero A et al, 2018[37]	Adjuvant	CAPOX or FOLFOX for three months	CAPOX FOLFOX for six months	DFS	Negative	Absent	-	-	-	-	-	-	-	-

5-FU: 5-Fluorouracil; AUC: Area Under the Curve; CAPOX: Capecitabine-Oxaliplatin; CRT: Chemo-Radiotherapy; DFS: Disease Free Survival; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer 29; EORTC QLQ-CR38: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer 38; EQ5D: Euro Qol five-dimensional questionnaire; FACT-GOG/Ntx: FACT - Gynecologic Oncology Group/Neurotoxicity; FOLFIRI: 5FU-Leucovorin-Irinotecan; FOLFOX: 5FU-Leucovorin-Oxaliplatin; FUP: Follow up; QoL: Quality of Life; RFS: Relapse Free Survival; RT: Radiotherapy;

Table 3: Studies in first-line or maintenance setting

Study	Setting	Experimental arm	Control arm	Primary endpoint	Study result	QoL endpoint	QoL results	Method of analysis	Tools	QoL present in study	Focus items QoL	Timing QoL	Missing data	Compliance
Hoff PM et al, 2012[38]	Metastatic - First-line	Cediranib+ FOLFOX6 or CAPOX	FOLFOX6 or CAPOX	PFS; OS	Negative	Absent	-	-	-	-	-	-	-	-
Hong YS et al, 2012[39]	Metastatic - First-line	S-1 plus oxaliplatin	CAPOX	PFS	Positive	Secondary	Negative	Mean changes	EORTC QLQ-C30	Present	Global, functioning and symptom scales	Final visit	No information	Yes
Schmoll HJ et al, 2012[40]	Metastatic - First-line	Cediranib + FOLFOX6	Bevacizumab+ FOLFOX6	PFS	Negative	Secondary	Negative	Time to deterioration; proportion of worsening patients	FACT-C	Present	TOI, symptoms, total scores	All course of treatment	No information	Yes
Tveit KM et al, 2012[41]	Metastatic - First-line	Cetuximab plus FLOX continuously Cetuximab plus	FLOX	PFS	Negative	Secondary	Negative (secondary publication)	Mean scores	EORTC QLQ-C30	Absent – Secondary publication	Global, functioning and sympt	All course of treatment (Prese	No information	Yes

		FLOX intermittently									om scales	nted up to 12 cycles)		
Carrato A et al, 2013[42]	Metastatic - First-line	Sunitinib + FOLFIRI	FOLFIRI	PFS	Negative	Secondary	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.
Cunningham D et al, 2013[43]	Metastatic - First-line	Capecitabine + Bevacizumab	Capecitabine	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Johnsson A et al, 2013[44]	Metastatic - Maintenance after First-line	Bevacizumab + Erlotinib	Bevacizumab	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Yamada Y et al, 2013[45]	Metastatic - First-line	S-1 + Oxaliplatin + Bevacizumab	mFOLFOX6 + Bevacizumab	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Ye LC et al, 2013[46]	Metastatic - First-line	Cetuximab + FOLFOX or FOLFIRI	FOLFOX or FOLFIRI	Rate of patients converted to resection	Positive	Absent	-	-	-	-	-	-	-	-

Heinemann V et al, 2014[47]	Metastatic - First-line	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	ORR	Negative	Absent	-	-	-	-	-	-	-	-
Loupakis F et al, 2014[48]	Metastatic - First-line	FOLFOXIRI + Bevacizumab	FOLFIRI + Bevacizumab	PFS2	Positive	Absent	-	-	-	-	-	-	-	-
Primrose J et al, 2014[49]	Metastatic - First-line	mFOLFOX6 or CAPOX + Cetuximab	mFOLFOX6 or CAPOX	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Hegewisch-Becker S et al, 2015[50]	Metastatic - Maintenance after First-line	Bevacizumab	Fluoropyrimidine + Bevacizumab	Time to failure of strategy	Positive (Bevacizumab) Negative (Observation)	Secondary	Negative (primary and secondary publication)	Mean scores (primary and secondary publication); proportion of responders (secondary publication)	EORTC QLQ-C30 / CR29 / "other instruments"	Present + Secondary publication	Global (primary); all scales (secondary)	All course of treatment and beyond, up to 24 weeks	No information	No (primary) Yes (secondary)
		FUP												
Koeberle D et al, 2015[51]	Metastatic - Maintenance	Bevacizumab	FUP	TTP	Negative	Absent	-	-	-	-	-	-	-	-

	after First-line													
Simkens LH et al, 2015[52]	Metastatic - Maintenance after First-line	Capecitabine + Bevacizumab	FUP	PFS2	Positive	Secondary	Negative	Mean changes	EORTC QLQ-C30	Present	Global, functioning and symptom scales	All course of treatment	No information	Yes
Tournigand C et al, 2015[53]	Metastatic - Maintenance after First-line	Bevacizumab + Erlotinib	Bevacizumab	PFS	Positive	Secondary	Negative	Median scores	EQ5D	Present	Global	Up to 4 months (only 2 months Presented)	No information	Yes
Aparicio T et al, 2016[54]	Metastatic - First-line	Factorial (2 x 2) design:		PFS	Negative	Secondary	Negative (secondary publication)	Time to deterioration (secondary publication)	QoL VAS	Absent – Secondary publication	Global (secondary)	All course of treatment	No information	Yes
		5FU+Leucovorin (+/- Irinotecan)	Simplified 5FU+Leucovorin (+/- Irinotecan)											
		5FU+Leucovorin (standard or simplified) + Irinotecan	5FU+Leucovorin (standard or simplified											

			)											
Hagman H et al, 2016[55]	Metastatic - Maintenance after First-line	Bevacizumab ± Erlotinib	Bevacizumab or Capecitabine	PFS rate at 3 months	Negative	Absent	-	-	-	-	-	-	-	-
van Hazel GA et al, 2016[56]	Metastatic - First-line	mFOLFOX6 ±Bevacizumab + SIRT	mFOLFOX6 ±Bevacizumab	PFS	Negative	Secondary	Negative (secondary publication)	Mean scores (secondary publication)	EQ5D	Absent – Secondary publication	EQ5D utility scores	Up to 60 months (Presented up to 24) (secondary)	No statistical imputation for missing data	Yes (secondary)
Luo HY et al, 2016[57]	Metastatic - Maintenance after First-line	Capecitabine	FUP	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Yamazaki K et	Metastatic	Bevacizumab + FOLFIRI	Bevacizumab+	PFS	Positive	Secondary	Positive	Mean scores	FACT-C / FACT-	Present	TOI / FACT-	All course	Imputat	No details

al, 2016[58]	- First-line		FOLFOX						GOG/Ntx		GOG/Ntx	of treatment (up to 18 months)	ion, assuming missing at random	
Kwakman JJM et al, 2017[59]	Metastatic – First-line	S-1	Capecitabine	Incidence of any grade HFS	Positive	Absent	-	-	-	-	-	-	-	-
Venook AP et al, 2017[2]	Metastatic – First-line	Cetuximab + FOLFOX or FOLFIRI	Bevacizumab + FOLFOX or FOLFIRI	OS	Negative	Secondary	-	n.s.	EORTC QLQ-C30*; Changes in function*; Dermatology-specific QoL*; EQ5D*	Absent	n.s.	n.s.	n.s.	n.s.
Aparicio T et al, 2018[60]	Maintenance after First-	Bevacizumab	FUP	TCD	Negative	Secondary	Negative	Time to deterioration	EORTC QLQ-C30	Present	Global, physical functi	All course of treatment	No information	Yes

	line										oning, asthenia			
Qin S et al, 2018[61]	Metastatic – First-line	Cetuximab + FOLFOX	FOLFOX	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Yamada Y et al, 2018[62]	Metastatic – First-line	S-1, Irinotecan + Bevacizumab	mFOLFOX6 or CAPOX + Bevacizumab	PFS	Positive	Secondary	Positive	Mean scores	FACT-C FACT/GOG-Ntx	Present	FACT-C TOI, FACT/GOG-Ntx	16 & 24 weeks	No information	Yes

* declared in the protocol but results not present in the work

5-FU: 5-Fluorouracil; CAPOX: Capecitabine-Oxaliplatin; EQ5D: Euro Qol five-dimensional questionnaire; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer 29; FACT-C: Functional Assessment of Cancer Therapy- Colorectal cancer; FACT-GOG/Ntx: FACT-Gynecologic Oncology Group/Neurotoxicity; FLOX: 5FU- Leucovorin- Oxaliplatin; FOLFIRI: 5FU-Leucovorin-Irinotecan; FOLFOX: 5FU-Leucovorin-Oxaliplatin; FOLFOXIRI: 5FU-Leucovorin-Irinotecan-Oxaliplatin; FUP: Follow up; mFOLFOX: modified FOLFOX; n.s.: not specified; OS: overall survival; PFS: progression-free survival; QoL VAS: QoL-Visual Analogue Scale; QoL: Quality of Life; SIRT: selective internal radiotherapy; TCD: Tumor control duration; TOI: Trial Outcome Index; TTP: time to progression.

Table 4: Studies in second and further lines

Study	Setting	Experimental arm	Control arm	Primary endpoint	Study result	QoL endpoint	QoL results	Method of analysis	Tools	QoL present in study	Focus items QoL	Timing QoL	Missing data	Compliance
Van Cutsem E et al, 2012[63]	Metastatic - Second line	Ablibercept + FOLFIRI	FOLFIRI	OS	Positive	Absent	-	-	-	-	-	-	-	-
Grothey A et al, 2013[4]	Metastatic - Second and further lines	Regorafenib	Placebo	OS	Positive	Exploratory (tertiary)	Negative	Mean scores at baseline and at the end of treatment	EORTC QLQ-C30; EQ5D	Present	Only global	Only end of treatment	No imputation for missing data	No details
Bennouna J et al, 2013[64]	Metastatic - Second line	Bevacizumab + Oxaliplatin-based or Irino	Oxaliplatin-based or Irinotecan-based chemotherapy	OS	Positive	Absent	-	-	-	-	-	-	-	-

		teca n-base d che mot hera py												
Middleton G et al 2013*[65]	Metastatic - Second line	Ciclosporine + Irinotecan	Irinotecan	OS; PFS	Negative	Exploratory	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.
Seymour MT et al, 2013*[66]	Metastatic - Second line	Panitumumab + Irinotecan	Irinotecan	OS	Negative	Secondary	Negative	Mean scores at 24 weeks	EORTC QLQ-C30; EQ5D; Dermatology Life Quality Index	Present	Global (details at 24 weeks); symptoms /adverse events scales (no details)	Only 24 weeks	No information	Yes (% at 24 weeks)
Siu LL et al, 2013[67]	Metastatic - Third and further lines	Brivanib + Cetuximab	Cetuximab	OS	Negative	Secondary	Negative (primary and secondary publication)	Time to deterioration; Proportion of responders	EORTC QLQ-C30	Present + Secondary publication	All items	All course of treatment	No information	Yes (details)
Price TJ et al,	Metastatic -	Panitumu	Cetuximab	OS	Positive	Secondary	Negative	Mean change	EQ5D; FACT-	Present	Global, functional	Up to diseas	No infor	Yes

2014[68]	Second line	mab						s (linear mixed model)	Colorectal Symptom Index		scales	e progression	matio n	
Iwamoto S et al, 2015[69]	Metastatic - Second line	Bevacizumab 10 mg/kg + FOLFIRI	Bevacizumab 5 mg/kg + FOLFIRI	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Li J et al, 2015[70]	Metastatic – Third and further lines	Regorafenib	Plabebo	OS	Positive	Exploratory (tertiary)	Negative	Mean scores at baseline and at end of treatment	EORTC QLQ-C30; EQ5D	Present	Only global	End of treatment; AUC during treatment	No imputation for missing data	-
Lim SH et al, 2015[71]	Metastatic - Second line	Simvastatine + FOLFIRI or XELIRI	FOLFIRI or XELIRI	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Mayer RJ et al, 2015[5]	Metastatic and	Trifluridine/ti	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-

	third and further lines	piracil												
Masi G et al, 2015[72]	Metastatic - Second line	Bevacizumab + mFOLFOX-6 or FOLFIRI	mFOLFOX-6 or FOLFIRI	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Sclafani F et al, 2015[73]	Metastatic - Third and further lines	Cetuximab + Irinotecan + Dalotuzumab 10 mg/m^2	Cetuximab + Irinotecan	PFS; OS	Negative	Secondary	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.
		Cetuximab + Irinotecan + Dalo												

		tuzumab 7.5 mg/ m^2												
Tabernero J et al, 2015[74]	Metastatic - Second line	Ramucirumab + FOLFIRI	FOLFIRI	OS	Positive	Secondary	Negative	Proportion of responders (EORTC); mean changes (EQ5D)	EORTC QLQ-C30; EQ5D	Present	Only global	All course of treatment	No information	Yes (% rates)
Kim TW et al, 2016[75]	Metastatic – Third line	Panitumumab	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-
Cascinu S et al, 2017[76]	Metastatic – Second and further lines	Irinotecan, Cetuximab followed by FOLFOX-4	FOLFOX-4 followed by Irinotecan, Cetuximab	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Hickish T et al, 2017[77]	Metastatic – Third	MABp1	Placebo	QoL	Positive	Primary (comb	Positive	Mean changes	EORTC QLQ-C30	Present	Global, functioning scales,	Only at 8 weeks	Missing consi	Yes (details at

	and further lines					ined endpoint)					selected symptoms		dered as failures	week 8)
Li J et al, 2018[78]	Metastatic – Third and further lines	Fruquintinib	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-
Xu J et al, 2018[79]	Metastatic – Third and further lines	Trifluridine/tipiracil	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-
Xu RH et al, 2018[80]	Metastatic – Second line	XELIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	OS	Positive	Absent	-	-	-	-	-	-	-	-
Van Cutsem E et al, 2018[81]	Metastatic – Third and further lines	Nintedanib	Placebo	OS; PFS	Negative	Exploratory	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.

* We have considered these studies as separated because two different publications were issued.

5-FU: 5-Fluorouracil; AUC: Area Under the Curve; CAPOX: Capecitabine-Oxaliplatin; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30; EORTC: European Organization for Research and Treatment of Cancer; EQ5D: EuroQol five-dimensional questionnaire; FACT: Functional Assessment of Cancer Therapy; FOLFIRI: 5FU-Leucovorin-Irinotecan; FOLFOX: 5FU-

Leucovorin-Oxaliplatin; mFOLFOX: modified FOLFOX; n.s.: not specified; OS: overall survival; PFS: progression-free survival; QoL: quality of life; XELIRI: Capecitabine-Irinotecan;

Table 5. Inclusion of health-related quality of life among study endpoints according to characteristics of study and publication.

	Number of publications	QoL primary endpoint	QoL secondary endpoint	QoL not included among Endpoints
Whole series	67	1 (1.5%)	25 (37.3%)	41 (61.2%)
Year of primary manuscript				
2012	9	-	4 (44.4%)	5 (55.6%)
2013	11	-	5 (45.5%)	6 (54.5%)
2014	7	-	1 (14.3%)	6 (85.7%)
2015	16	-	7 (43.8%)	9 (56.2%)
2016	9	-	3 (33.3%)	6 (66.7%)
2017	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
2018	11	-	4 (36.4%)	7 (63.6%)
Journal Impact Factor				
Low (<15)	29	1 (3.4%)	8 (27.6%)	20 (69.0%)
Intermediate (15-30)	31	-	14 (45.2%)	17 (54.8%)
High (>30)	7	-	3 (42.9%)	4 (57.1%)
Sources of funding				
Profit	26	1 (3.8%)	11 (42.3%)	14 (53.9%)
Non-profit	41	-	14 (34.1%)	27 (65.9%)
Setting of disease				
Adjuvant/neoadjuvant setting	20	-	3 (15.0%)	17 (85.0%)
First-line or maintenance setting	26	-	13 (50.0%)	13 (50.0%)
Second and further lines	21	1 (4.8%)	9 (42.8%)	11 (52.4%)
Study design				
Superiority	53	1 (1.9%)	18 (34.0%)	34 (64.1%)
Non-inferiority	14	-	7 (50%)	7 (50.0%)
Masking				
Open label	52	-	17 (32.7%)	35 (67.3%)
Blinded	15	1 (6.7%)	8 (53.3%)	6 (40%)
Type of experimental therapy*				
Chemotherapy +/- other	52	-	17 (32.7%)	35 (67.3%)
Targeted therapy +/- other	40	1 (2.5%)	18 (45.0%)	21 (52.5%)
Primary endpoint				
Overall survival	21	-	10 (47.6%)	11 (52.4%)
Other	46	1 (2.2%)	15 (32.6%)	30 (65.2%)
Study result				
Positive	32	1 (3.1%)	11 (34.4%)	20 (62.5%)
Negative	35	-	14 (40.0%)	21 (60.0%)

*Categories are not mutually exclusive

Table 6. Details about health-related quality of life in trials

	Number of publications	QoL results available in primary publication	QoL results absent in primary publication
Whole series	67	16 (23.9%)	51 (76.1%)
Year of primary manuscript			
2012	9	2 (22.2%)	7 (77.8%)
2013	11	3 (27.3%)	8 (72.7%)
2014	7	1 (14.3%)	6 (85.7%)
2015	16	5 (31.2%)	11 (68.8%)
2016	9	1 (11.1%)	8 (88.9%)
2017	4	1 (25.0%)	3 (75.0%)
2018	11	3 (27.3%)	8 (72.7%)
Journal Impact Factor			
Low (<15)	29	4 (13.8%)	25 (86.2%)
Intermediate (15-30)	31	10 (32.3%)	21 (67.7%)
High (>30)	7	2 (28.6%)	5 (71.4%)
Sources of funding			
Profit	26	7 (26.9%)	19 (73.1%)
Non-profit	41	9 (21.9%)	32 (78.1%)
Setting of disease			
Adjuvant/neoadjuvant setting	20	1 (5.0%)	19 (95.0%)
First-line or maintenance setting	26	8 (30.8%)	18 (69.2%)
Second and further lines	21	7 (33.3%)	14 (66.7%)
Study design			
Superiority	53	10 (18.9%)	43 (81.1%)
Non-inferiority	14	6 (42.9%)	8 (57.1%)
Masking			
Open label	52	10 (19.2%)	42 (80.8%)
Blinded	15	6 (40.0%)	9 (60.0%)
Type of experimental therapy*			
Chemotherapy +/- other	52	8 (15.4%)	44 (84.6%)
Targeted therapy +/- other	40	13 (32.5%)	27 (67.5%)
Primary endpoint			
Overall survival	21	6 (28.6%)	15 (71.4%)
Other	46	10 (21.7%)	36 (78.3%)
Study result			
Positive	32	12 (37.5%)	20 (62.5%)
Negative	35	4 (11.4%)	31 (88.6%)

*Categories are not mutually exclusive

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DISCLOSURE

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*Title Page WITH Author Information

Quality of life (QoL) assessment and reporting in colorectal cancer: a systematic review of phase III trials published between 2012 and 2018.

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Quality of life (QoL) assessment and reporting in colorectal cancer: a systematic review of phase III trials published between 2012 and 2018.

Short title: QoL in CRC phase III trials

ABSTRACT

Background: In this study, our aim was to describe QoL prevalence and heterogeneity in QoL reporting in colorectal cancer phase III trials.

Methods: We included all phase III trials evaluating anticancer drugs in colorectal cancer patients published between 2012 and 2018 by 11 major journals.

Results: Out of the 67 publications identified, in 41 (61.2%) QoL was not listed among endpoints. Out of 26 primary publications of trials including QoL among endpoints, QoL results were not reported in 10 (38.5%). Overall, no QoL data were available in 51/67 (76.1%) primary publications. In particular, in the metastatic setting, QoL data were not available in 12/18 (66.7%) trials with primary endpoint overall survival, and in 20/29 (69.0%) trials with other primary endpoints.

Conclusions: QoL was absent in a high proportion of recently published phase III trials in colorectal cancer, even in trials of second or further lines, where attention to QoL should be particularly high.

Keywords: health-related quality of life; colorectal cancer; endpoints; patient-reported outcomes; randomized controlled trials

1. INTRODUCTION

Colorectal cancer (CRC) represents the third most common cancer affecting both men and women worldwide[1]. Although metastatic CRC (mCRC) remains a highly lethal disease, recent advances in the outcome of these patients have been achieved. This prognostic improvement could be attributed to several factors, including the availability of new drugs and/or new combinations, with a median overall survival (mOS) considerably increased from 12 months in the 5-fluorouracil (5-FU)-based chemotherapy era to approximately 30 months observed in recent clinical trials[2,3].

Notwithstanding the increased anti-tumoral activity and efficacy of systemic treatments, the impact of drug toxicity, that could negatively affect patients' quality of life (QoL), should not be forgotten, particularly in those clinical settings characterized by a ~~lower~~ limited life expectancy and a more delicate balance between benefits and harms of treatment. In the latter settings, uncertainty could remain~~s~~ concerning the net clinical benefit, especially for patients with chemo-refractory mCRC treated in and beyond third-line setting. In these patients, several drugs recently approved for use in clinical practice, like regorafenib and TAS-102, produce a modest survival benefit, with not negligible toxicity issues[4,5]. Therefore, particularly in this scenario, an integrated analysis of "cost-benefit" ratio for the patient should become mandatory[6], as well as the evaluation of patients' experience with patient reported outcomes (PROs).

PROs, which are outcomes assessed directly by the patient[7], may produce a different patients' perspective on the disease and treatment received, complementing the conventional reporting of anti-tumor efficacy data and the physician-based description of adverse events [8]. Health-related quality of life (HRQoL) is a specific type of PRO which evaluates the patient's perspective *"of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being*"[7]. In dedicated documents, European Medicines Agency (EMA) and Food and Drug Administration (FDA) emphasized the importance of the impact of treatments on health-related quality of life in everyday life[7,9]. These aspects are crucial for the evaluation of the clinical benefits of new drugs. Indeed, PROs provide data on patient's QoL, symptoms, treatment adherence or satisfaction with care by including any information~~s~~ directly reported by the patient himself/herself on his/her perception of the disease and its treatment. PROs try to capture a personal perspective, that

may vary from person to person, using well-established methods. PROs should be more widely used to complement the range of traditional indicators of efficacy in oncology and provide information regarding both positive and negative patient experiences. Moreover, in 2015, both American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) proposed frameworks to quantify the benefit of oncology medications, and QoL is included in both instruments[10,11].

In a previous systematic review, not specifically focused on CRC, we showed that QoL was not included among endpoints in a high proportion (210 of the 446 publications analyzed, 47%) of oncology phase III randomized trials published by major journals between 2012 and 2016. In addition, –even when QoL was included among study endpoints, we found that QoL results were significantly underreported and often affected by a significant delay in publication[12].

Aim of this systematic review is to describe QoL prevalence as an endpoint in randomized phase III trials testing anticancer drugs in colorectal cancer patients, published between 2012 and 2018. In addition, we described the underreporting of QoL results and critical methodological issues of QoL assessment.

2. METHODS

Articles published by 11 major scientific journals, ~~previously~~already ~~-~~selected for ~~the~~our original analysis in all solid tumors as the journals where oncology randomized controlled trials are usually published [12], ~~-~~were retrieved for this ~~analysis~~update spcecifically focused on colorectal cancer trials.~~:~~ N~~n~~amely, our search included 3 general medical journals (*New England Journal of Medicine, Lancet, JAMA*) and 8 oncology journals (*Lancet Oncology, Journal of Clinical Oncology, JAMA Oncology, Journal of the National Cancer Institute, Annals of Oncology, European Journal of Cancer, British Journal of Cancer, Cancer*). With the aim to identify primary publications of randomized phase III trials testing anticancer drugs in patients with solid tumors, all issues of the ~~afor~~mentioned journals published between January 2012 and December 2018 were hand-searched. The original analysis[12],~~–~~ limited to papers published between 2012 and 2016, has been updated for the present analysis, with the addition of articles on CRC published in 2017 and 2018.

Trials testing non-pharmacologic interventions were excluded from the analysis. Both trials conducted in early stages of disease (e.g., adjuvant chemotherapy, neo-adjuvant chemo-radiotherapy) and trials conducted in advanced / metastatic setting were included, while trials testing prevention strategies were excluded.

To collect data from each selected paper, the same dedicated case report form used for the previous analysis[12] was adopted, and the electronic database, with one record for each paper, was updated. For each trial, information about publication (journal, year, first author, date of definitive issue and ahead-of-print publication, availability of online supplemental material and/or study protocol) was collected. Impact factor (IF), corresponding to the year of each publication, was retrieved from the Journal of Citation Reports, and publications were divided into 3 categories according to IF: low (<15), intermediate (15-30), high (>30). Information recorded about the clinical trial included: sponsorship (for-profit vs. non-profit), study design (open-label vs. blinded; superiority vs. non-inferiority), details of treatment of both experimental and control arms, disease setting. Articles were divided in 3 categories: (i) adjuvant or neoadjuvant treatment in early stages; (ii) first-line treatment for metastatic disease; (iii) second and/or further lines of treatment for metastatic disease. Similarly to our previous analysis, trials were classified as for-profit when sponsored by the drug company and as non-profit when sponsored by an academic institution or a cooperative group, even if receiving drug supply and/or economic support from one or more drug

companies (when not ~~explicited~~explicated in the publication, details about the study sponsorship were retrieved from ClinicalTrials.gov study record, if available). Experimental treatments were classified into 2 main groups (that were not mutually exclusive): chemotherapy +/- other drugs; targeted agents +/- other drugs. According to study results in terms of primary endpoint, clinical trials were classified into positive or negative.

Information about study endpoints (both primary and secondary, tertiary or exploratory) was derived from the Methods section of the publication and/or from the study protocol (when available as online supplementary material). When QoL was not listed among endpoints in the paper and study protocol was not available, QoL was considered as "apparently absent", except when QoL results were actually presented in the Results section or in a secondary publication: in the latter case, QoL was included *de facto* among endpoints. For all records, secondary QoL publications were searched in PubMed, by using the name of the drug(s) and/or the name of authors of the primary publication and/or the study acronym / code, when available. Time to secondary QoL publication was calculated according to Kaplan-Meier method, from the date of primary definitive publication to the date of secondary QoL definitive publication, if existing, or to the date of last PubMed check (February 15th, 2019).

Details of QoL methodology (type of QoL tools adopted, type of statistical analysis and presentation of results) were collected. As for type of statistical analysis, several non-mutually exclusive categories were identified: mean scores at different time points, mean changes from baseline, proportion of responding patients, time to deterioration. Among details of QoL methodology, we verified whether statistical approaches for dealing with missing data were explicitly stated in the paper and whether data about compliance to QoL questionnaires were reported in the publication.

All analyses were performed with SPSS for Windows, version 25.0.

3. RESULTS

3.1 Study characteristics

Overall, 67 eligible publications were identified. The main characteristics of the eligible publications are reported in **Table 1** (the complete list is reported in the table 2 - 4).

The three most represented journals were Lancet Oncology (20 papers, 29.9%), Annals of Oncology (18 papers, 26.9%) and Journal of Clinical Oncology (14 papers, 20.9%).

Median IF of the eligible publications was 18.038 (interquartile range 11.612—26.303, range 4.819—59.558).

The majority of trials (47, 70.1%) were conducted in patients with advanced/metastatic disease, but studies are well distributed among the 3 setting categories that we defined for classification: adjuvant/neoadjuvant setting (20, 29.9%), first-line or maintenance setting (26, 38.8%) and second and further lines setting (21, 31.3%). Experimental treatment was chemotherapy ± other drugs in 52 trials (77,6%) and targeted therapy ± other drugs in 40 trials (59,7%). More than one-third of the trials (26, 38.8%) were sponsored by a drug company, while the remaining (41, 61.2%) were promoted by an academic institution or a cooperative group.

The details of each eligible publication are reported in **Table 2** (studies conducted in early stages), in **Table 3** (studies conducted in the first-line or maintenance setting) and in **Table 4** (studies conducted in second- and further lines setting), respectively.

3.2 Inclusion of QoL among study endpoints

The inclusion of QoL among endpoints according to study characteristics is detailed in **Table 5**. In the whole series, QoL was a primary endpoint in 1 trial (1.5%), a secondary / exploratory endpoint in 21 trials (21.3%), while in the remaining 41 (61.2%) QoL was not listed at all among study endpoints. The proportion of trials without QoL as an endpoint was 69%, 54.8% and 57.1% among papers published in journals with low, intermediate and high IF, respectively. QoL was not included among endpoints in a relevant proportion both in for-profit trials (53.8%) and even more in non-profit trials (65.8%).

QoL was not listed among endpoints in 17 trials (85.0%) in adjuvant/neoadjuvant setting, in 13 trials (50.0%) in first line, and 11 trials (52.4%) in second and further lines. Proportion of trials not including QoL among endpoints was similar over time: QoL was not listed in 26 trials (60.5%) publications between 2012 and 2015 vs. 15 trials (62.5%) between 2016 and 2018.

3.3 Presence of QoL results in the primary publication

The presence of QoL results according to study characteristics is detailed in **Table 6**. Out of 26 primary publications of trials including QoL among endpoints, QoL results were not reported in 10 (38.5%). Due to the absence among study endpoints or to the lack of results in the publication, QoL results were available in 16 publications (23.9%), while QoL results were absent in the remaining 51 (76.1%): namely, 19 trials out of 20 (95.0%) in adjuvant/neoadjuvant setting, 18 trials out of 26 (69.2%) in first line and 14 trials out of 21 (66.7%) in second and further lines.

The proportion of publications without QoL results, due to absent endpoint or unpublished results, was 86.2%, 67.7% and 71.4% among papers published in journals with low, intermediate and high IF, respectively. QoL results were lacking in a relevant proportion both in publications of for-profit trials (73.1%) and non-profit trials (78.1%).

Proportion of trials without available QoL results in primary publication was similar over time: QoL was lacking in 32 (74.4%) publications between 2012 and 2015 vs. 19 (79.2%) publications between 2016 and 2018.

3.4 QoL secondary publications

Overall, with a median follow-up of 45.3 months, 7 secondary QoL publications were found (the complete list of secondary publications is available in the **Table 2 - 4**). Median IF of the secondary QoL publications was 6.029 (interquartile range 5.548– 9.523, range 2.806 – 36.421), compared to 18.038 (interquartile range 14.907—21.023, range 9.269—26.509) of the respective primary publication. For the 10 trials including QoL as an endpoint, but without any QoL result in the primary publication, probability of secondary publication was 0%, 33.3% and 50.0% after 1, 3 and 5 years respectively. (**Figure 1**).

3.5 QoL reporting according to study primary endpoint and study results

21 trials (31.3%) had overall survival as primary endpoint, while the remaining 46 (68.7%) had endpoints other than overall survival. Among the latter 46 trials, 30 (65.2%) did not include QoL as an endpoint, and among 16 trials including QoL as an endpoint, 6 did not report QoL results in primary publication. Overall, due to the absence of endpoint or unpublished results, QoL results were not reported in 36 (78.3%) publications of trials with a primary endpoint other than overall survival.

According to authors' conclusions, studies were divided into positive (32, 47.8%) and negative (35, 52.2%). Among 32 trials with positive results, 20 (62.5%) did not include QoL as an endpoint. Despite all trials with positive results including QoL as an endpoint reported QoL results in the primary publication (12 / 12, 100%), overall, due to absent endpoint, the majority of trials with positive results were lacking QoL results (20 / 32, 62.5%). Out of the 12 trials ~~with~~including QoL results, 5 trials reported a positive QoL result, while 7 trials reported negative QoL results.

On the other hand, among 35 trials with negative results, 21 (60%) did not include QoL as an endpoint. Out of 14 negative trials ~~with~~including QoL among endpoints, 4 (28.6%) included QoL results in the primary publication and 5 (35.7%) reported QoL in a secondary publication: all these trials reported a negative QoL result. In the remaining 5 (35.7%) negative trials including QoL as an endpoint, results have not been published.

In the investigated period, we identified 5 trials which prompted authorization for use in clinical practice by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), all of which were done in the setting of advanced disease. Three of these trials did not include QoL among endpoints.

3.6 QoL methodology

In 21 trials with available QoL results (including secondary publications), most common QoL tools were EORTC QLQ-C30 (14, 66.7%); EORTC colorectal cancer module (3, 14.3%); EQ5D (8, 38.1%); FACT-C (3, 14.3%) and other FACT tools (4, 19.0%).

Common methods of analysis were mean scores over time (10, 47.6%), mean changes (6, 28.6%), time to deterioration (5, 23.8%) and proportion of responders or worsening patients (4, 19.0%).

Out of 26 trials with QoL as endpoint, 9 (34.6%) trials did not report details about compliance to QoL questionnaires, and 21 (80.7%) did not include any explicit statement about statistical approaches adopted for dealing with missing QoL data.

4. DISCUSSION

This review of recently published randomized phase III trials conducted in CRC patients shows that QoL results are lacking, due to exclusion from study endpoints or absence of results, in a high proportion of publications. This deficiency is particularly relevant in trials of advanced disease, where attention to QoL should be necessarily higher. Of note, we found that QoL data were not available in 66.7% of the publications regarding second or further lines of treatment. Furthermore, our data show that methodology of QoL analysis is quite heterogeneous in terms of type of instruments, analysis and presentation of results. These results underline that, although QoL assessment in clinical trials is unanimously considered relevant, this principle is often not respected when clinical trials are designed and when results are analyzed and published.

Similarly to our previous analyses, conducted in all solid tumors[12] and in prostate cancer trials[13], we collected the information about the presence of QoL among endpoints from the manuscript of the publication and from the study protocol, when the latter was available. However, we did not have access to study protocol for all the publications included in the analysis and, in some cases, we might have considered QoL apparently absent although it was actually included among endpoints. Consequently, the real prevalence of QoL could be higher than reported in our analysis. However, this limitation may reinforce our disappointing conclusions, because if a study included QoL among endpoints but this was completely neglected in the study publication, the importance attributed to QoL by the authors was *de facto* really marginal.

Recent years have been characterized by the conduction and publication of many pivotal trials of new drugs and/or new combinations in CRC. However, inclusion of QoL among study endpoints results quite low (38.8% of publications considered) and this is reflected in the even lower proportion of trials with available QoL results (23.9% of primary publications), with a stable trend over the time period considered in the analysis (25.6% between 2012 and 2015 vs. 20.8% between 2016 and 2018). As a matter of fact, the high proportion of absent QoL results in the adjuvant setting could be not surprising, considering that the negative treatment impact - hopefully temporary - on QoL could be considered a “justified” risk, to obtain an improvement in the chance of a definitive cure. This could justify,

at least in part, the lower attention to QoL evaluation in early setting: nearly all trials (95%) we analyzed did not include QoL among the endpoints, and this proportion in CRC is even higher than the result observed in all solid tumors[12]. However, absence of QoL is particularly relevant in the setting of metastatic patients, where only 31.9% of primary publications reported QoL results. Differently from trials conducted in early stages, the palliative setting is characterized by a relevant proportion of symptomatic patients and many treatments are characterized by a modest benefit in terms of PFS and OS. For these reasons, a complete evaluation of the balance between benefits and harms of treatments should necessarily include QoL evaluation. Furthermore, knowledge of QoL data could improve the information to patients, and facilitate clinical choice between alternative treatments, particularly if they show similar survival outcomes.

For instance, in recent years, two different new drugs, namely regorafenib and trifluridine/tipiracil [4,5], have been tested in the third-line setting, showing a modest survival benefit, that led to approval by regulatory agencies and inclusion in clinical practice guidelines. However, while in the CORRECT study, testing the efficacy of regorafenib, a formal assessment of QoL was performed, in the RECOURSE study, testing TAS-102, QoL was not among study endpoints. In the latter case, the absence of QoL assessment has led study investigators to perform an indirect assessment of patients' QoL, that is encumbered by several limitations, first of all the use of a non-validated instrument not based on patient-reported outcomes[14].

Our literature research found that QoL results were presented in a secondary publication for seven trials. Although we recognize that splitting up QoL data in a separate publication from survival results seems to be an opportunity for a comprehensive way of reporting, probability of a secondary publication was only 50.0% even 5 years after first publication. Moreover, separate reporting of QoL results may reduce their value in clinical decision making, as clinicians less likely read or could be not aware of the successive papers[15]. Our findings corroborate previous observations, according to which most drugs enter the market without explicit evidence of benefit on QoL[16].

We also investigated the impact of QoL assessment in studies promoted by academic researchers and/or independent cooperative groups vs for-profit studies. Concordantly with

our previous results in all solid tumors, both for-profit and, even more, non-profit trials did not include QoL among endpoints in a considerable percentage (73.1% for profit- trials and 78.1% in non-profit trials). In our view, this result is particularly disappointing, considering that academic trials, if really aiming to optimize treatment choices in clinical practice, should be characterized by higher attention to QoL.

Several methodological issues can be associated with the adoption of QoL among the endpoints of a clinical trial. For example, the choice of the correct QoL questionnaire and of the proper timing of questionnaires administration, the method of analysis and description of results, and the statistical management of missing data may be particularly challenging. CRC, especially in patients who have already received multiple lines of treatment, is exposed to a ~~non negligible~~non-negligible proportion of early deterioration and treatment withdrawal compared to other tumors characterized by a better prognosis (e.g. breast cancer or prostate cancer). In these clinically challenging scenarios, missing data can represent a methodological problem, and we suppose that many researchers could consider this issue as a barrier to adoption of QoL questionnaires. While data missing at baseline are substantially related to defects in the quality of study procedures, missing data at later time points may be frequently related to treatment toxicities, tumor progression and/or symptomatic worsening, with difficulty in completing questionnaires. This aspect could introduce possible selection bias (patients who complete questionnaires feel better than those who do not complete) and could lead to misleading results regarding QoL, which is particularly relevant in patients with advanced and progressive disease. Unfortunately, we found that only a minority of publications clarified methods of management of missing data in QoL analysis.

As well as for other solid tumors, several validated QoL tools are currently available for trials conducted in CRC cancer, each one with its strengths and weaknesses. As expected, we found differences in their adoption among trials. The most common instrument used for QoL assessment was the EORTC Quality of Life Questionnaire C30 (66.7% of trials with available QoL details), supplemented in few cases by the CRC-specific module. However, some studies used other types of QoL assessments.

Not surprisingly, similarly to what we described in other settings[13], we found a significant heterogeneity in the methods used for the analysis and presentation of QoL

results. As expected, we found that description of mean scores or mean changes from baseline at different time points was commonly used to summarize QoL results (47.6% and 28.6% of trials with available QoL results, respectively). This method allows a simple graphical and numerical representation of results, it is familiar to most readers and it is widely accepted to compare QoL trajectory among different study arms. However, this method is weak in capturing a potentially relevant heterogeneity in the QoL response experienced by individual patients[17]. From this point of view, analysis of responders (proportion of subjects with improved or stable or worse score, compared to baseline) in each specific QoL domain gives a useful complementary information, but our analysis showed that it is adopted only in a minority of studies (19%). In addition, many studies describe QoL results with a particular emphasis on the early phase of treatment (that is of course useful to reassure about the absence of a negative impact of treatment toxicity on patients' status), but only a minority of studies focus on QoL description at the time of instrumental progression and treatment failure. Curves describing the time to deterioration of global QoL or specific symptoms are particularly useful in describing the real efficacy of experimental treatment in delaying symptomatic worsening of disease. Unfortunately, we found this kind of analysis only in 23.8% of the trials analyzed.

Of course, no single method of analysis and presentation can assure an exhaustive description of QoL results. Moreover, even in those cases where more methods are planned in the study protocol, the presentation of results is often suboptimal, as the space dedicated to QoL is often marginal[12].This appears rather surprising, because the limitations in article length could be easily exceeded by the possibility to integrate the main article with online supplement and appendix materials.

In conclusion, our review of trials conducted in colorectal cancer and published in recent years shows that the inclusion of QoL among study endpoints and the timely and complete reporting of QoL results are definitely suboptimal. The heterogeneity in the choice of instruments, timing, modality and presentation of analysis and presentation of results make more difficult the interpretation of results.

Figures and tables

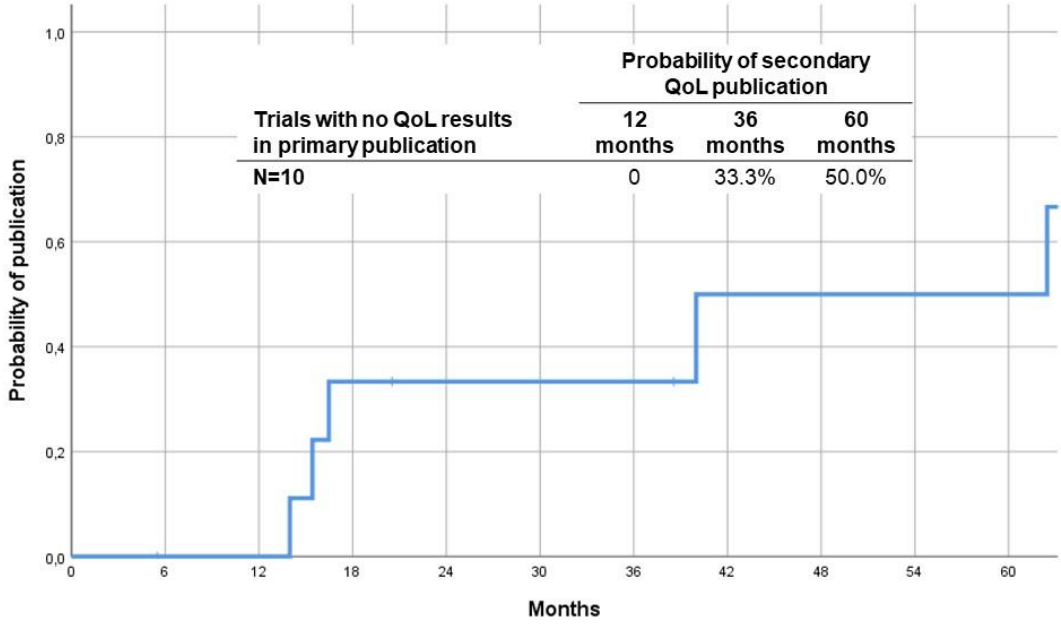

Figure 1. Kaplan-Meier curves of time to secondary publication with quality of life (QoL) results, for trials including QoL as a secondary / exploratory endpoint, but without any QoL result in the primary publication.

Table 1. Characteristics of the 67 primary publications included in the analysis.

	Number of publications	(%)
Year of primary manuscript		
2012	9	13,4%
2013	11	16,4%
2014	7	10,5%
2015	16	23,9%
2016	9	13,4%
2017	4	6,0%
2018	11	16,4%
Primary manuscript journal		
Annals of Oncology	18	26,8%
British Journal of Cancer	2	3,0%
European Journal of Cancer	4	6,0%
JAMA	3	4,5%
Journal of Clinical Oncology	14	20,9%
Journal of National Cancer Institute	2	3,0%
Lancet	2	3,0%
Lancet Oncology	20	29,8%
New England Journal of Medicine	2	3,0%
Sources of funding		
Profit	26	38,8%
Non-profit	41	61,2%
Setting of disease		
Adjuvant/neoadjuvant setting	20	29,9%
First-line or maintenance setting	26	38,8%
Second and further lines	21	31,3%
Study design		
Superiority	53	79,1%
Non-inferiority	14	20,9%
Masking		
Open label	52	77,6%
Blinded	15	22,4%
Countries involved		
Single country	33	49,3%
2 or more countries	34	50,7%
Type of experimental therapy*		
Chemotherapy +/- other	52	77,6%
Targeted therapy +/- other	40	59,7%
Primary endpoint		
Overall survival	21	31,3%
Other	46	68,7%
Study result		
Positive	32	47,8%
Negative	35	52,2%

*Categories are not mutually exclusive

Table 2: Studies in adjuvant/neoadjuvant setting

Study	Setting	Experimental arm	Control arm	Primary endpoint	Study result	QoL endpoint	QoL ~~endpoint~~ results ~~result~~	Method of analysis	Tools	QoL present in study	Focus items QoL	Timing QoL	Missing data	Compliance
Alberts SR et al, 2012[18]	Adjuvant	Cetuximab - FOLFOX	FOLFOX	DFS	Negative	Absent	-	-	-	-	-	-	-	-
de Gramont A et al, 2012[19]	Adjuvant	Bevacizumab + FOLFOX or CAPOX	FOLFOX	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Ngan SY et al, 2012[20]	Neoadjuvant	Short Course-RT followed by surgery and 5FU+Leucovorin as adjuvant therapy	Long Course-RT with 5FU followed by surgery and 5FU+Leucovorin as adjuvant therapy	Local recurrence	Negative	Secondary	Negative (secondary publication)	Mean changes / AUC	EORTC QLQC30 / CR38	Absent – Secondary publication	Global, functioning and symptom scales	During treatment and up to 12 months	Imputation with proxy measurement by physicians	Yes
Hofheinz RD et al, 2012[21]	Neoadjuvant	Capecitabine + CRT (Capecitabine)	5 FU + CRT (5FU)	OS	Positive	Absent	-	-	-	-	-	-	-	-

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Köhne CH et al, 2013[22]	Adjuvant	High-dose 5-flurouracil ± Leucovorin	Standard bolus 5-FU regimen with leucovorin	RFS; OS.	Negative	Absent	-	-	-	-	-	-	-	-
Glynne-Jones R et al, 2014[23]	Adjuvant	CAPOX	FUP only	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Taieb J et al, 2014[24]	Adjuvant	Cetuximab - FOLFOX	FOLFOX	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Yoshida M et al, 2014[25]	Adjuvant	S1	Tegafur-uracil + leucovorin	DFS	Positive	Absent	-	-	-	-	-	-	-	-
Allegra CJ et al, 2015[26]	Neoadjuvant	Factorial (2x2) design:		Local recurrence	Positive (Capecitabine) Negative (Oxaliplatin)	Absent	-	-	-	-	-	-	-	-
		RT + Capecitabine (+/- oxaliplatin)	RT + 5FU (+/- oxaliplatin)											
		RT + Fluoropyrimidine (Capecitabine or FU) + Oxaliplatin	RT + Fluoropyrimidine (Capecitabine or FU)											

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Breugom AJ et al, 2015[27]	Adjuvant	CT or CRT (5FU-Leucovorin or Capecitabine)	FUP only	OS	Negative	Absent	-	-	-	-	-	-	-	-
Hebbar M et al, 2015[28]	Neoadjuvant, Adjuvant	6 cycles of FOLFOX 7 followed by 6 cycles of FOLFIRI	12 cycles of FOLFOX 4	DFS	Negative	Secondary	Negative (secondary publication)	Time to deterioration	EORTC QLQ-C30	Absent – Secondary publication	Global, functioning and symptom scales	All course of treatment	Included in the definition of analysis. Imputation analysis	Yes
Rödel C et al, 2015[29]	Neoadjuvant, Adjuvant	Preoperative CRT (5FU+Oxaliplatin) followed by 5FU-Leucovorin-Oxaliplatin as adjuvant therapy	Preoperative CRT (5FU) followed by 5FU as adjuvant therapy	DFS	Positive	Absent	-	-	-	-	-	-	-	-
Sadahiro S et al,	Adjuvant	Consecutive 5 days per	Tegafur-uracil + leucovori	DFS	Negative	Absent	-	-	-	-	-	-	-	-

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2015[30]		week for 18 months of Tegafur-uracil + leucovorin	n for 28 of 35 days for 6 months											
Bujko K et al, 2016[31]	Adjuvant	SC-RT followed by FOLFOX 4	Long-course chemoradiation (5FU, Leucovorin, Oxaliplatin)	R0 resection rate	Negative	Absent	-	-	-	-	-	-	-	-
Kerr RS et al, 2016[32]	Adjuvant	Bevacizumab + Capecitabine	Capecitabine	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Oki E et al, 2016[33]	Adjuvant	S-1	Tegafur-uracil	RFS	Positive	Absent	-	-	-	-	-	-	-	-
André T et al, 2018[34]	Adjuvant	CAPOX or FOLFOX for three months	CAPOX FOLFOX for six months	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Iveson TJ et al, 2018[35]	Adjuvant	CAPOX or FOLFOX for three months	CAPOX FOLFOX for six months	DFS	Positive	Secondary	Positive	Mean scores, AUC	EORTC QLQ-CR30,	Present	Global, functioning and	All courses of treatment	Multiple imputation analy	Yes

									CR29, EQ5D, FACT-GOG/Ntx		symptom scales	and follow-up	sis	
Matsuda C et al, 2018[36]	Adjuvant	Tegafur-uracil	FUP alone	DFS	Negative	Absent	-	-	-	-	-	-	-	-
Sobrero A et al, 2018[37]	Adjuvant	CAPOX or FOLFOX for three months	CAPOX FOLFOX for six months	DFS	Negative	Absent	-	-	-	-	-	-	-	-

5-FU: 5-Fluorouracil; AUC: Area Under the Curve; CAPOX: Capecitabine-Oxaliplatin; CRT: Chemo-Radiotherapy; DFS: Disease Free Survival; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer 29; EORTC QLQ-CR38: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer 38; EQ5D: Euro Qol five-dimensional questionnaire; FACT-GOG/Ntx: FACT - Gynecologic Oncology Group/Neurotoxicity; FOLFIRI: 5FU-Leucovorin-Irinotecan; FOLFOX: 5FU-Leucovorin-Oxaliplatin; FUP: Follow up; QoL: Quality of Life; RFS: Relapse Free Survival; RT: Radiotherapy;

Table 3: Studies in first-line or maintenance setting

Study	Setting	Experimental arm	Control arm	Primary endpoint	Study result	QoL endpoint	QoL ~~endpoint~~ results	Method of analysis	Tools	QoL present in study	Focus items QoL	Timing QoL	Missing data	Covariance
Hoff PM et al, 2012[38]	Metastatic - First-line	Cediranib+ FOLFOX6 or CAPOX	FOLFOX6 or CAPOX	PFS; OS	Negative	Absent	-	-	-	-	-	-	-	-
Hong YS et al, 2012[39]	Metastatic - First-line	S-1 plus oxaliplatin	CAPOX	PFS	Positive	Secondary	Negative	Mean changes	EORTC QLQ-C30	Present	Global, functioning and symptom scales	Final visit	No information	Yes
Schmoll HJ et al, 2012[40]	Metastatic - First-line	Cediranib + FOLFOX6	Bevacizumab+ FOLFOX6	PFS	Negative	Secondary	Negative	Time to deterioration; proportion of worsening patients	FACT-C	Present	TOI, symptoms, total scores	All course of treatment	No information	Yes
Tveit KM et al, 2012[41]	Metastatic - First-line	Cetuximab plus FLOX continuously Cetuximab plus	FLOX	PFS	Negative	Secondary	Negative (secondary publication)	Mean scores	EORTC QLQ-C30	Absent – Secondary publication	Global, functioning and sympt	All course of treatment (Prese	No information	Yes

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		FLOX intermittently									om scales	nted up to 12 cycles)		
Carrato A et al, 2013[42]	Metastatic - First-line	Sunitinib + FOLFIRI	FOLFIRI	PFS	Negative	Secondary	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.
Cunningham D et al, 2013[43]	Metastatic - First-line	Capecitabine + Bevacizumab	Capecitabine	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Johnsson A et al, 2013[44]	Metastatic - Maintenance after First-line	Bevacizumab + Erlotinib	Bevacizumab	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Yamada Y et al, 2013[45]	Metastatic - First-line	S-1 + Oxaliplatin + Bevacizumab	mFOLFOX6 + Bevacizumab	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Ye LC et al, 2013[46]	Metastatic - First-line	Cetuximab + FOLFOX or FOLFIRI	FOLFOX or FOLFIRI	Rate of patients converted to resection	Positive	Absent	-	-	-	-	-	-	-	-

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Heinemann V et al, 2014[47]	Metastatic - First-line	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	ORR	Negative	Absent	-	-	-	-	-	-	-	-
Loupakis F et al, 2014[48]	Metastatic - First-line	FOLFOXIRI + Bevacizumab	FOLFIRI + Bevacizumab	PFS2	Positive	Absent	-	-	-	-	-	-	-	-
Primrose J et al, 2014[49]	Metastatic - First-line	mFOLFOX6 or CAPOX + Cetuximab	mFOLFOX6 or CAPOX	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Hegewisch-Becker S et al, 2015[50]	Metastatic - Maintenance after First-line	Bevacizumab FUP	Fluoropyrimidine + Bevacizumab	Time to failure of strategy	Positive (Bevacizumab) Negative (Observation)	Secondary	Negative (primary and secondary publication)	Mean scores (primary and secondary publication); proportion of responders (secondary publication)	EORTC QLQ-C30 / CR29 / "other instruments"	Present + Secondary publication	Global (primary); all scales (secondary)	All course of treatment and beyond, up to 24 weeks	No information	N (primary) Yes (secondary)
Koeberle D et al, 2015[51]	Metastatic - Maintenance	Bevacizumab	FUP	TTP	Negative	Absent	-	-	-	-	-	-	-	-

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	after First-line													
Simkens LH et al, 2015[52]	Metastatic - Maintenance after First-line	Capecitabine + Bevacizumab	FUP	PFS2	Positive	Secondary	Negative	Mean changes	EORTC QLQ-C30	Present	Global, functioning and symptom scales	All course of treatment	No information	Yes
Tournigand C et al, 2015[53]	Metastatic - Maintenance after First-line	Bevacizumab + Erlotinib	Bevacizumab	PFS	Positive	Secondary	Negative	Median scores	EQ5D	Present	Global	Up to 4 months (only 2 months Presented)	No information	Yes
Aparicio T et al, 2016[54]	Metastatic - First-line	Factorial (2 x 2) design:		PFS	Negative	Secondary	Negative (secondary publication)	Time to deterioration (secondary publication)	QoL VAS	Absent – Secondary publication	Global (secondary)	All course of treatment	No information	Yes
		5FU+Leucovorin (+/- Irinotecan)	Simplified 5FU+Leucovorin (+/- Irinotecan)											
		5FU+Leucovorin (standard or simplified) + Irinotecan	5FU+Leucovorin (standard or simplified											

			)											
Hagman H et al, 2016[55]	Metastatic - Maintenance after First-line	Bevacizumab ± Erlotinib	Bevacizumab or Capecitabine	PFS rate at 3 months	Negative	Absent	-	-	-	-	-	-	-	-
van Hazel GA et al, 2016[56]	Metastatic - First-line	mFOLFOX6 ±Bevacizumab + SIRT	mFOLFOX6 ±Bevacizumab	PFS	Negative	Secondary	Negative (secondary publication)	Mean scores (secondary publication)	EQ5D	Absent – Secondary publication	EQ5D utility scores	Up to 60 months (Presented up to 24) (secondary)	No statistical imputation for missing data	Ye (secondary)
Luo HY et al, 2016[57]	Metastatic - Maintenance after First-line	Capecitabine	FUP	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Yamazaki K et	Metastatic	Bevacizumab + FOLFIRI	Bevacizumab+	PFS	Positive	Secondary	Positive	Mean scores	FACT-C / FACT-	Present	TOI / FACT-	All course	Imputat	No details

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al, 2016[58]	- First-line		FOLFOX						GOG/Ntx		GOG/Ntx	of treatment (up to 18 months)	ion, assuming missing at random	
Kwakman JJM et al, 2017[59]	Metastatic – First-line	S-1	Capecitabine	Incidence of any grade HFS	Positive	Absent	-	-	-	-	-	-	-	-
Venook AP et al, 2017[2]	Metastatic – First-line	Cetuximab + FOLFOX or FOLFIRI	Bevacizumab + FOLFOX or FOLFIRI	OS	Negative	Secondary	-	n.s.	EORTC QLQ-C30*; Changes in function*; Dermatology-specific QoL*; EQ5D*	Absent	n.s.	n.s.	n.s.	n.s.
Aparicio T et al, 2018[60]	Maintenance after First-	Bevacizumab	FUP	TCD	Negative	Secondary	Negative	Time to deterioration	EORTC QLQ-C30	Present	Global, physical functi	All course of treatment	No information	Yes

	line										oning, asthenia			
Qin S et al, 2018[61]	Metastatic – First-line	Cetuximab + FOLFOX	FOLFOX	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Yamada Y et al, 2018[62]	Metastatic – First-line	S-1, Irinotecan + Bevacizumab	mFOLFOX6 or CAPOX + Bevacizumab	PFS	Positive	Secondary	Positive	Mean scores	FACT-C FACT/GOG-Ntx	Present	FACT-C TOI, FACT/GOG-Ntx	16 & 24 weeks	No information	Yes

* declared in the protocol but results not present in the work

5-FU: 5-Fluorouracil; CAPOX: Capecitabine-Oxaliplatin; EQ5D: Euro Qol five-dimensional questionnaire; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer 29; FACT-C: Functional Assessment of Cancer Therapy- Colorectal cancer; FACT-GOG/Ntx: FACT-Gynecologic Oncology Group/Neurotoxicity; FLOX: 5FU- Leucovorin- Oxaliplatin; FOLFIRI: 5FU-Leucovorin-Irinotecan; FOLFOX: 5FU-Leucovorin-Oxaliplatin; FOLFOXIRI: 5FU-Leucovorin-Irinotecan-Oxaliplatin; FUP: Follow up; mFOLFOX: modified FOLFOX; n.s.: not specified; OS: overall survival; PFS: progression-free survival; QoL VAS: QoL-Visual Analogue Scale; QoL: Quality of Life; SIRT: selective internal radiotherapy; TCD: Tumor control duration; TOI: Trial Outcome Index; TTP: time to progression.

Table 4: Studies in second and further lines

Study	Setting	Experimental arm	Control arm	Primary endpoint	Study result	QoL endpoint	QoL ~~endpoint~~ results	Method of analysis	Tools	QoL present in study	Focus items QoL	Timing QoL	Missing data	Compliance
Van Cutsem E et al, 2012[63]	Metastatic - Second line	Aflibercept + FOLFIRI	FOLFIRI	OS	Positive	Absent	-	-	-	-	-	-	-	-
Grothey A et al, 2013[4]	Metastatic - Second and further lines	Regorafenib	Placebo	OS	Positive	Exploratory (tertiary)	Negative	Mean scores at baseline and at the end of treatment	EORTC QLQ-C30; EQ5D	Present	Only global	Only end of treatment	No imputation for missing data	No details
Bennouna J et al, 2013[64]	Metastatic - Second line	Bevacizumab + Oxaliplatin-based or Irinotecan-based chemotherapy	Oxaliplatin-based or Irino	OS	Positive	Absent	-	-	-	-	-	-	-	-

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		tecan-based chemotherapy												
Middleton G et al 2013*[65]	Metastatic - Second line	Ciclosporine + Irinotecan	Irinotecan	OS; PFS	Negative	Exploratory	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.
Seymour MT et al, 2013*[66]	Metastatic - Second line	Panitumumab + Irinotecan	Irinotecan	OS	Negative	Secondary	Negative	Mean scores at 24 weeks	EORTC QLQ-C30; EQ5D; Dermatology Life Quality Index	Present	Global (details at 24 weeks); symptoms/adverse events scales (no details)	Only 24 weeks	No information	Yes (% at 24 weeks)
Siu LL et al, 2013[67]	Metastatic - Third and further lines	Brivanib + Cetuximab	Cetuximab	OS	Negative	Secondary	Negative (primary and secondary publication)	Time to deterioration; Proportion of responders	EORTC QLQ-C30	Present + Secondary publication	All items	All course of treatment	No information	Yes (details)
Price TJ et al,	Metastatic -	Panitumu	Cetuximab	OS	Positive	Secondary	Negative	Mean change	EQ5D; FACT-	Present	Global, functional	Up to diseas	No infor	Yes

2014[68]	Second line	mab						s (linear mixed model)	Colorectal Symptom Index		scales	e progression	mation	
Iwamoto S et al, 2015[69]	Metastatic - Second line	Bevacizumab 10 mg/kg + FOLFIRI	Bevacizumab 5 mg/kg + FOLFIRI	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Li J et al, 2015[70]	Metastatic – Third and further lines	Regorafenib	Plabebo	OS	Positive	Exploratory (tertiary)	Negative	Mean scores at baseline and at end of treatment	EORTC QLQ-C30; EQ5D	Present	Only global	End of treatment; AUC during treatment	No imputation for missing data	-
Lim SH et al, 2015[71]	Metastatic - Second line	Simvastatine + FOLFIRI or XELIRI	FOLFIRI or XELIRI	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Mayer RJ et al, 2015[5]	Metastatic and	Trifluridine/ti	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-

	third and further lines	piracil												
Masi G et al, 2015[72]	Metastatic - Second line	Bevacizumab + mFOLFOX-6 or FOLFIRI	mFOLFOX-6 or FOLFIRI	PFS	Positive	Absent	-	-	-	-	-	-	-	-
Sclafani F et al, 2015[73]	Metastatic - Third and further lines	Cetuximab + Irinotecan + Dalotuzumab 10 mg/m^2	Cetuximab + Irinotecan	PFS; OS	Negative	Secondary	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.
		Cetuximab + Irinotecan + Dalo												

		tuzumab 7.5 mg/m^2												
Tabernero J et al, 2015[74]	Metastatic - Second line	Ramucirumab + FOLFIRI	FOLFIRI	OS	Positive	Secondary	Negative	Proportion of responders (EORTC); mean changes (EQ5D)	EORTC QLQ-C30; EQ5D	Present	Only global	All course of treatment	No information	Yes (% rates)
Kim TW et al, 2016[75]	Metastatic – Third line	Panitumumab	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-
Cascinu S et al, 2017[76]	Metastatic – Second and further lines	Irinotecan, Cetuximab followed by FOLFOX-4	FOLFOX-4 followed by Irinotecan, Cetuximab	PFS	Negative	Absent	-	-	-	-	-	-	-	-
Hickish T et al, 2017[77]	Metastatic – Third	MABp1	Placebo	QoL	Positive	Primary (comb	Positive	Mean changes	EORTC QLQ-C30	Present	Global, functioning scales,	Only at 8 weeks	Missing consi	Yes (details at

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	and further lines					ined endpoint)					selected symptoms		dered as failures	week 8)
Li J et al, 2018[78]	Metastatic – Third and further lines	Fruquintinib	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-
Xu J et al, 2018[79]	Metastatic – Third and further lines	Trifluridine/tipiracil	Placebo	OS	Positive	Absent	-	-	-	-	-	-	-	-
Xu RH et al, 2018[80]	Metastatic – Second line	XELIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	OS	Positive	Absent	-	-	-	-	-	-	-	-
Van Cutsem E et al, 2018[81]	Metastatic – Third and further lines	Nintedanib	Placebo	OS; PFS	Negative	Exploratory	-	n.s.	n.s.	Absent	n.s.	n.s.	n.s.	n.s.

* We have considered these studies as separated because two different publications were issued.

5-FU: 5-Fluorouracil; AUC: Area Under the Curve; CAPOX: Capecitabine-Oxaliplatin; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30; EORTC: European Organization for Research and Treatment of Cancer; EQ5D: EuroQol five-dimensional questionnaire; FACT: Functional Assessment of Cancer Therapy; FOLFIRI: 5FU-Leucovorin-Irinotecan; FOLFOX: 5FU-

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Leucovorin-Oxaliplatin; mFOLFOX: modified FOLFOX; n.s.: not specified; OS: overall survival; PFS: progression-free survival; QoL: quality of life; XELIRI: Capecitabine-Irinotecan;

Table 5. Inclusion of health-related quality of life among study endpoints according to characteristics of study and publication.

	Number of publications	QoL primary endpoint	QoL secondary endpoint	QoL not included among Endpoints
Whole series	67	1 (1.5%)	25 (37.3%)	41 (61.2%)
Year of primary manuscript				
2012	9	-	4 (44.4%)	5 (55.6%)
2013	11	-	5 (45.5%)	6 (54.5%)
2014	7	-	1 (14.3%)	6 (85.7%)
2015	16	-	7 (43.8%)	9 (56.2%)
2016	9	-	3 (33.3%)	6 (66.7%)
2017	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
2018	11	-	4 (36.4%)	7 (63.6%)
Journal Impact Factor				
Low (<15)	29	1 (3.4%)	8 (27.6%)	20 (69.0%)
Intermediate (15-30)	31	-	14 (45.2%)	17 (54.8%)
High (>30)	7	-	3 (42.9%)	4 (57.1%)
Sources of funding				
Profit	26	1 (3.8%)	11 (42.3%)	14 (53.9%)
Non-profit	41	-	14 (34.1%)	27 (65.9%)
Setting of disease				
Adjuvant/neoadjuvant setting	20	-	3 (15.0%)	17 (85.0%)
First-line or maintenance setting	26	-	13 (50.0%)	13 (50.0%)
Second and further lines	21	1 (4.8%)	9 (42.8%)	11 (52.4%)
Study design				
Superiority	53	1 (1.9%)	18 (34.0%)	34 (64.1%)
Non-inferiority	14	-	7 (50%)	7 (50.0%)
Masking				
Open label	52	-	17 (32.7%)	35 (67.3%)
Blinded	15	1 (6.7%)	8 (53.3%)	6 (40%)
Type of experimental therapy*				
Chemotherapy +/- other	52	-	17 (32.7%)	35 (67.3%)
Targeted therapy +/- other	40	1 (2.5%)	18 (45.0%)	21 (52.5%)
Primary endpoint				
Overall survival	21	-	10 (47.6%)	11 (52.4%)
Other	46	1 (2.2%)	15 (32.6%)	30 (65.2%)
Study result				
Positive	32	1 (3.1%)	11 (34.4%)	20 (62.5%)
Negative	35	-	14 (40.0%)	21 (60.0%)

*Categories are not mutually exclusive

Table 6. Details about health-related quality of life in trials

	Number of publications	QoL results available in primary publication	QoL results absent in primary publication
Whole series	67	16 (23.9%)	51 (76.1%)
Year of primary manuscript			
2012	9	2 (22.2%)	7 (77.8%)
2013	11	3 (27.3%)	8 (72.7%)
2014	7	1 (14.3%)	6 (85.7%)
2015	16	5 (31.2%)	11 (68.8%)
2016	9	1 (11.1%)	8 (88.9%)
2017	4	1 (25.0%)	3 (75.0%)
2018	11	3 (27.3%)	8 (72.7%)
Journal Impact Factor			
Low (<15)	29	4 (13.8%)	25 (86.2%)
Intermediate (15-30)	31	10 (32.3%)	21 (67.7%)
High (>30)	7	2 (28.6%)	5 (71.4%)
Sources of funding			
Profit	26	7 (26.9%)	19 (73.1%)
Non-profit	41	9 (21.9%)	32 (78.1%)
Setting of disease			
Adjuvant/neoadjuvant setting	20	1 (5.0%)	19 (95.0%)
First-line or maintenance setting	26	8 (30.8%)	18 (69.2%)
Second and further lines	21	7 (33.3%)	14 (66.7%)
Study design			
Superiority	53	10 (18.9%)	43 (81.1%)
Non-inferiority	14	6 (42.9%)	8 (57.1%)
Masking			
Open label	52	10 (19.2%)	42 (80.8%)
Blinded	15	6 (40.0%)	9 (60.0%)
Type of experimental therapy*			
Chemotherapy +/- other	52	8 (15.4%)	44 (84.6%)
Targeted therapy +/- other	40	13 (32.5%)	27 (67.5%)
Primary endpoint			
Overall survival	21	6 (28.6%)	15 (71.4%)
Other	46	10 (21.7%)	36 (78.3%)
Study result			
Positive	32	12 (37.5%)	20 (62.5%)
Negative	35	4 (11.4%)	31 (88.6%)

*Categories are not mutually exclusive

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DISCLOSURE

Massimo Aglietta had roles as consultant or advisor for Roche, Bristol Myers Squibb, Merck and Co.; Giorgio Vittorio Scagliotti received honoraria, research funding and had roles as consultant or advisor for Roche, Pfizer, AstraZeneca, Lilly Pharma and MSD; Francesco Perrone received honoraria for regulatory or educational advisory board from AstraZeneca, Bayer, Celgene, Incyte, Janssen-Cilag, Pierre Fabre, Sandoz and received research funding from AstraZeneca, Baxter, Bayer, Incyte, Merck, Pfizer, Roche and Tesaro; Massimo Di Maio received honoraria and had roles as consultant or advisor for AstraZeneca, Lilly Pharma, Bristol Myers Squibb, MSD and Janssen. All remaining authors declared no conflicts of interest.

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