Optimizing psychosocial support and symptom management for patients with advanced cancer

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CHAPTER 6

Does severe toxicity affect quality of life in patients with metastatic colorectal cancer during systemic palliative treatment? A systematic review

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Abstract

Background

New palliative systemic treatment regimens in patients with metastatic colorectal cancer (mCRC) have significantly improved overall survival and prognosis. These treatment regimens are often accompanied by increased toxicity, which may impair patients' quality of life (QOL). We systematically reviewed whether severe toxicity affects global QOL in patients with mCRC receiving palliative systemic treatment in recent published randomized controlled trials (RCTs).

Materials and Methods

Phase III RCTs comparing palliative systemic treatments in patients with mCRC and published between 2004 and 2016 were considered. Studies were evaluated on the basis of global QOL scores, toxicity during treatment (assessed by scoring relevant adverse events) and primary outcomes.

Results

A total of 30 studies were identified in which 19863 patients were included. In 25 out of these 30 trials (83%), no difference in global QOL between treatment arms was observed. In contrast, 22 out of 30 trials (73%) showed increased toxicity during treatment in the experimental arm as compared to the control arm. In 19 out of 22 trials with higher toxicity (86%) global QOL outcomes remained unaffected or improved. In ten out of eleven studies with a better primary outcome, no improvement in global QOL was seen.

Conclusion

Global QOL of patients with mCRC included in phase III RCTs evaluating palliative systemic treatment did not differ across treatment arms despite consistently higher toxicity during treatment of the experimental compared to the standard treatment arms. Based on these findings we conclude that the use of global QOL for comparing treatment arms in RCTs for patients with mCRC does not provide information of clinical relevance. Further consideration of how to better assess the net effect of new agents on patients' QOL is urgently needed.

Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers and causes of cancer-related mortality in developed countries, with over 1.3 million new cancer cases and 694,000 estimated deaths worldwide in 2012[1,2]. Approximately 40-50% of patients develop metastatic disease. New cytotoxic and biologic agents have emerged for the treatment of unresectable metastatic colorectal cancer (mCRC) with their potential efficacy being evaluated in randomized controlled trials (RCTs)[3]. The availability of new treatment regimens has increased median overall survival and prognosis of patients with mCRC. Life expectancy of patients with metastatic disease has raised from a mean of 6 months without therapy up to about 30 months with currently available agents[4]. As patients' life expectancy is increased, they suffer more from the toxicities of systemic therapies and live longer with the possible negative consequences of their disease and treatment. Therefore, maintaining patients' quality of life (QOL) has become an important objective and patient-reported QOL is increasingly reported as an endpoint in oncological RCTs[5]. It is assumed that toxicity during treatment affects QOL, with more toxicity leading to worse QOL[6]. With this assumption in mind, QOL outcomes are used in clinical decision making as they are supposed to inform about possible risks and benefits of new agents. Most available QOL questionnaires comprise several functional and symptom scales and one or more items on global QOL[7]. Interestingly, reports on oncological RCTs frequently refer exclusively to global QOL, ignoring the domain scores. In published RCTs, an improvement in primary endpoint is generally accompanied by increased toxicity during treatment. One would expect this increase in toxicity to coincide with decreased global QOL. However, often it is concluded that toxicity of the experimental arm was worse, but apparently tolerable as it did not affect the global QOL scores[8].

A systematic evaluation of this apparent contradiction between treatment-related toxicity and global QOL outcomes is not available. Our aim was to systematically review how severe toxicity during palliative systemic treatment in patients with mCRC relates to global QOL in order to evaluate the validity of the global QOL score for comparing treatments arms in phase III RCTs.

Methods

Literature selection

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-

Analysis (PRISMA)-statement (www.prisma-statement.org). Embase.com, Wiley/Cochrane Library and PubMed were searched from inception (by CS and JCFK) up to 10 February 2016. The following terms were used (including synonyms and closely related words) as index terms or free-text words: 'colon' or 'colorectal' and 'metastases' and 'RCT'. The full search strategies for all the databases can be found in Supplemental Table S1. Duplicate articles were excluded. In addition, a cross-check in two clinical trial registries, Clinicaltrials.gov and the ISRCTN registry, was performed to ensure completeness of study identification[9].

Study selection

A study was included if (a) it concerned a phase III RCT in patients with unresectable mCRC; (b) it was published in English between January 2004 and February 2016; (c) a new regimen of palliative systemic therapy was compared to the best available standard of care; and (d) it included both QOL and toxicity outcomes. Only full text articles were included. Studies comparing regimens with possible curative intent (e.g. (neo)adjuvant systemic therapies instead of palliative systemic therapies), studies reporting no original data, and studies that did not compare QOL outcomes between treatment arms were excluded. References cited in the included articles were screened to identify additional relevant articles.

The titles and abstracts retrieved by electronic searches were exported to a reference management database to remove duplicates. In the first selection stage, titles and abstracts of identified articles were screened by two reviewers (AB and CS). When available, the full texts were obtained for all potentially eligible articles for further examination.

Data extraction

Two reviewers (AB and CS) independently extracted data from the included trials using an extraction form that was developed based on recommendations from the Cochrane Handbook for Systematic Reviews of Interventions[10]. The data extraction form was piloted before use. The following data were extracted from each paper: study design, study characteristics (number of participants, treatment arm, treatment line, risk of bias), global QOL, adverse events (AEs), primary outcome, progression-free (PFS), and overall trial outcome. Disagreements between the two reviewers were resolved by discussion and consensus and if necessary, a third reviewer (IK).

Methods of evaluation

To evaluate how toxicity and QOL were related to each other in each trial, we identified the longitudinal results regarding AEs and global QOL. For each trial we labeled the results as better (+), neutral (=), or worse (-) in the experimental arm compared with the control arm. For global QOL outcomes, the (lack of) a statistically significant difference was used to rate the study as better, neutral, or worse. In order to objectively classify toxicity outcomes between the experimental and control arms, we scored any non-hematologic adverse grade 3 or grade 4 event that had a difference of at least 5 percent points in occurrence between treatment arms. When the total number of these AEs between the treatment arms in a trial differed by two or more, this was considered as a relevant difference in treatment-related toxicity (better or worse). If the number of the AEs with a difference of at least 5 percent points between the treatment arms was ≤ 1, this was considered as a neutral outcome regarding toxicity during treatment. We undertook several actions to maximize the objectivity and replicability of this approach: (i) we piloted our model in five randomly selected trials before use; (ii) AEs were categorized independently by two reviewers; (iii) the conclusions of the trial authors concerning toxicity were taken into account; (iv) inconsistencies between the reviewers or the authors were resolved by an expert panel.

Other outcomes such as primary outcome, PFS, and overall trial outcome were evaluated in a similar manner as described for the QOL outcomes, coding these outcomes as better, neutral, or worse between treatment arms, based on the statistically tested results from each trial.

The quality of patient-reported outcome (PRO) reporting was evaluated in all RCTs by two reviewers (AB and CS) according to a PROs reporting score based on the CONSORT Patient-Reported Outcome Extension[11]. The score was based on 6 items derived from 6 recommendations. Each item was scored 1 if it was adequately reported; or 0 if it was not clearly reported, or not reported at all.

The quality of all included trials was evaluated using The Cochrane Collaboration's tool in the Cochrane Handbook for Systematic Review of Interventions[10].

Statistical analysis

Descriptive analyses were conducted to evaluate outcomes and demographic characteristics. Except for the PRO reporting score all variables were tabulated as proportions and frequency distributions. For the statistical comparison of the PRO reporting score and QOL outcomes a one-way ANOVA test was performed.

Results

Literature search results

The literature search yielded 11480 individual records. Examination of titles and abstracts resulted in 64 full text articles potentially eligible for inclusion. After reading the full text, 34 studies were excluded, resulting in a total of 30 eligible randomized studies meeting the inclusion criteria for this systematic review (Figure 1).

Overview of the studies

An overview of all 30 studies[12-41] is provided in Table 1. A total of 19863 patients were analyzed, with an average age of 63 years. The majority of patients were treated in a first line setting (63.3%) and in more than three-quarter of the studies an open-label design was conducted. Patients had no prior treatment of metastatic disease in nineteen studies, the eleven remaining studies comprising patients who already received at least one previous treatment line. The average median duration of treatment in all studies was 4.5 months (SD 2.2 months). Most studies (25/30) had a superiority design. The remaining five were non-inferiority studies. Six trials did not have an active control arm, but were placebo controlled or consisted of best supportive care as the best available standard of care[13,21,25,28,35,41]. Primary outcome was overall survival (OS) in thirteen studies, progression-free survival (PFS) in twelve studies and response rate (RR) in five studies. A large variety of tools to assess QOL was observed (Table 1), but in 23 studies the EORTC QLQ-C30 questionnaire was used[42]. On average global QOL data were available for 65% of patients. In 5 studies[21,22,28,32,41] completion rates of QOL questionnaires were not provided. The mean PRO reporting score for all items was 3.1 on the 6-point scale (range: 0-6, 95% CI of the mean 2.6-3.6) including four studies with a score of ≤ 1 and four studies with a score of ≥ 5. In general, the quality of the studies was high with the exception of the frequent risk of performance and detection bias due to open-label designs. Detailed information regarding study quality can be found in the Supplemental Figure S2.

Global QOL and toxicity during treatment

Out of 30 studies, 25 (83.3%) showed no difference in global QOL outcomes between the treatment arms (Table 2 / Figure 2). Two studies[25,27] showed a significantly better global QOL in the experimental arm, while

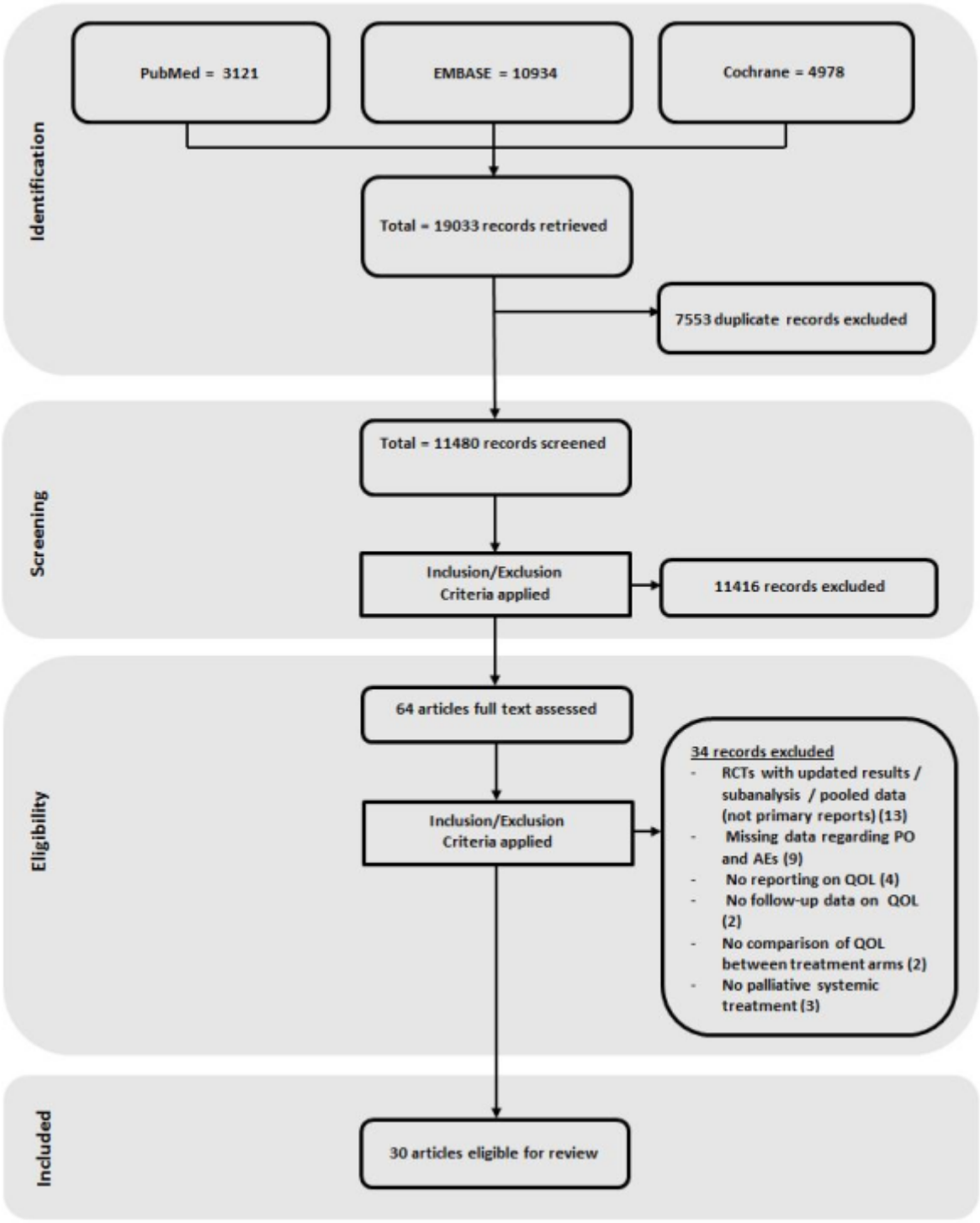

Figure 1 Flow diagram illustrating flow of studies identified from the search strategy

three studies[31,36,39] showed worse global QOL. Twenty-two out of 30 studies (73.4%) showed worse AE outcomes in the experimental arm compared to the control arms (Table 2). Differences in incidence of grade 3/4 AEs between treatment arms were most commonly seen for diarrhea, followed by skin toxicity, lethargy/fatigue, hypertension, and hand-foot syndrome.

Table 1 Overview of included studies									
Study	Treatment arms	Study design	Patients no.	Treatment line	PO measurement	QOL measurement	Result PO	AE	QOL
Adams, 2011[14] MRC COIN	Intermittent Oxaliplatin + Fluoropyrimidine vs Continuous Oxaliplatin + Fluoropyrimidine	Open-label	1630	1st	OS	EORTC QLQ-C30, 5 additional questions	-	=	=
Comella, 2009[15]	OXXEL vs OXAFAFU	Open-label	322	1st	RR	EORTC QLQ-C30	=	=	=
Douillard, 2010[16] PRIME	Panitumumab + FOLFOX4 vs FOLFOX4	Open-label	656	1st	PFS	EQ-5D HIS, EQ-5D VAS	+	-	=
Ducreux, 2011[17]	XELOX vs FOLFOX-6	Open-label	306	1st	RR	EORTC QLQ-C30, FACIT-CCSQ	=	=	=
Ducreux, 2011[18] FFCD 2000-05	LV5FU2 » FOLFOX6 » FOLFIRI vs FOLFOX6 » FOLFIRI	Open-label	410	1st	PFS	EORTC QLQ-C30	=	-	=
Falcone, 2007[19]	FOLFOXIRI vs FOLFORI	Open-label	244	1st	RR	EORTC QLQ-C30	+	-	=
Grothey, 2013[20], CORRECT	Regorafenib vs Placebo	Blinded	760	≥2nd	OS	EORTC QLQ-C30, EQ-5D, VAS	+	-	=
Hegewisch-Becker, 2015[21], AIO 0207	Fluoropyrimidine + Bevacizumab vs Bevacizumab vs No treatment (after FOLFOX-B or CAPOXB)	Open-label	472	1st	PFS	EORTC QLQ-C30	=	=	=
Hong, 2012[13]	SOX vs CAPOX	Open-label	340	1st	PFS	EORTC QLQ-C30	=	-	=
Hospers, 2006[22]	Biweekly 5-FU/LV vs Monthly 5-FU/LV/Oxaliplatin	Open-label	302	1st	RR	VASQOL	+	+	=
Hurwitz, 2004[23]	IFL + Bevacizumab vs IFL + Placebo	Blinded	813	1st	OS	FACT-C, TOI-C, CCS	+	-	=
Jonker, 2007[24]	Cetuximab vs BSC	Open-label	572	≥2nd	OS	EORTC QLQ-C30	+	-	+
Koopman, 2007[25], CAIRO	Capecitabine » Irinotecan » CAPOX vs CAPIRI » CAPOX	Open-label	820	1st	OS	EORTC QLQ-C30	=	=	=
Lal, 2004[26]	Defined-duration Irinotecan vs Continuous Irinotecan	Open-label	55	≥2nd	PFS	EORTC QLQ-C30	=	-	=
Li, 2015[27], CONCUR	Regorafenib vs Placebo	Blinded	204	≥3rd	OS	EORTC QLQ-C30, EQ-5D, VAS	+	-	=
Price, 2004[28]	PVI 5-FU/Mitomycin-C vs CTI 5-FU/Mitomycin-C	Open-label	320	1st	RR	EORTC QLQ-C30	=	-	=
Price, 2014[29], ASPECCT	Panitumumab vs Cetuximab	Open-label	1010	≥2nd	OS	EQ-5D, FCSI, EQ VAS	=	=	=
Rao, 2004[12]	R115777 vs Placebo	Blinded	368	≥3rd	OS	EORTC QLQ-C30	=	-	=
Schmoll, 2012[30], HORIZON III	Cediranib + mFOLFOX6 vs Bevacizumab + mFOLFOX6	Blinded	1422	1st	PFS	FACT-C	=	-	-
Seymour, 2007[31],MRC FOCUS	FU » Irinotecan vs FU » IrFu or OxFU vs IrFu or OxFU	Open-label	2135	1st	OS	EORTC QLQ-C30	=	-	=
Table 1 Overview of included studies				*continued*					

Seymour, 2011[32], MRC FOCUS2	FU vs OxFU + Cap vs CapOx	Open-label	459	1st	PFS / QOL	EORTC QLQ-C30	=	-	=
Seymour, 2013[33], PICCOLO	Panitumumab + Irinotecan vs Panitumumab	Open-label	460	≥2nd	OS	EORTC QLQ-C30	=	-	=
Simkens, 2015[34], CAIRO3	Maintenance CAP-B vs Observation	Open-label	558	1st	PFS	EORTC, QLQ-C30	+	-	=
Siu, 2013[35], AGITG CO.20 Trial	Cetuximab + Brivanib Alaninate vs Cetuximab + Placebo	Blinded	750	≥2nd	OS	EORTC QLQ-C30	=	-	-
Sobrero, 2008[36], EPIC	Cetuximab + Irinotecan vs Irinotecan	Open-label	1298	2nd	OS	EORTC QLQ-C30	=	-	+
Tabernero, 2015[37], RAISE	Ramucirumab + FOLFIRI vs Placebo + FOLFIRI	Blinded	1072	2nd	OS	EORTC, QLQ-C30 EQ-5D	+	-	=
Tebbutt, 2010[11], MAX	Capecitabine vs Capecitabine + Bevacizumab vs Capecitabine + Mitomycin	Open-label	471	1st	PFS	EQ-5D, UBQ-C, CAQ	+	-	=
Tol, 2009[38]	CAPOX-B vs CAPOX-B + Cetuximab	Open-label	755	1st	PFS	EORTC QLQ-C30	-	-	-
Tournigand, 2015[39], OPTIMOX3	Bevacizumab vs Bevacizumab + Erlotinib	Open-label	452	1st	PFS	EQ-5D	=	-	=
Van Cutsem, 2007[40]	Panitumumab vs BSC	Open-label	463	≥3rd	PFS	EQ-5D VAS, NCCN FACT, EORTC QLQ-C30 subscales, dermatology question	+	=	=

Abbreviations: PO = Primary outcome; AE = Adverse events; QOL = Quality of life; » = Followed by; OS = Overall survival; RR = Response rate; PFS = Progression-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ5D = EuroQol five dimensions questionnaire; VAS = Visual Analogue Scale; FACIT-CCSQ = FACIT Chemotherapy convenience and satisfaction questionnaire; TOI-C = Trial Outcome Index-Colorectal; CCS = Colorectal Cancer Subscale (part of FACT-C); UBQ-C = Utility-Based Quality of Life Questionnaire - Cancer ; CAQ = Chemotherapy Acceptability Questionnaire
+ Better; - Worse; = Neutral.

Table 2 QOL and toxicity during treatment in identified studies

n=30		Adverse Events No. (%) of studies			
		Better	Neutral	Worse	Total
Quality of Life No. (%) of studies	Better	0 (0)	0 (0	2 (6.7)	2 (6.7)
	Neutral	1 (3.3)	7 (23.3)	17 (56.7)	25 (83.4)
	Worse	0 (0)	0 (0)	3 (10)	3 (10)
	Total	1 (3.3)	7 (23.3)	22 (73.4)	30 (100)

Abbreviations: QOL = Quality of life

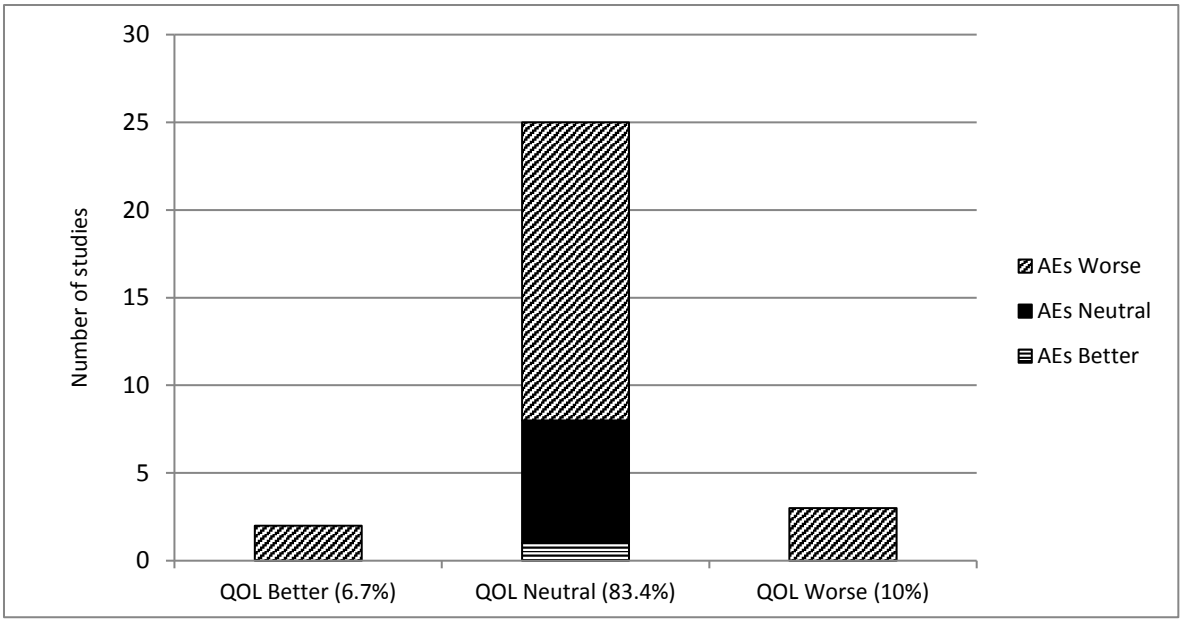

Figure 2 Global QOL and toxicity during treatment in identified studies

N = 30; QOL = Quality of life; AEs = Adverse events

Total number and percentage of studies resulting in a better, neutral or worse global QOL result, respectively, are displayed on the X-axis. The associated result of studies in AEs; better, neutral or worse, respectively, are grouped on the Y-axis.

Interestingly, the majority of studies with more AEs in the experimental arm were accompanied by a neutral global QOL outcome (17 out of 22 studies). In the other studies with more toxicity, global QOL was better in two[25,27] and worse in the remaining three studies[31,36,39]. The six trials without an active control arm showed a similar pattern. Five out of six studies (83.3%) showed worse AE outcomes in the experimental arm, the same amount of studies resulted in neutral QOL outcomes between compared arms.

Primary outcome, global QOL and toxicity during treatment

Eleven (36.7%) studies reported a better result in primary outcome for the intention to treat population in the experimental treatment arm. In ten (90.9%) of these studies, this was accompanied by global QOL outcomes that did not differ between treatment arms (Figure 3A / Supplemental Table S3).

Seventeen (56.7%) studies did not show a statistically significant benefit in primary outcome for the intervention group (the majority of these (=13) were aimed to demonstrate superiority). In fourteen of these studies, global QOL was neutral. In two studies[15,39], a worse primary outcome was observed, while QOL was neutral or worse. The combination of a better primary outcome and acceptable toxicity profile (better or neutral outcome in AEs) as seen in two studies[23,41], did not result in better global QOL (Figure 3B /

Supplemental Table S4). Five out of six studies (83.3%) without an active control arm reported better results in primary outcome in the experimental arm; the same amount of studies resulted in neutral QOL outcomes.

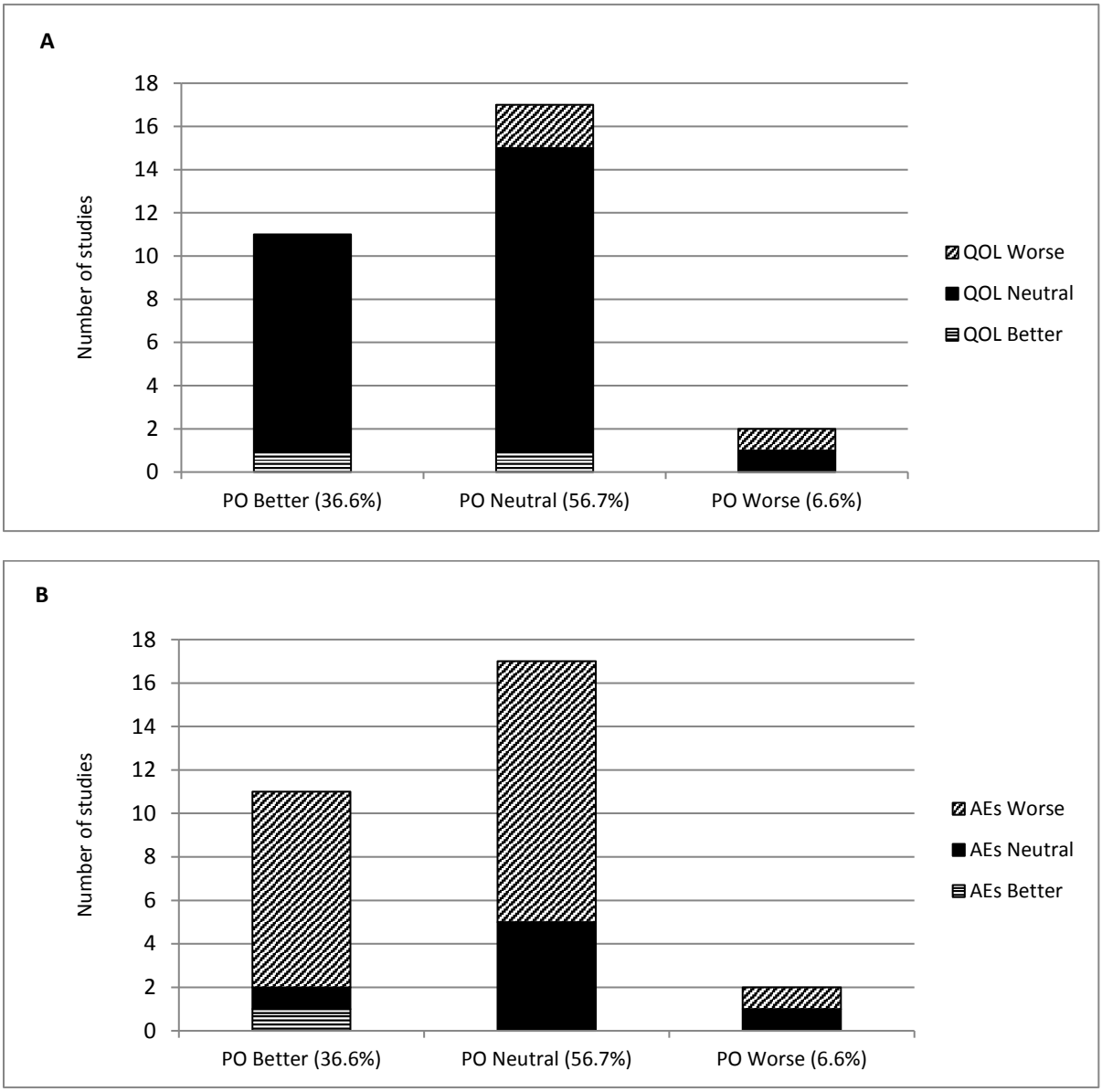

Figure 3A Primary Outcome (PO) and Global QOL in identified studies
B Primary Outcome (PO) and AEs in identified studies

N = 30; PO = Primary outcome; QOL = Quality of life; AEs = Adverse events

Total number and percentage of studies resulting in a better, neutral or worse PO result, respectively, are displayed on the X-axis. The associated result of studies in global QOL; better, neutral or worse, respectively, are grouped on the Y-axis in Figure 3A. The associated result of studies in AEs; better, neutral or worse, respectively, are grouped on the Y-axis in Figure 3B.

Progression-free Survival, global QOL and toxicity during treatment

Fourteen studies showed a statistically significant increase in PFS of the experimental treatment arm compared

to the control arm while PFS was significantly shorter in one study[39]. Irrespective of PFS outcome, most studies revealed no differences in reported global QOL between treatment arms (Figure 4A / Supplemental Table S5). Two out of fourteen studies with a better PFS were associated with better global QOL in the experimental arm regardless of the increased AEs found in both of these studies[25,27].

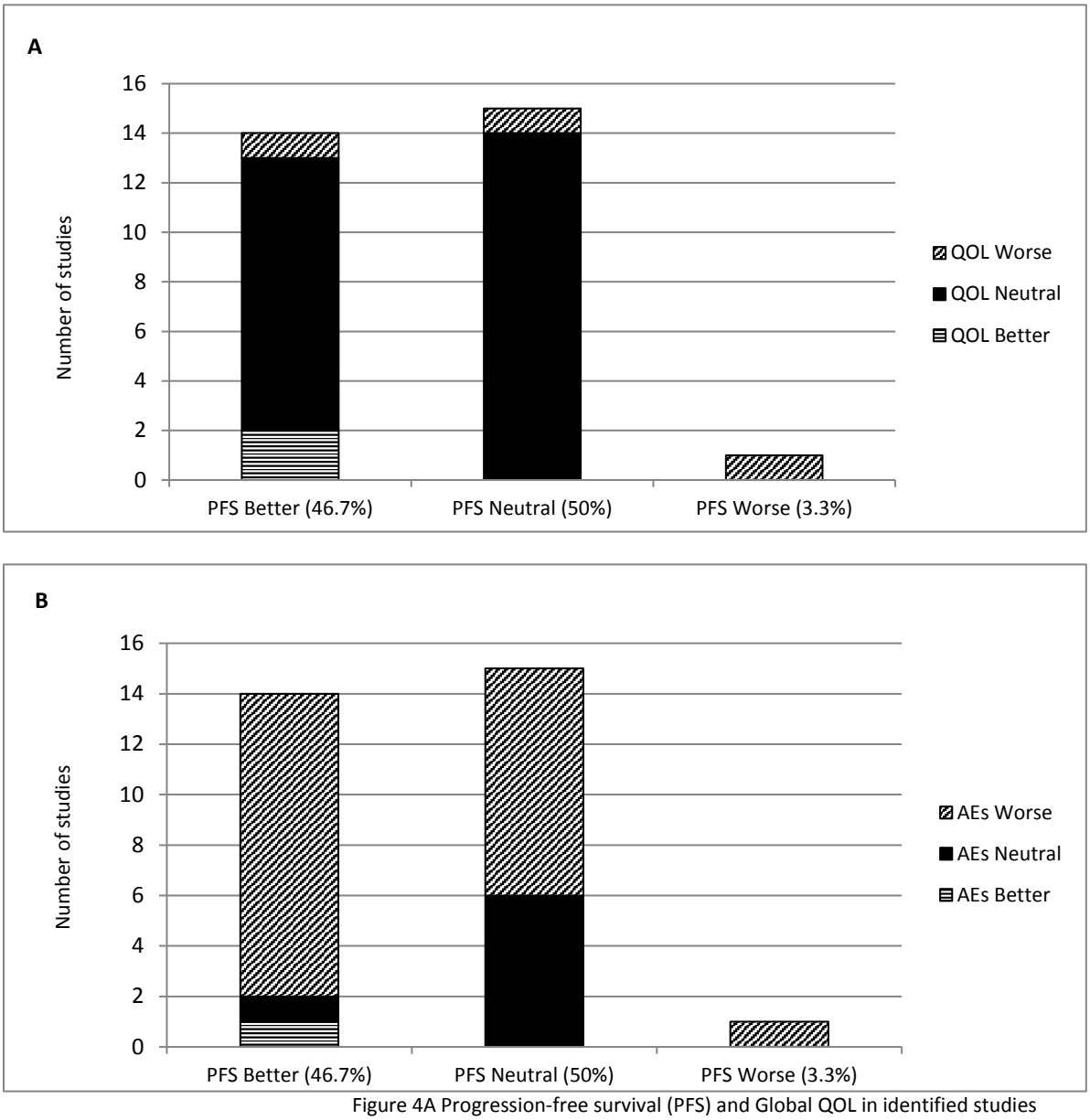

Figure 4A Progression-free survival (PFS) and Global QOL in identified studies
B Progression-free survival (PFS) and AEs in identified studies

N = 30; PFS = Progression-free survival; QOL = Quality of life; AEs = Adverse events

Total number and percentage of studies resulting in a better, neutral or worse PFS result, respectively, are displayed on the X-axis. The associated result of studies in global QOL; better, neutral or worse, respectively, are grouped on the Y-axis in Figure 4A. The associated result of studies in AEs; better, neutral or worse, respectively, are grouped on the Y-axis in Figure 4B.

In twelve out of the fourteen experimental treatments (85.7%) resulting in a longer PFS clinical benefit was associated with more toxicity. The combination of a longer PFS and acceptable toxicity profile (better or neutral outcome in AEs), as seen in two studies[23,41], did not result in better global QOL (Figure 4B / Supplemental Table S6).

Discussion

We reviewed whether severe toxicity during treatment in 30 phase III RCTs comparing palliative systemic treatment regimens in patients with mCRC affects global QOL. We found that the great majority of trials did not demonstrate differences in global QOL between treatment arms, while more than two-thirds of trials showed higher toxicity in the experimental treatment arm as compared to the control arm. In most trials with higher toxicity, global QOL outcomes did not differ between treatment arms. In addition, global QOL did not seem to be affected by differential OS. This was also observed in the majority of the RCTs in which the experimental treatment arm resulted in a longer PFS. In these trials, global QOL was also unaffected regardless of toxicity during treatment. Similar observations were also made in trials without an active control arm.

The results in this review lead to one key question: how valid is the measurement of global QOL for use in RCTs? Our findings suggest that toxicity and global QOL as currently assessed are not related to each other, as is often assumed. We believe that global QOL is not an adequate measure for comparing the impact of toxicity between treatment arms. This was also suggested in a recent cross-sectional study[43], which compared QOL measurements between a large group of patients with cancer and a sample of the general population. The results revealed that global QOL in the cancer population was nearly equal to that of the general population. In contrast to global QOL, both functional scales and symptom scores did show markedly worse QOL. This suggests that functional scales and symptom scores are more informative on how disease symptoms or treatment side effects affect QOL. However, most studies included in this review reported only on global QOL, making it impossible to consider results from specific QOL domain scores. More specific assessments of QOL that target the expected toxicity profiles and impairments in functioning could be a promising approach in the evaluation of new palliative systemic treatment regimens in patients with mCRC.

Several other factors could have contributed to the discrepancy between higher toxicity and the absence of

differences in global QOL outcomes. First, the lack of deterioration of patients' global QOL, despite increased toxicity could be due to patients' psychological adaptation to their changing health status over time, also known as response shift. Even though oncological treatment may induce toxicity, patients may adapt to this increased symptom level by changing their internal standard (recalibration) and values regarding relative importance of different domains of QOL (reprioritization)[44,45]. Second, many patients receiving palliative systemic treatment inaccurately believe that it may cure them, as shown in studies with patients with advanced colorectal cancer[46]. The reassuring psychological effect of 'being treated' could counteract the effects of toxicity and disease progression. Moreover, some patients may have the erroneous belief that treatment induced toxicity is a sign of treatment efficacy. To eliminate the patient perception effect, only blinded randomized trials would truly be appropriate for analysis. Unfortunately, few cancer therapies can be tested in a blinded fashion, namely the ones without major subjective toxicities (e.g. VEGF inhibitors).Third, another possible reason for the apparent missing relation between toxicity and QOL could be the quality of the toxicity information provided in RCTs. Inconsistencies within and between clinician and patient reporting of toxicity have been described previously, and a general lack of reporting standards for AEs in RCTs regarding duration, time of onset and occurrence of grade 1 and 2 AEs has been highlighted[47-51]. Furthermore, it is important to acknowledge that the cumulative effect of AEs may differ from the sum of the individual AEs. The Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted throughout oncology as the standard classification and severity grading scale for AEs in RCTs. However, both this clinical version and the recently validated PRO version of the CTCAE[50,52] do not provide an overview of cumulative toxicity. For instance, a patient might feel more functionally impaired by suffering from multiple, long-standing grade 2 AEs than from one grade 3 or 4 AE. Fourth, earlier studies indicated that a large degree of AEs might be needed for patients to experience a deterioration of their QOL[53]. Therefore, the preselection of clinically manageable and tolerable experimental arms based on prior phase I/II clinical trials may have contributed to the absence of differences in global QOL in the present review[54]. Lastly, a risk of reporting bias may exist, if trials resulting in negative QOL outcomes in the experimental treatment arm do not report their QOL data[5]. We might have missed those trials given the lack of QOL reporting.

To our knowledge, we are the first to systematically evaluate the question whether global QOL is related to the number and severity of AEs in longitudinal treatment studies. When interpreting the results of this review, it is

important to consider the following. First, the overall presentation and effort to interpret QOL data differed considerably between studies. Missing data were not addressed in 5 out of 30 trials, which together with a questionnaire completion compliance of 65% gives rise to a risk of bias. Synthesizing data from these studies into a single summary effect size, would have provided information about the magnitude of toxicity during treatment on global QOL. However, the heterogeneity of the study designs and incomplete presentation of the QOL data, hindered the performance of such a meta-analysis.

Further, our findings could have been different if other tumor types had been included in the review. Cancer type specific characteristics, e.g. average age of onset, course of disease, and associated physical impairment, may influence patients' experienced QOL. Results obtained from this review in patients with mCRC may therefore not equal those that would be found in another cancer type. However, in RCTs conducted in patients with various types of advanced cancer also no worsening of global QOL was observed during palliative systemic treatment[46,55,56]. Finally, toxicity related outcomes are hard to compare objectively between trials. Often, different reporting methods are used, e.g. displaying AE prevalence, significance, percentages. In many studies analyzed in this review, only the most frequently occurring toxicities were presented and in four of the 30 studies, only AEs with an incidence of ≥ 5% were reported[18,25,35,36]. Moreover, in two studies only AEs with an incidence of ≥10%[13,28] and in one study only AEs with an incidence of ≥ 20% were reported[31]. Because currently no golden standard exists for assessing toxicity during treatment, we took into account grade 3 or 4 non-hematologic AEs with a difference of ≥5 percent points in prevalence between treatment arms, from which clinically meaningful disadvantages for patients' QOL were expected.

In conclusion, our results indicate that observed changes in global QOL scores are generally small between treatment arms and seem unaffected by severity of AEs in RCTs conducted in patients with mCRC. These findings seriously question the validity of the frequently used global QOL measurements for comparing different treatment arms in RCTs. Future studies need to focus on developing improved measures of QOL that adequately reflect potential benefits and harms of new treatments. This is of imperative importance for QOL data to achieve their original potential in providing valuable information for better understanding the effectiveness of novel therapies.

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Supplemental table S1 Search strategies

Search strategy for Embase.com (10 February 2016)

/exp = EMtree keyword with explosion

/de = EMtree keyword without explosion

:ab,ti = words in title or abstract

NEXT/x = words next to each other, x places apart

No.	Query	Results
#6	#4 AND #5	**10,934**
#5	#1 AND #2 OR #3	**108,888**
#4	random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp	**1,880,790**
#3	mcrc*:ab,ti	**4,038**
#2	'metastasis'/exp OR metasta*:ab,ti OR advanced:ab,ti	**965,310**
#1	'colon tumor'/de OR 'colon cancer'/exp OR 'colorectal tumor'/exp OR 'large intestine tumor'/de OR 'appendix tumor'/exp OR 'cecum tumor'/exp OR 'large intestine cancer'/exp OR 'rectum tumor'/exp OR (carcinoma*:ab,ti OR neoplas*:ab,ti OR tumour*:ab,ti OR adenocar*:ab,ti OR adenoid*:ab,ti OR tumor*:ab,ti OR cancer*:ab,ti OR malignan*:ab,ti AND ('large intestine'/de OR 'cecum'/exp OR 'colon'/exp OR 'rectum'/exp OR colorectal*:ab,ti OR colon*:ab,ti OR rectal*:ab,ti OR appendi*:ab,ti OR cecum*:ab,ti OR coecum*:ab,ti OR caecum*:ab,ti OR cecal*:ab,ti OR coecal*:ab,ti OR caecal*:ab,ti OR sigmoid*:ab,ti))	**388,368**

Search strategy for Wiley/Cochrane Library (10 February 2016)

ti,ab,kw = words in title, abstract or keyword

No.	Query	Results
#1	((carcinoma* or neoplas* or tumour* or adenocar* or adenoid* or tumor* or cancer* or malignan*) and (colorectal* or colon* or rectal* or appendi* or cecum* or coecum* or caecum* or cecal* or coecal* or caecal* or sigmoid*)):ti,ab,kw (Word variations have been searched)	**14,224**
#2	metasta* or advanced:ti,ab,kw (Word variations have been searched)	**42,222**
#3	mcrc*:ti,ab,kw (Word variations have been searched)	**506**
#4	(#1 and #2) or #3	**4,978**

Number of items per database: CDSR: 55; DARE: 212; CENTRAL: 4541; Methods: 30; HTA: 62; EED: 78.

Search strategy for PubMed (10 February 2016)

[Mesh] = Medical subject headings (MeSH)

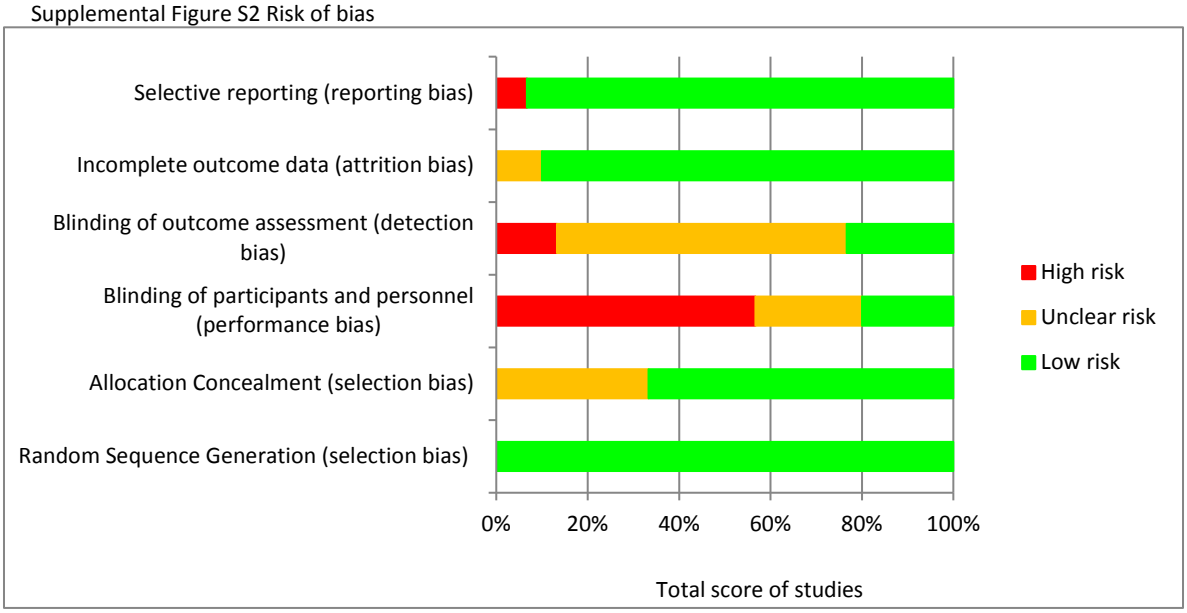
[Mesh:NoExp] = MeSH, without explosion

[tiab] = words in title OR abstract

No.	Query	Results
#6	(#5 AND #4)	**3,121**
#5	((#1 AND #2) OR #3)	**67,775**
#4	(random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR vs[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab])) OR randomized controlled trial[pt])	**664,073**
#3	mcrc*[tiab]	**1,533**
#2	"Neoplasm Metastasis"[Mesh] OR metasta*[tiab] OR advanced[tiab]	**691,609**

#1	"Colorectal Neoplasms"[Mesh] OR "Appendiceal Neoplasms"[Mesh] OR ((carcinoma*[tiab] OR neoplas*[tiab] OR tumour*[tiab] OR adenocar*[tiab] OR adenoid*[tiab] OR tumor*[tiab] OR cancer*[tiab] OR malignan*[tiab]) AND ("Intestine, Large"[Mesh:NoExp] OR "Cecum"[Mesh] OR "Colon"[Mesh] OR "Rectum"[Mesh] OR colorectal*[tiab] OR colon*[tiab] OR rectal*[tiab] OR appendi*[tiab] OR cecum*[tiab] OR coecum*[tiab] OR caecum*[tiab] OR cecal*[tiab] OR coecal*[tiab] OR caecal*[tiab] OR sigmoid*[tiab]))	**273,554**

Supplemental Figure S2 Risk of bias



Risk of bias assessment for the included studies using the Cochrane Collaboration tool. *N* = 30

Supplemental Table S3 Primary outcome and global QOL in identified studies

n=30		Primary Outcome No. (%) of studies			
		Better	Neutral	Worse	Total
Quality of Life No. (%) of studies	Better	1 (3.3)	1 (3.3)	0 (0)	2 (6.6)
	Neutral	10 (33.3)	14 (46.7)	1 (3.3)	25 (83.3)
	Worse	0 (0)	2 (6.7)	1 (3.3)	3 (10)
	Total	11 (36.6)	17 (56.7)	2 (6.6)	30 (100)

Supplemental Table S4 Primary outcome and toxicity during treatment in identified studies

n=30		Primary Outcome No. (%) of studies			
		Better	Neutral	Worse	Total
Adverse Events No. (%) of studies	Better	1 (3.3)	0 (0)	0 (0)	1 (3.3)
	Neutral	1 (3.3)	5 (16.7)	1 (3.3)	7 (23.3)
	Worse	9 (30)	12 (40)	1 (3.3)	22 (73.4)
	Total	11 (36.7)	17 (56.7)	2 (6.6)	30 (100)

Supplemental Table S5 Progression-free survival and global QOL in identified studies

n=30		Progression-Free Survival No. (%) of studies			
		Better	Neutral	Worse	Total
Quality of Life No. (%) of studies	Better	2 (6.7)	0 (0)	0 (0)	2 (6.7)
	Neutral	11 (36.7)	14 (46.7)	0 (0)	25 (83.4)
	Worse	1 (3.3)	1 (3.3)	1 (3.3)	3 (9.9)
	Total	14 (46.7)	15 (50)	1 (3.3)	30 (100)

Supplementary Table S6 Progression-free survival and toxicity during treatment in identified studies

n=30		Progression-Free Survival No. (%) of studies			
		Better	Neutral	Worse	Total
Adverse Events No. (%) of studies	Better	1 (3.3)	0 (0)	0 (0)	1 (3.3)
	Neutral	1 (3.3)	6 (20)	0 (0)	7 (23.7)
	Worse	12 (40)	9 (30)	1 (3.3)	22 (73.3)
	Total	14 (46.7)	15 (50)	1 (3.3)	30 (100)