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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
Figure 1.	7
RESULTS	9
Figure 2.	10
Figure 3.	12
Figure 4.	12
Figure 5.	12
Figure 6.	12
DISCUSSION	13
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	15
CHARACTERISTICS OF STUDIES	17
DATA AND ANALYSES	22
Analysis 1.1. Comparison 1 Overall survival, Outcome 1 Overall survival.	23
Analysis 2.1. Comparison 2 Toxicity, Outcome 1 Nausea and vomiting.	23
Analysis 2.2. Comparison 2 Toxicity, Outcome 2 Stomatitis.	23
Analysis 2.3. Comparison 2 Toxicity, Outcome 3 Diarrhoea.	24
ADDITIONAL TABLES	24
APPENDICES	25
CONTRIBUTIONS OF AUTHORS	31
DECLARATIONS OF INTEREST	31
SOURCES OF SUPPORT	31
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	31
INDEX TERMS	31

[Intervention Review]

Survival differences with immediate versus delayed chemotherapy for asymptomatic incurable metastatic colorectal cancer

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ABSTRACT

Background

For patients with asymptomatic, incurable, metastatic colorectal cancer, palliative, systemic treatment can be started immediately, or can be delayed until disease-related symptoms occur. How the potential survival benefit of starting palliative, systemic treatment immediately after diagnosis weighs up against the potential side effects is currently under debate, and was investigated in this review.

Objectives

To assess the effects of immediate versus delayed chemotherapy, with or without targeted therapy, on overall survival, toxicity, quality of life, progression-free survival, and compliance with chemotherapy for individuals with asymptomatic, metastatic, incurable colorectal cancer.

Search methods

We searched CENTRAL; 2018, Issue 8, MEDLINE Ovid, Embase Ovid, PsycINFO, the World Health Organization International Clinical Trials Registry Platform, and Clinicaltrials.gov, from inception to 23 August 2018. We did not apply limitations based on language or date of publication. We searched the reference lists of all included studies to identify trials that may not have been identified from the electronic searches.

Selection criteria

Randomised controlled trials evaluating immediate versus delayed chemotherapy in persons with asymptomatic, metastatic, incurable colorectal cancer.

Data collection and analysis

We applied standard methodological procedures, according to the recommendations of Cochrane and Cochrane Colorectal Cancer. Two review authors independently reviewed the studies identified by literature searches, selected relevant trials, extracted data, and assessed risk of bias of the included studies. We used the Cochrane tool to assess risk of bias, Review Manager 5 software for meta-analysis, GRADE methods to evaluate the quality of the evidence, and GRADEpro GDT software to develop a 'Summary of findings' table.

Main results

We included three randomised controlled trials (351 participants) investigating immediate versus delayed chemotherapy in people diagnosed with asymptomatic, metastatic, incurable colorectal cancer. Giving immediate versus delayed chemotherapy may make little

or no difference to overall survival (hazard ratio (HR) 1.17, 95% confidence interval (CI) 0.93 to 1.46; 3 studies, 351 persons; low-quality evidence). For toxicity, giving immediate versus delayed chemotherapy may make little or no difference to the risk of grade 3 or 4 nausea and vomiting (risk ratio (RR) 0.84, 95% CI 0.31 to 2.25; 2 studies, 140 persons; very low-quality evidence), stomatitis (RR 1.10, 95% CI 0.47 to 2.55; 2 studies, 140 persons; very low-quality evidence), or diarrhoea (RR 0.69, 95% CI 0.34 to 1.40; 2 studies, 140 persons, very low-quality evidence). We are uncertain whether delayed chemotherapy made a difference to quality of life (very low-quality evidence), progression-free survival (low-quality evidence), or compliance with chemotherapy (low-quality evidence), as we had insufficient data to pool for these outcomes.

Authors' conclusions

Based on a limited number of trials, very sparse data, and uncertainty of the evidence, this review was unable to establish whether there was a difference in overall survival or other clinically relevant outcomes, between immediate or delayed chemotherapy in persons with metastatic, incurable, colorectal cancer. The results should be interpreted with caution.

PLAIN LANGUAGE SUMMARY

Does giving chemotherapy straight away or waiting for symptoms prolong life for persons who have incurable colorectal cancer without symptoms?

Review question

We performed a systematic review to investigate whether people with incurable colorectal cancer, without symptoms, in which the cancer has spread to a different part of the body (metastasised), live longer and maintain quality of life, when you give chemotherapy straight away or wait until disease-related symptoms occur (delayed chemotherapy).

Background

One in five people with colorectal cancer cannot be cured. For them, the best treatment is palliative chemotherapy. Chemotherapy can cause side effects, such as diarrhoea or liver failure. If a person is diagnosed with incurable colorectal cancer, but has not developed symptoms yet, one possible intervention strategy could be to delay chemotherapy until symptom do appear, to avoid side effects and discomfort for the person receiving the treatment.

We wanted to explore whether delaying chemotherapy treatment would have an effect on survival and other relevant outcomes, such as toxicity, and quality of life, compared to initiating chemotherapy straight away.

Study characteristics

We included three randomised clinical trials. In these trials, people with metastatic and incurable colorectal cancer, without symptoms, received chemotherapy straight away (standard group) or their chemotherapy was delayed (intervention group). There were a total of 176 participants in the standard groups and 175 in the intervention groups.

Key results

The available data allowed us to complete analyses for overall survival and toxicities. Participants with metastatic, incurable colorectal cancer without symptoms, who received chemotherapy straight away, did not live longer than those whose chemotherapy was delayed until symptoms appeared. For toxicities measures, our findings were inconclusive due to sparse data from only two trials and few participants. There were insufficient data to compare other outcomes of interest, such as quality of life, progression-free survival (the length of time during and after treatment that a person lives with the disease, but it does not get worse), and compliance with chemotherapy (whether a participant was able to complete the chemotherapy regimen).

Quality of the evidence

Based on very sparse data and uncertainty of the evidence, we were unable to establish whether there was a difference in overall survival and other important outcomes in people with metastatic, incurable, colorectal cancer, who received chemotherapy either straight away or waited until after symptoms had appeared.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Delayed chemotherapy compared with immediate chemotherapy for patients with asymptomatic, incurable, metastatic colorectal cancer

Delayed chemotherapy compared with immediate chemotherapy

Patient or population: patients with asymptomatic, incurable, metastatic colorectal cancer

Setting: hospital

Intervention: delayed chemotherapy

Comparison: immediate chemotherapy

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI) or comments		Nº of Participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 1.17 (0.93 to 1.46)	Risk with immediate chemotherapy 705 per 1000	Risk with delayed chemotherapy 55 more per 1000 (22 fewer to 127 more)	351 (3)	Low ^a ⊕⊕○○	
Toxicity – nausea and vomiting	RR 0.84 (0.31 to 2.25)	Risk with immediate chemotherapy 108 per 1000	Risk with delayed chemotherapy 17 fewer per 1000 (75 fewer to 136 more)	140 (2)	Very low ^{a, b} ⊕○○○	
Toxicity – stomatitis	RR 1.10 (0.47 to 2.55)	Risk with immediate chemotherapy 120 per 1000	Risk with delayed chemotherapy 12 more per 1000 (64 fewer to 187 more)	140 (2)	Very low ^{a, b} ⊕○○○	
Toxicity – diarrhoea	RR 0.69 (0.34 to 1.40)	Risk with immediate chemotherapy 229 per 1000	Risk with delayed chemotherapy 71 fewer per 1000 (151 fewer to 92 more)	140 (2)	Very low ^{a, b} ⊕○○○	
Quality of life	-	Two studies reported data about quality of life and showed no clear difference between the study arms		161 (2)	Very low ^{a, c} ⊕○○○	
Progression-free survival	-	Pooled data of two studies: HR 1.01 (95% CI 0.72 to 1.41)		351 (3)	Low ^a ⊕⊕○○	

		Third study: immediate chemotherapy group median = 10 months; delayed chemotherapy group median = 2 months		
Compliance to chemotherapy	-	In the pooled data of two studies, 70% of those in the delayed chemotherapy group received treatment, compared to 57% in the third study	174 (3)	Low ^a ⊕⊕○○

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the immediate chemotherapy (comparison) group and the **relative effect** of delayed chemotherapy (intervention; (and its 95% CI)).

CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^a Downgraded two levels because of very serious concerns regarding imprecision, due to very limited number of participants

^b Downgraded one level because of inconsistency, due to unexplained heterogeneity and lack of blinding

^c Downgraded one level due to indirect outcomes

BACKGROUND

Description of the condition

Colorectal cancer is the third most commonly diagnosed cancer worldwide, with a total of 1.36 million new cases in 2012 (Ferlay 2015). Approximately 20% of all newly diagnosed individuals with colorectal cancer have metastatic (stage IV) disease at initial presentation (Siegel 2015), and approximately 20% of all persons with stage I to III colorectal cancer will develop recurrent disease (Elferink 2015). The only option to cure metastatic colorectal cancer is to resect the primary tumour and all metastases. Although an increasing proportion can be treated with curative intent, the majority of people with metastatic colorectal cancer are diagnosed with an incurable disease (Brouquet 2011; Kopetz 2009; Pfannschmidt 2007; Tampellini 2012; Yan 2006). For these, palliative systemic treatment is the only option, with or without palliative resection of the primary tumour.

Survival for individuals with incurable metastatic colorectal cancer has improved significantly over recent decades. Median overall survival for those who only receive the 'best supportive care' is approximately five to six months (Scheithauer 1993). With the introduction of fluoropyrimidines, the median overall survival has increased to 11 to 12 months, and up to almost two years with combination chemotherapy (Grothey 2004; Khattak 2012; Tournigand 2004). A population-based study in the Netherlands showed that only about 55% of those with metastatic colorectal cancer, diagnosed between 2005 and 2007, were treated with chemotherapy (van der Pool 2012). Outcomes for individuals with incurable metastatic colorectal cancer have improved even further with the combination of fluoropyrimidine-based chemotherapy and targeted therapy. Targeted therapy can be either humanised monoclonal antibodies against vascular endothelial growth factor (VEGF), such as bevacizumab, or anti-epidermal growth factor receptor (EGFR), such as cetuximab or panitumumab (Douillard 2010; Hurwitz 2004; Kabbinavar 2005; Saltz 2008; Tebbutt 2010; Van Cutsem 2011).

Not every person diagnosed with colorectal cancer has disease-related symptoms at the time of diagnosis of distant metastasis. In the study by Majumdar 1999, 17% of all colorectal cancer cases showed no disease-related symptoms. Asymptomatic colorectal cancer is characterised by the absence of frequently reported disease-related symptoms, such as pain requiring regular narcotic analgesics, weight loss over 5 kg, persistent nausea requiring medication, deterioration in the performance of activities of daily living (measured by the Eastern Cooperative Oncology Group Performance Status (ECOG; Oken 1982), obstructive bowel symptoms, persistent fever related to metastatic disease, and other symptoms, which in the opinion of the clinician, are due to progressive metastatic cancer. Metastatic disease could be diagnosed incidentally or during routine follow-up visits after a previous diagnosis of localised colon or rectal cancer. However, the percentage of people with asymptomatic, incurable, metastatic colorectal cancer has, to our knowledge, never been described in detail. If it turns out that people with asymptomatic metastatic colorectal cancer are incurable, the start of palliative, systemic treatment could be initiated at the time of a diagnosis of distant metastasis, or could be delayed until disease-related symptoms occur. Of further interest, how the potential survival benefit of starting palliative, systemic treatment immediately after a diagnosis of distant metastasis weighs up against the potential side

effects. This is currently under debate, and is investigated in this review.

Description of the intervention

The intervention was systemic anti-cancer therapy, comprised of chemotherapy, with or without targeted therapies or novel agents. Systematic anti-cancer therapy should kill cancer cells, or inhibit their division, resulting in a decrease of the metastatic disease. Two treatment strategies can be considered: chemotherapy started immediately after a diagnosis of distant metastasis, or delayed until disease-related symptoms occur.

How the intervention might work

Starting palliative chemotherapy immediately, in people diagnosed with asymptomatic incurable metastatic colorectal cancer, might result in a survival benefit, due to the earlier initiation of treatment, compared with delaying chemotherapy until disease-related symptoms occur. This might be a result of potentially maintaining liver function, and fewer infections. However, adverse events caused by the chemotherapy can deteriorate quality of life in people who do not yet suffer from disease symptoms. Therefore, a more favourable strategy may be to delay chemotherapy until symptoms occur.

Why it is important to do this review

In people with metastatic colorectal cancer who cannot be cured, treatment should focus on symptom control and maintenance of quality of life without compromising survival. When to commence chemotherapy during the disease course in people with asymptomatic incurable metastatic colorectal cancer is yet to be determined (Ackland 2005; Nordic Gastrointestinal Tumor Therapy Group 1992; Pyrhonen 1992). Since people with incurable metastatic colorectal cancer have a limited life expectancy, it is important to determine the best time to start chemotherapy, in order to optimise the benefits of chemotherapy relative to the side effects (Grothey 2004; Khattak 2012; Tournigand 2004; van der Pool 2012).

OBJECTIVES

To assess the effects of immediate versus delayed chemotherapy, with or without targeted therapy, on overall survival, toxicity, quality of life, progression-free survival, and compliance with chemotherapy for individuals with asymptomatic, metastatic, incurable colorectal cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All types of randomised controlled trials (RCTs), comparing immediate with delayed chemotherapy were eligible. We did not exclude studies based on either publication status or language. We excluded quasi-randomised studies.

Types of participants

Persons of any age, with asymptomatic, incurable, metastatic colorectal cancer (including persons who were not fit for surgery), whose primary tumour had been diagnosed histologically or cytologically, who had not received previous chemotherapy for

metastatic disease. Asymptomatic disease was defined as the absence of frequently reported disease-related symptoms, such as pain requiring regular narcotic analgesics, weight loss over 5 kg, persistent nausea requiring medication, deterioration in performance of activities of daily living (measured by the Eastern Cooperative Oncology Group Performance Status (ECOG; [Oken 1982](#)), obstructive bowel symptoms, persistent fever related to metastatic disease, and other symptoms, which in the opinion of the clinician, were due to progressive metastatic cancer. Incurable disease was determined by the clinician. We included individuals with or without palliative resection of the primary tumour, resection of metastases (metastatectomy), or targeted therapies. For trials in which not all participants were relevant for the review, we extracted relevant participants, in case results of these groups were separately reported.

Types of interventions

- The control group received immediate chemotherapy, defined as chemotherapy, with or without targeted therapies or novel agents, started within two weeks of diagnosis of distant metastasis.
- The intervention group received delayed chemotherapy, defined as chemotherapy, with or without targeted therapies or novel agents, delayed until disease-related symptoms commenced.

Chemotherapy included any agent, regimen (including different chemotherapy regimens across trial arms), method of delivery, dose, duration intensity, permissible co-interventions, with or without the addition of targeted therapies or novel agents.

Types of outcome measures

Primary outcomes

- 1.0 Overall survival; defined as time from randomisation to death from any cause, or to the end of follow-up

Secondary outcomes

- 2.1 Toxicity: comparing the number of events of grade 3 and 4 toxicities (see [Appendix 1](#)) between the two groups, classified according to the World Health Organization (WHO) guidelines ([Miller 1981](#)), irrespective of treatment-related toxicity or disease-related symptoms during the study period. Incidence of the most important toxicities; defined as nausea and vomiting, stomatitis, and diarrhoea.
- 2.2 Quality of life; using validated quality of life scoring systems, and measured at one, three, and five years after starting the treatment. If data were not reported for these time points, we considered alternative time points reported in the trials (close to those of interest as stated in this review). Minimal important difference in quality of life was five points ([Osaba 1998](#)).
- 2.3 Progression-free survival; defined as time from randomisation to time at which disease 'progressed', or to the date on which the participant died from any cause ([Saad 2009](#)).
- 2.4 Compliance with chemotherapy; defined as receiving > 90% of prescribed chemotherapy.

Search methods for identification of studies

Electronic searches

We searched the following databases to identify studies that met the inclusion criteria.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 8) in the Cochrane Library (searched 23 August 2018; [Appendix 2](#));
- MEDLINE(R) Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Ovid Daily and MEDLINE(R) Ovid (1946 to 23 August 2018; [Appendix 3](#));
- Embase Ovid (1974 to 23 August 2018; [Appendix 4](#));
- PsycINFO (1806 to 23 August 2018);
- World Health Organization International Clinical Trials Registry Platform (searched 23 August 2018);
- US National Library of Medicine ClinicalTrials.gov (searched 23 August 2018).

We did not impose any limitations on language or publication status. We searched the databases from the date of their inception. The Information Specialist from the Cochrane Colorectal Cancer Group conducted and verified the searches.

Searching other resources

We identified additional studies by searching the bibliographies of all retrieved and relevant publications identified by the above search strategies. We also scanned reference lists and conference abstracts from 2005 to August 2018.

Data collection and analysis

Selection of studies

Two review authors (YC, MV or AB) independently assessed the titles and abstracts identified by the search strategy for potentially relevant studies. After excluding the studies which did not meet the inclusion criteria, the remaining articles were full-text screened for eligibility. The same two review authors independently read the full text of the papers to ensure they met the inclusion criteria. Disagreements between the two review authors were resolved by discussion with a third review author (EK). Data and risk of bias assessment from included studies were verified using Covidence software ([Covidence](#)). In case more publications of a single trial were identified, we have indicated a primary data source. We contacted study authors where clarification was necessary. We listed included studies in the '[Characteristics of included studies](#)' table, and listed excluded studies and reasons for exclusion in the '[Characteristics of excluded studies](#)' table. We documented the inclusion and exclusion of studies in a PRISMA flow chart, and complied with MECIR guidelines ([editorial-unit.cochrane.org/mecir](#); [Moher 2009](#)).

Data extraction and management

Two review authors (YC and MV) independently extracted data from the studies using a standardised data extraction form that we piloted. The data extraction form included the following.

- General information: study title, authors, source, publication date, contact address, language.

- Population characteristics: number, age, gender, site of metastatic disease, no previous adjuvant chemotherapy (in a curative setting), site of primary tumour (colon or rectum), performance status ([Oken 1982](#)).
- Intervention characteristics: method of chemotherapy administration, dosage and duration of the intervention, details of the comparison regimen, number of drop-outs or lost to follow-up.
- Outcomes: overall survival, chemotherapy-induced toxicities, progression-free survival, quality of life, chemotherapy compliance.

We reported time-to-event data as hazard ratios (HRs) with 95% confidence intervals (CIs). We extracted HRs and CIs from the included articles; where necessary, we extrapolated them from Kaplan-Meier survival curves, using standardised methods ([Parmar 1998](#)). We transferred the HRs and CIs directly into Review Manager 5 ([RevMan 2014](#)).

Where different quality of life scales were used, we transformed these into the same scale, externally advised by a Professor in Psychology at Leiden University Medical Center, with expertise in the field of quality of life, and combining different quality of life scales. When appropriate, we calculated a standardised mean difference.

Assessment of risk of bias in included studies

Two review authors (YC and MV) independently assessed the risk of bias of the included studies using the Cochrane tool for assessing risk of bias ([Higgins 2011](#)). We discussed our findings and resolved disagreement by consulting with a third review author (EK). We assessed the risk of bias according to the following domains:

- Selection bias: random sequence generation, allocation concealment;
- Performance bias: blinding of persons and personnel;
- Detection bias: blinding of outcome assessment;
- Attrition bias: incomplete outcome data;
- Reporting bias: selective reporting;
- Other bias: other sources of bias.

We summarised the judgments of the risk of bias for each listed domain in the 'Risk of bias' table ([Figure 1](#)).

We classified overall risk of bias as low if a study appeared to be free of any sources of bias, as high if a study included one or more domains at high risk of bias, or as unclear if insufficient information was available to assess whether an important risk of bias existed.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Overall survival was an objective outcome (investigator-reported), quality of life was a subjective outcome (self-reported), toxicity, progression-free survival, and compliance with chemotherapy were adjudicated outcomes.

See [Appendix 5](#) for criteria for judging risk of bias ([Higgins 2011](#)).

Measures of treatment effect

We reported time-to-event data as hazard ratios (HRs) with 95% confidence intervals (CIs). We extracted HRs and CIs from the included articles; where necessary for determining overall survival and progression-free survival, we extrapolated them from Kaplan-Meier survival curves, using standardised methods ([Parmar](#)

[1998](#)). A HR below 1.0 favoured the experimental group (delayed chemotherapy). Preferably, we looked at HRs at one year, three years, and five years; where these were not reported, we considered measures at alternative durations of follow-up reported in the trials. Where HRs were not available, we used median overall survival with 95% CIs.

We calculated risk ratios (RRs) with 95% CI for dichotomous variables, e.g. toxicity rate. For continuous outcomes, e.g. quality of life measurements, we had planned to use mean differences with 95% CIs.

Unit of analysis issues

We expected only two-arm parallel RCTs where the unit of analysis was the individual participant. Although unlikely to be conducted, we considered cluster-RCTs (e.g. groups randomised rather than individuals) to be eligible, if identified. If cluster-RCTs were identified and included, we would have adjusted their sample sizes, using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, using an estimate of the intra cluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population (Chapter 16.3.4 or 16.3.6, [Higgins 2011a](#)). If we used ICCs from other sources, we would have reported this, and conducted a sensitivity analysis to investigate the effect of a variation in the ICC. If we identified both cluster-randomised trials and individually-randomised trials, we had planned to synthesise the relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between the study designs, and the interaction between the effect of the intervention and the choice of randomisation unit was considered to be unlikely.

Cross-over RCTs were not a feasible study design, as participants in the control group (immediate chemotherapy) could not be switched to the experimental group (delayed chemotherapy), or vice versa.

Dealing with missing data

We contacted principal investigators or key authors of included studies for missing data (missing participants due to loss to follow-up, drop out, or withdrawal, and missing statistics). We made every effort to minimise the amount of missing data. Our expectation was that the amount of missing data would be minimal, and that the included trials would investigate the same outcome measures. In addition, we performed a 'worst-case intention-to-treat analysis'. We did this by assuming that all missing participants had an event; this way we obtained the most conservative and pessimistic estimate.

Assessment of heterogeneity

We tested for heterogeneity between study results. First, we determined the presence or absence of overlap in the CI's. The absence of overlap in the CIs indicated heterogeneity between study results. Second, we performed the χ^2 test for heterogeneity. If P was < 0.10 , we considered data to be heterogeneous. Finally, we calculated the I^2 statistic, interpreting it as "the proportion of total variation in the estimates of treatment effect that was due to heterogeneity between studies" ([Higgins 2002](#)).

According to the recommendations from the *Cochrane Handbook for Systematic Reviews of Intervention*, we applied the following thresholds for the interpretation of the I^2 statistic ([Deeks 2011](#)):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We did not pool data if substantial or considerable statistical heterogeneity was identified. We had planned to explore possible reasons for heterogeneity in subgroup analyses.

Assessment of reporting biases

We had planned to assess reporting biases with the use of funnel plots for each outcome where there were more than 10 included studies, as recommended in *Cochrane Handbook for Systematic Reviews of Interventions* ([Sterne 2017](#)).

Data synthesis

For dichotomous data we pooled trials using a fixed-effect meta-analysis (Mantel-Haenszel method), as random-effects models are not suitable for pooling five or fewer studies ([Higgins 2011a](#)). However, if the number of RCTs increases in the future, it may be appropriate to use a random-effects or fixed-effect model for the meta-analysis, depending on the heterogeneity of the included studies.

Where different quality of life scales were used, we transformed these into the same scale ([Groenwold 1997](#)). When appropriate, we calculated a standardised mean difference.

Subgroup analysis and investigation of heterogeneity

We had planned the following subgroup analyses.

- Type of chemotherapy regimen: developments in chemotherapy regimens over the last few decades may have had an impact on results ([Gustavsson 2015](#)). We used date of trial as a surrogate if regimen details were not reported. In cases where regimens of chemotherapy in the treatment arms differed, we compared these results with those that used the same regimen in both arms. We conducted subgroup analyses on treatments with and without anti vascular endothelial growth factor (VEGF)/epidermal growth factor receptor (EGFR) and FOLFOX (a chemotherapy regimen made up of folinic acid, fluorouracil, and oxaliplatin) versus FOLFIRI (a chemotherapy regimen made up of folinic acid, fluorouracil, and irinotecan). We grouped the regimens between 5-FU and those with oxaliplatin. If the type of chemotherapy was not reported, key authors were contacted to find out.
- Age groups: older colorectal cancer patients have a poorer survival prognosis relative to younger patients ([Ferlay 2015](#)). Older was defined as ≥ 70 years and older, and young as < 70 years.
- Gender: as mortality rates are higher in men with colorectal cancer compared to women, gender could play an important role ([Ferlay 2015](#)).
- Site of cancer: patients with rectal cancer have a poorer survival prognosis than patients with colon cancer ([Holleccek 2015](#)).

Sensitivity analysis

For assessment of the susceptibility of the findings of the meta-analyses in this review, we had planned two sensitivity analyses.

- only including participants that received per-protocol therapy.
- only including studies that we judged to be at low risk of bias. We classified overall risk of bias as low if a study appeared to be free of any sources of bias, as high if a study included one or more domains at high risk of bias, or as unclear if insufficient information was available to assess whether an important risk of bias existed ([Higgins 2002](#)).

We were unable to perform the planned sensitivity analyses due to insufficient available data from the included studies.

'Summary of findings' table

We analysed the quality of evidence of our outcomes, overall survival, toxicity, quality of life, progression-free survival, and compliance with chemotherapy, in our assessment of immediate versus delayed chemotherapy for asymptomatic metastatic colorectal cancer, by using the GRADE approach, and presented it in a 'Summary of findings' table ([Atkins 2004](#); [Higgins 2011](#)).

We used GRADEPRO GDT software to prepare and present the quality of evidence of the outcomes in '[Summary of findings for the main comparison](#)' ([GRADEpro GDT 2015](#)).

For randomised controlled trials (RCT), the quality of evidence could be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons: risk of bias, inconsistency (unexplained heterogeneity, inconsistency of results), indirectness (indirect population, intervention, control, outcomes), imprecision (wide confidence intervals, single trial), and publication bias.

RESULTS

Description of studies

Results of the search

The PRISMA flow diagram for eligible studies is shown in [Figure 2](#).

Figure 2. Study flow diagram

In total, we identified 716 references from the search. After removing duplicates, 459 references were left for screening. During screening, we excluded 451 references, retrieving eight studies for full-text screening for eligibility. Of these, we excluded four studies due to the wrong study design, and included three individual RCT's (in four references) for qualitative and quantitative synthesis.

Included studies

See 'Characteristics of included studies' table for full details.

In total, we included three randomised clinical trials, of which one was from Australia and New Zealand (Ackland 2005), one from Canada (Ackland 2005a), and one from Sweden and Norway (Nordic Gastrointestinal Tumor Therapy Group 1992). The results from the Ackland 2005 and Ackland 2005a trial were reported in one joint paper. Participants of these 2 studies were recruited from 17 different hospitals. In the study of Nordic Gastrointestinal Tumor Therapy Group 1992, participants were recruited from 12 hospitals. We did not include any cluster-randomised trials. All three trials compared two arms consisting of immediate versus delayed chemotherapy.

See Table 1 and Table 2 for outcomes and study populations.

Chemotherapy regimens differed across the trials. In one trial, they only allowed the Mayo regimen (5-FU 425 mg/m² intravenous bolus and LV 20 mg/m² intravenous (Ackland 2005a); in another trial, they allowed the Mayo regimen or weekly 5-FU-LV (5-FU 500 mg/m² intravenous bolus and LV 20 mg/m² intravenous bolus (Ackland 2005). Chemotherapy in the third trial consisted of sequential methotrexate 250 mg/m² during the first two hours, and 5-FU 500 mg/m² at hours 3 and 23, followed by leucovorin rescue, initiated at hour 24, for 8 courses (Nordic Gastrointestinal Tumor Therapy Group 1992).

Excluded studies

See 'Characteristics of excluded studies' table for full details.

In total, we excluded four studies (Arnold 2015; Giles 1984; Hegewisch-Becker 2015; Maung 2002).

Risk of bias in included studies

See overall risk of bias assessment in included studies in Figure 1 and 'Characteristics of included studies' tables.

Allocation

All three studies contained limited information about randomisation and allocation concealment, therefore, we judged them to be unclear risk of bias (Ackland 2005; Ackland 2005a; Nordic Gastrointestinal Tumor Therapy Group 1992).

Blinding

None of the studies blinded participants or personnel (Ackland 2005; Ackland 2005a; Nordic Gastrointestinal Tumor Therapy Group

1992). As symptom-free survival, progression-free survival, and toxicity are subjective outcomes, we considered risk of detection bias to be high in all three studies. Risk of bias may also exist for quality of life, as this was reported by the participant, and not by the clinician.

Incomplete outcome data

We considered attrition bias to be high in both Ackland 2005 and Ackland 2005a, due to missing reporting on whether there were protocol violations for the delayed treatment group.

Selective reporting

In the study by Nordic Gastrointestinal Tumor Therapy Group 1992, we considered reporting bias to be high because (i) there was no study protocol available, and (ii) the criteria for 'symptomatic disease' in the delayed chemotherapy group were missing. There was also high risk of reporting bias in the Ackland 2005 and Ackland 2005a studies, as quality of life scores, using EORTC QLQ-C30, were not formally reported, but consisted of 'good' scores, which were not specified in the methods sections.

Other potential sources of bias

We assessed there to be other potential sources of bias in the study by Nordic Gastrointestinal Tumor Therapy Group 1992, as participants in the immediate chemotherapy group were monitored more often than participants in the delayed chemotherapy group.

Effects of interventions

See: **Summary of findings for the main comparison** Delayed chemotherapy compared with immediate chemotherapy for patients with asymptomatic, incurable, metastatic colorectal cancer

We included three randomised clinical trials in the current meta-analysis, accounting for 351 persons (176 persons randomised to receive immediate chemotherapy and 175 persons to receive delayed chemotherapy). For quality of life, progression-free survival, and compliance, we were unable to pool the data.

1. Primary outcome

1.0 Overall survival

Receipt of immediate or delayed chemotherapy may make little or no difference to overall survival (hazard ratio (HR) 1.17, 95% confidence interval (CI) 0.93 to 1.46; 3 RCTs, 351 participants; Analysis 1.1; Figure 3). The statistical heterogeneity between the study results was low ($I^2 = 0\%$, $P = 0.747$). We judged the evidence to be low quality because of very serious concerns regarding imprecision, due to very few participants.

Figure 3. Forest plot for outcome 1.1 Overall survival

The reported one-year survival was 57% in the immediate chemotherapy group, and 46% in the delayed chemotherapy group in [Ackland 2005](#) and [Ackland 2005a](#); and 55% in the immediate chemotherapy group, and 38% in the delayed chemotherapy group in [Nordic Gastrointestinal Tumor Therapy Group 1992](#).

2. Secondary outcomes

2.1 Toxicity

Two studies ($N = 140$) reported on toxicity ([Ackland 2005](#); [Ackland 2005a](#)). We found no clear differences between the immediate

and delayed chemotherapy groups for nausea and vomiting (risk ratio (RR) 0.84, 95% CI 0.31 to 2.25; $I^2 = 80\%$; [Analysis 2.1](#); [Figure 4](#)), stomatitis (RR 1.10, 95% CI 0.47 to 2.55; $I^2 = 75\%$; [Analysis 2.2](#); [Figure 5](#)), and diarrhoea (RR 0.69, 95% CI 0.34 to 1.40, $I^2 = 0\%$ [Figure 6](#)). We judged the overall quality of evidence as being very low for all three toxicity measures because of very serious concerns regarding imprecision, due to limited number of trials and participants, unexplained heterogeneity, and risk of bias issues (lack of blinding).

Figure 4. Forest plot for toxicity, outcome: 2.1 Nausea and vomiting

Figure 5. Forest plot for toxicity, outcome: 2.2 Stomatitis

Figure 6. Forest plot for toxicity, outcome: 2.3 Diarrhoea

2.2 Quality of life

Two studies reported on quality of life ($N = 161$) ([Ackland 2005](#); [Ackland 2005a](#)). We found no clear difference between the study arms. We assessed the evidence to be very low-quality because of very serious concerns regarding imprecision, due to limited number of participants, indirectness of the outcomes, and lack of blinding.

2.3 Progression-free survival

All three included studies reported on progression-free survival, however we were unable to pool the results due to clinical heterogeneity.

There were no clear difference between groups in the pooled data from [Ackland 2005](#) and [Ackland 2005a](#) (immediate) 10.2

months versus (delayed) 10.8 months); HR 1.01, 95% CI 0.72 to 1.41, test for heterogeneity $P = 0.047$; 351 participants). The [Nordic Gastrointestinal Tumor Therapy Group 1992](#) paper stated that the median progression-free survival was 10 months in the immediate group versus 2 months in the delayed group. We judged the quality of the evidence to be low due to very serious concerns regarding imprecision and limited number of participants.

2.4 Compliance with chemotherapy

In the study by the [Nordic Gastrointestinal Tumor Therapy Group 1992](#), 51 of the 90 participants (57%) received chemotherapy in the delayed group; in [Ackland 2005](#) and [Ackland 2005a](#), 70% (59 of the 84 participants) received chemotherapy in the delayed treatment group. We considered the evidence to be low quality because of very serious concerns regarding imprecision and limited number of participants.

3. Subgroup and sensitivity analyses

We had planned to conduct subgroup and sensitivity analyses. However, due to the limited number of included studies, we were unable to conduct these analyses.

DISCUSSION

With the increasing population worldwide, the number of individuals with colorectal cancer is growing; subsequently, there are more people diagnosed with metastatic colorectal cancer. When these people are not symptomatic at the time metastases is diagnosed, it can be difficult for clinicians to decide whether they should give chemotherapy, the therapy of choice, immediately, or wait until patients become symptomatic. To answer this question, we conducted this review. To our knowledge, it was the first Cochrane review investigating this clinically relevant issue.

Summary of main results

Low-quality evidence suggested that administering immediate or delayed chemotherapy may make little or no difference to overall survival. We were only able to include three trials in the current review.

Overall completeness and applicability of evidence

Although these results give clinicians useful information, they should be interpreted with some caution, as we judged the evidence from the literature regarding this topic to be low quality, and we could not complete all planned analyses. We had planned to perform subgroup and sensitivity analyses. However, due to the very limited number of included studies, we were unable to do so.

In the absence of a clear survival benefit of immediate treatment, some people will choose a deteriorated quality of life from chemotherapy toxicity over delayed treatment. On the other hand, there will also be people who will choose a longer period of quality of life over immediate treatment, recognising there is a risk that therapy may no longer be an option if their condition deteriorates. These considerations might be different for each patient, and should be extensively discussed between patient and clinician in order to make a calculated decision. Informed shared decision-making results, by balancing patient characteristics, patient preference, toxicity profile, and tolerability.

This review has several limitations. The study of the [Nordic Gastrointestinal Tumor Therapy Group 1992](#) was published in 1992. As a result, it should be questioned whether these results, of this approximately 25 years old trial, are still relevant for current practice. In recent decades, improvement has been achieved in several areas of the care of patients with colorectal cancer: the definition of incurable, staging, regimens of chemotherapy, optimal dose of chemotherapy, improvement in (peri-)operative care, the rise of the use of biologicals, and combination strategies.

We pooled overall survival data from all three included studies. Unfortunately, we were not able to do so for progression-free survival, as [Nordic Gastrointestinal Tumor Therapy Group 1992](#) only showed the probability curve and provided median symptom-free survival, whereas [Ackland 2005](#) and [Ackland 2005a](#) provided a hazard ratio.

All three included studies examined combination chemotherapy regimens, whereas nowadays, more often monotherapy and biological therapy are used, resulting in less toxicity and less impact on quality of life.

Quality of the evidence

We used GRADE classification for levels of evidence in the current review. For the primary outcome, overall survival, we studied three RCT's (351 persons). We did not downgrade for inconsistency or indirectness of population, interventions, controls, or outcomes. We downgraded two levels because of imprecision, as the studies only included 351 participants. We did not downgrade for publication bias. As a consequence, we considered the evidence regarding overall survival to be of low quality.

Toxicity was one of the secondary outcomes. It was investigated in two RCTs (140 persons). Consequently, we downgraded by two levels for imprecision, due to a limited number of participants and events, and one level because of explained heterogeneity. We did not downgrade for indirectness or publication bias. In conclusion, we considered the evidence for toxicity to be very low quality.

Quality of life, one of the secondary outcomes, was described in two RCTs (161 persons), and we downgraded by two levels for imprecision, due to limited number of participants. We did not downgrade for inconsistency. We did downgrade by one level for indirectness, as the authors considered a score higher than 75% as 'good quality of life'. We did not downgrade for publication bias. We considered the evidence for quality of life to be very low quality.

We did not downgrade the quality of the evidence for progression-free survival, a secondary outcome, for inconsistency or indirectness. Progression-free survival was reported in 351 persons (three RCTs), therefore, we downgraded the evidence by two levels for imprecision, due to the limited number of participants. We did not downgrade for publication bias. We considered the level of evidence for progression-free survival to be low quality.

Compliance with chemotherapy was one of the secondary outcomes in this review. We did not downgrade for inconsistency or indirectness. We downgraded two levels for imprecision, due to the limited number of participants and events (three RCTs, 351 participants). We did not downgrade for publication bias. We assess the quality of the evidence for compliance with chemotherapy to be low quality.

Overall, using the GRADE criteria, there is a low level of evidence that immediate chemotherapy leads to increased overall survival or progression-free survival compared to delayed chemotherapy. There is a very low level of evidence that there are any differences between immediate or delayed chemotherapy with regard to toxicity or quality of life.

Potential biases in the review process

We identified several potential biases in this review. The included studies made no mention of blinding, and it is likely that lack of blinding did influence subjective outcomes, such as quality of life. Symptomatic disease, an essential element in two of the studies, was subjectively determined ([Ackland 2005](#); [Ackland 2005a](#)). The third study made no mention of quality of life, and followed different follow-up regimens ([Nordic Gastrointestinal Tumor Therapy Group 1992](#)).

All three included studies reported moderate compliance with chemotherapy in the delayed treatment group (70% ([Ackland 2005](#); [Ackland 2005a](#))) and 57% ([Nordic Gastrointestinal Tumor Therapy Group 1992](#))). This might have been due to the physical inability of some to undergo treatment when treatment was delayed too long, or it might have been an individual's choice. Either way, this could have affected our results.

We were unable to perform a subgroup analysis in this review, which could have introduced bias. While we searched a number of established reference databases, we might have missed some studies, since, for instance, non-English language publications are hard to find.

Agreements and disagreements with other studies or reviews

A review of the literature on this topic has not been performed before. As a consequence, we cannot compare the results of the current review with other reviews. On the other hand, this

emphasises the value of the current review, in spite of the limitations.

AUTHORS' CONCLUSIONS

Implications for practice

In persons with metastatic, incurable colorectal disease, immediate treatment with chemotherapy does not provide a clear survival benefit, compared to delayed chemotherapy. However, due to low-quality evidence, and a very limited number of trials providing data, conclusions must be interpreted with caution. There were insufficient data on toxicity to enable us to provide implications for clinical practice.

Implications for research

Future randomised clinical trials examining differences between immediate and delayed chemotherapy for patients with incurable, metastatic colorectal cancer, seem unlikely, due to ethical issues and the expectation of poor accrual. This emphasises the value of the current review. To gain more insight into this controversial topic, prediction models, based on population-based data should be developed. With this type of research, the heterogeneity of this group of patients can be taken into account, and influencing factors that can help to determine whether chemotherapy should be given immediately or delayed can be determined. In addition to survival outcomes, toxicity and quality of life should also be taken into account, especially in this group of patients, for whom a cure is not possible.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ackland 2005

Methods	Study design: multicenter randomised controlled trial
	Accrual: 1994 to 1999
	Country: Australia and New Zealand
Participants	Inclusion criteria: histologically proven colorectal carcinoma with local recurrence or metastases not amenable to curative treatment; no symptoms related to advanced disease; no prior chemotherapy for metastatic disease; evaluable or measurable disease according to the criteria of Miller; adequate bone marrow function and renal function; no central nervous system metastases; no history of prior invasive

Ackland 2005 (Continued)

malignant disease; and no uncontrolled medical condition that would be aggravated by treatment; no pregnancy and agreed to adequate contraception for the duration of the study

Exclusion criteria: none mentioned

Sample size: 101 participants (50 participants immediate chemotherapy, 51 participants delayed chemotherapy)

Age (years): immediate chemotherapy median age 66.8; delayed chemotherapy median age 65.3

Sex (% male): immediate chemotherapy 76%; delayed chemotherapy 73%

Interventions	<p>Participants were stratified according to treatment centre and prior adjuvant chemotherapy (yes or no), then randomised to immediate treatment (to begin within 2 weeks) or treatment delayed until the development of symptoms.</p> <p>Clinicians could choose between the Mayo clinic schedule: 5-FU 425 mg/m² intravenous bolus and LV 20 mg/m² intravenous (Mayo regimen) or 5-FU-LV (5-FU 500 mg/m² intravenous bolus and LV 20 mg/m² intravenous bolus) but nominated the schedule before randomisation.</p>
Outcomes	<p>Primary end point: overall survival (not defined)</p> <p>Secondary end points: time-to-disease progression (defined as time from randomisation until first evidence of progression after chemotherapy, tumour imaging every 3 months), quality of life (not defined, measured every two months by EORTC QLQ-30), adverse effects: nausea and vomiting, stomatitis, diarrhoea (not defined and time points not reported, measured by number of participants having grade 3 or 4 toxicity).</p>
Notes	<p>One of the two randomised trials described in one paper.</p> <p>Supported by New South Wales Cancer Council Project Grant RG50/00 (2001-2003) and National Health and Medical Research Council Program Grant (1994-2000)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no mention of blinding, but it is likely that lack of blinding did influence subjective outcomes. Subjective criteria for symptomatic disease, whereby the number of participants who started with chemotherapy because of this reason was not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessments for quality of life could have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>In the delayed group 70% of the combined study population (Ackland 2005 and Ackland 2005a) ultimately received 5-FU chemotherapy. Reasons for exclusion or drop-outs in the delayed treatment group were not described.</p> <p>Number of participants reported/number randomised by outcome were as follows:</p> <p>Overall survival: 50/50 (100%) in immediate group and 51/51 (100%) in delayed group</p>

Ackland 2005 (Continued)

Nausea and vomiting: 49/50 (98%) in immediate group and 31/51 (61%) in delayed group

Stomatitis: 49/50 (98%) in immediate group and 31/51 (61%) in delayed group

Diarrhoea: 49/50 (98%) in immediate group and 31/51 (61%) in delayed group

Quality of life: at baseline, 100% in immediate group and 100% in delayed group; at 12 months, 85% in immediate group and 74% in delayed group (the number of participants were not provided, the percentages that were reported were combined results of the [Ackland 2005](#) and [Ackland 2005a](#) study)

Compliance: 50/50 (100%) in immediate group and 51/51 (100%) in delayed group

Selective reporting (reporting bias)	High risk	The analysis of quality of life score using EORTC QLQ-C30 was not formally reported and consisted of 'good' scores which were not specified in the methods section.
Other bias	Low risk	No other sources of bias identified.

Ackland 2005a

Methods	Study design: multicenter randomised controlled trial Accrual: 1994 to 1999 Country: Canada
Participants	Inclusion criteria: histologically proven colorectal carcinoma with local recurrence or metastases not amenable to curative treatment; no symptoms related to advanced disease; no prior chemotherapy for metastatic disease; evaluable or measurable disease according to the criteria of Miller; adequate bone marrow function and renal function; no central nervous system metastases; no history of prior invasive malignant disease; and no uncontrolled medical condition that would be aggravated by treatment; no pregnancy and agreed to adequate contraception for the duration of the study Exclusion criteria: none mentioned Sample size: 67 participants (34 participants immediate chemotherapy, 33 participants delayed chemotherapy) Age (years): in immediate chemotherapy median age 67.4; delayed chemotherapy median age 63.7 Sex (% male): immediate chemotherapy 76%; delayed chemotherapy 73%
Interventions	participants were stratified according to treatment centre and prior adjuvant chemotherapy (yes or no), then randomised to immediate treatment (to begin within 2 weeks) or treatment delayed until the development of symptoms. Only the Mayo clinic schedule was allowed consisting of: 5-FU 425 mg/m ² intravenous bolus and LV 20 mg/m ² intravenous
Outcomes	Primary end point: overall survival (not defined). Secondary end points: time-to-disease progression (defined as time from randomisation until first evidence of progression after chemotherapy, tumour imaging every 3 months), quality of life (not defined, measured every two months by EORTC QLQ-30), adverse effects: nausea and vomiting, stomatitis, diarrhoea (not defined, and time points not reported, measured by number of participants having grade 3 or 4 toxicity).
Notes	One of the two randomised trials described in one paper

Ackland 2005a (Continued)

Supported by New South Wales Cancer Council Project Grant RG50/00 (2001-2003) and National Health and Medical Research Council Program Grant (1994-2000)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no mention of blinding, but it is likely that lack of blinding did influence subjective outcomes. Subjective criteria for symptomatic disease, whereby the number of participants who started with chemotherapy because of this reason was not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessments for quality of life could have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>In the delayed group 70% of the combined study population (Ackland 2005 and Ackland 2005a) ultimately received 5-FU chemotherapy. Reasons for exclusion or drop-outs in the delayed treatment group were not described.</p> <p>Number of participants reported/number randomised by outcome:</p> <p>Overall survival: 34/34 (100%) in immediate group and 33/33 (100%) in delayed group</p> <p>Nausea and vomiting: 34/34 (100%) in immediate group and 26/33 (79%) in delayed group</p> <p>Stomatitis: 34/34 (100%) in immediate group and 26/33 (79%) in delayed group</p> <p>Diarrhoea: 34/34 (100%) in immediate group and 26/33 (79%) in delayed group</p> <p>Quality of life: at baseline, 100% in immediate group and 100% in delayed group; at 12 months, 85% in immediate group and 74% in delayed group (the number of participants were not provided, the percentages that were reported were combined results of the Ackland 2005 and Ackland 2005a studies)</p> <p>Compliance: 50/50 (100%) in immediate group and 51/51 (100%) in delayed group</p>
Selective reporting (reporting bias)	High risk	The analysis of quality of life score using EORTC QLQ-C30 was not formally reported and consisted of 'good' scores which were not specified in the methods section.
Other bias	Low risk	No other sources of bias identified.

Nordic Gastrointestinal Tumor Therapy Group 1992

Methods	Study design: multicenter randomised controlled trial
	Accrual: 1985 to 1990

Nordic Gastrointestinal Tumor Therapy Group 1992 (Continued)

Country: Sweden and Norway

Participants	<p>Inclusion criteria: 75 years or younger; normal kidney function; no icterus; no evidence of ascites or pleural effusion; known macroscopic disease, and informed consent</p> <p>Exclusion criteria: none mentioned</p> <p>Sample size: 183 participants (92 participants immediate chemotherapy, 91 participants delayed chemotherapy)</p> <p>Age (years): median age 60 in both treatment groups</p> <p>Sex (% male): immediate chemotherapy 58%, delayed chemotherapy 46%</p>
Interventions	<p>The participants were randomly allocated to either immediate chemotherapy for 6 months or delayed chemotherapy.</p> <p>Participants randomised for immediate chemotherapy started treatment within 2 weeks of randomisation, with MFL-regimen (methotrexate 250 mg/m² as an intravenous (IV) infusion during hours 0 to 2 followed by 5-FU 500 mg/m² IV bolus at hours 3 and 23). Therapy continued for 12 courses unless signs of tumour progression – objectively or subjectively – or severe adverse effects appeared.</p> <p>In the group of participants randomised to delayed chemotherapy, chemotherapy was allowed when the participant became symptomatic.</p>
Outcomes	<p>Primary end point: overall survival, calculated from the date of randomisation to the date of death from any cause</p> <p>Secondary end points: progression-free survival (not defined, was assessed every second month, or earlier if it was clinically indicated), symptom-free survival (not defined, was assessed every second month, or earlier if it was clinically indicated), toxicity (defined as grade 3 or grade 4 toxicity, according to the WHO guidelines: nausea and vomiting, stomatitis, and diarrhoea were only reported in the MFL group, determined only in the immediate chemotherapy group, time points not reported).</p>
Notes	<p>Supported by the Swedish Cancer Society grant no. 1921-B90-07XA</p> <p>The corresponding author was contacted by email and informed us that toxicity of the delayed group was not reported.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Very limited information regarding randomisation, 'patients were randomly allocated'
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no mention of blinding, but it is likely that lack of blinding did influence subjective outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There were subjective outcomes, and it was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Separate analyses with and without missing participants were reported.</p> <p>Number of participants reported/number randomised by outcome:</p>

Survival differences with immediate versus delayed chemotherapy for asymptomatic incurable metastatic colorectal cancer (Review)

Nordic Gastrointestinal Tumor Therapy Group 1992 *(Continued)*

Overall survival: 92/92 (100%) in immediate group and 91/91 (100%) in delayed group

Nausea and vomiting: 92/92 (100%) in immediate group and 0/91 (0%, not reported) in delayed group

Stomatitis: 92/92 (100%) in immediate group and 0/91 (0%, not reported) in delayed group

Diarrhoea: 92/92 (100%) in immediate group and 0/91 (0%, not reported) in delayed group

Quality of life: not reported

Compliance: 92/92 (100%) in immediate group and 91/91 (100%) in delayed group

Selective reporting (reporting bias)	High risk	No study protocol was available; criteria for symptomatic disease in the delayed chemotherapy group were missing
Other bias	High risk	Participants in the immediate chemotherapy group were monitored more often than participants in the delayed chemotherapy group.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arnold 2015	Wrong study design. In this trial, addition of a biomarker was tested, there was no 'delayed' chemotherapy arm.
Giles 1984	Wrong study design. Participants were randomised to a certain chemotherapy regimen or carefully followed, with identical attention to general medical care (so, no 'delayed' chemotherapy).
Hegewisch-Becker 2015	Wrong study design. In this trial, participants were randomised to chemotherapy and bevacizumab, bevacizumab alone, or no treatment. So there was no 'delayed treatment' with chemotherapy.
Maung 2002	Wrong study design. In this trial, three different chemotherapy regimens were compared, without a 'delayed' chemotherapy arm.

DATA AND ANALYSES

Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	351	Hazard Ratio (Fixed, 95% CI)	1.17 [0.93, 1.46]

Analysis 1.1. Comparison 1 Overall survival, Outcome 1 Overall survival.

Comparison 2. Toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea and vomiting	2	140	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.31, 2.25]
2 Stomatitis	2	140	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.47, 2.55]
3 Diarrhoea	2	140	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.34, 1.40]

Analysis 2.1. Comparison 2 Toxicity, Outcome 1 Nausea and vomiting.

Analysis 2.2. Comparison 2 Toxicity, Outcome 2 Stomatitis.

Analysis 2.3. Comparison 2 Toxicity, Outcome 3 Diarrhoea.

ADDITIONAL TABLES

Table 1. Outcomes

Study	Overall survival	Toxicity	Quality of life	Progression-free survival	Compliance
Ackland 2005	1-year survival, median survival, HR reported	Number of participants with grades 3 or 4 toxicities ^a	EORTC QLQ-C30 ^b every 2 months, assessed from randomisation to death	Median progression-free survival and HR reported, tumour imaging every 3 months	Number of participants who did not receive protocol therapy
Ackland 2005a	1-year survival, median survival, HR reported	Number of participants with grades 3 or 4 toxicities ^a	EORTC QLQ-C30 ^b every 2 months, assessed from randomisation to death	Median progression-free survival and HR reported, tumour imaging every 3 months	Number of participants who did not receive protocol therapy
Nordic Gastrointestinal Tumor Therapy Group 1992	6-month survival, 1-year survival, median survival	Number of participants with grades 1, 2, 3, or 4 toxicities ^a	Not reported	Assessed every second month, or earlier if clinically indicated	Number of treatment courses delivered

^a According to the World Health Organization guidelines, grade 3 toxicity is defined as severe or medically significant, but not immediately life-threatening; this includes hospitalisation or indication of prolongation of hospitalisation, disabling, and limiting self-care activities of daily living; grade 4 toxicity is defined as life-threatening consequences, where urgent intervention is indicated.

^b The European Organisation for Research and Treatment of Cancer Study Group on Quality of Life. Data were dichotomised into 'good' and 'poor' categories, as data distributions in this study were skewed.

Table 2. Study population

Study	Number of participants	Age (years)	Performance Status	Chemotherapy-naïve	Site (% colon/% rectum)	Chemotherapy regimen
Auckland 2005	immediate chemotherapy = 50 delayed chemotherapy = 51	median age immediate chemotherapy = 66.8 median age delayed chemotherapy = 65.3	Not reported	72% of immediate chemotherapy group 76% of delayed chemotherapy group	Not reported	Mayo regimen (5-FU and LV) or weekly 5-FU-LV
Auckland 2005a	immediate chemotherapy = 34 delayed chemotherapy = 33	median age immediate chemotherapy = 67.4 median age delayed chemotherapy = 63.7	100% score immediate chemotherapy = 41% 100% score delayed chemotherapy group = 64%	74% of immediate chemotherapy group 76% of delayed chemotherapy group	Not reported	Mayo regimen (5-FU and LV)
Nordic Gastrointestinal Tumor Therapy Group 1992	immediate chemotherapy = 92 delayed chemotherapy = 91	mean age in both study groups = 60	100% score immediate chemotherapy = 84% 100% score delayed chemotherapy = 84%	Not reported	62/38 immediate chemotherapy 79/21 delayed chemotherapy	MFL regimen: methotrexate and 5-FU

APPENDICES

Appendix 1. Definition of toxicity

Grade 3 toxicity is defined as severe or medically significant, but not immediately life-threatening; this includes hospitalisation or indication of prolongation of hospitalisation, disabling, and limiting self-care activities of daily living. Grade 4 toxicity is defined as life-threatening consequences, where urgent intervention is indicated. Furthermore, incidence of the most important toxicities, defined as neutropenia, stomatitis, and vomiting/ diarrhoea were described.

Appendix 2. CENTRAL search strategy

CENTRAL; 2018, Issue 8 in the Cochrane Library, searched 23 August 2018

#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees

#2 ((colorect* or colon* or rect* or anal or anus or intestin* or bowel* or sigmoid*) near/2 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or adenom*)):ti,ab,kw

#3 (#1 or #2)

#4 MeSH descriptor: [Neoplasm Metastasis] explode all trees

#5 (metastas* or metastatic* or micrometastas* or micrometastatic* or advance* or stage IV or stage 4 or stage four or irresectable or unresectable or palliati*):ti,ab,kw

#6 (#4 or #5)

#7 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees

#8 MeSH descriptor: [Antineoplastic Agents] explode all trees

#9 MeSH descriptor: [Antimetabolites, Antineoplastic] explode all trees

#10 MeSH descriptor: [Fluorouracil] explode all trees

#11 MeSH descriptor: [Leucovorin] explode all trees

#12 MeSH descriptor: [Methotrexate] explode all trees
 #13 MeSH descriptor: [Camptothecin] explode all trees
 #14 MeSH descriptor: [Thiophenes] explode all trees
 #15 MeSH descriptor: [Organoplatinum Compounds] explode all trees
 #16 (chemotherap* or antineoplastic* or capecitabin* or fluoropyrimidin* or fluorouracil* or 5-FU* or 5-fluorouracil* or 5FU* or 5 fluorouracil* or methothrexat* or folinic acid or Leucovorin* or oxaliplatin* or camptothecin* or thiophene* or irinotecan* or capecitabin* or panitumumab* or bevacizumab* or cetuximab* or regorafenib* or FOLFIRI* or FOLFOX* or CapeOX* or FLOX* or XELOX*):ti,ab,kw
 #17 (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
 #18 MeSH descriptor: [Time Factors] explode all trees
 #19 ((time or delay* or immediate or initial or expectancy or primary or early or deferred or deferral) and chemo*):ti
 #20 (#18 or #19)
 #21 (#3 or #6 and #17 and #20)

Appendix 3. MEDLINE search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to 23 August 2018

1. exp Colorectal Neoplasms/
2. ((colorect* or colon* or rect* or anal or anus or intestin* or bowel* or sigmoid*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or adenom*)):mp.
3. 1 or 2
4. exp Neoplasm Metastasis/
5. (metastas* or metastatic* or micrometastas* or micrometastatic* or advance* or stage IV or stage 4 or stage four or irresectable or unresectable or palliati*):mp.
6. 4 or 5
7. exp Antineoplastic Combined Chemotherapy Protocols/
8. exp Antineoplastic Agents/
9. exp Antimetabolites, Antineoplastic/
10. exp Fluorouracil/
11. exp Leucovorin/
12. exp Methotrexate/
13. exp Camptothecin/
14. exp Thiophenes/
15. exp Organoplatinum Compounds/
16. (chemotherap* or antineoplastic* or capecitabin* or fluoropyrimidin* or fluorouracil* or 5-FU* or 5-fluorouracil* or 5FU* or 5 fluorouracil* or methothrexat* or folinic acid or Leucovorin* or oxaliplatin* or camptothecin* or thiophene* or irinotecan* or capecitabin* or panitumumab* or bevacizumab* or cetuximab* or regorafenib* or FOLFIRI* or FOLFOX* or CapeOX* or FLOX* or XELOX*):mp.
17. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp Time Factors/
19. ((time or delay* or immediate or initial or expectancy or primary or early or deferred or deferral) and chemo*):m_titl.
20. 18 or 19
21. 3 or 6 and 17 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. clinical trials as topic.sh.
27. randomly.ab.
28. trial.ti.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. exp animals/ not humans.sh.
31. 29 not 30
32. 21 and 31

Appendix 4. Embase search strategy

Embase Ovid: 1974 to 23 August 2018

1. exp large intestine tumor/
2. ((colorect* or colon* or rect* or anal or anus or intestin* or bowel* or sigmoid*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or adenom*)):mp.
3. 1 or 2
4. exp metastasis/

5. exp advanced cancer/
6. (metastas* or metastatic* or micrometastas* or micrometastatic* or advance* or stage IV or stage 4 or stage four or irresectable or unresectable or palliati*).mp.
7. 4 or 5 or 6
8. exp antineoplastic agent/
9. exp antineoplastic antimetabolite/
10. exp folinic acid/
11. exp fluorouracil/
12. exp platinum complex/
13. exp camptothecin/
14. exp thiophene derivative/
15. exp oxaliplatin/
16. exp irinotecan/
17. exp capecitabine/
18. exp cancer combination chemotherapy/
19. (chemotherap* or antineoplastic* or capecitabin* or fluoropyrimidin* or fluorouracil* or 5-FU* or 5-fluorouracil* or 5FU* or 5 fluorouracil* or methothrexat* or folinic acid or Leucovorin* or oxaliplatin* or camptothecin* or thiophene* or irinotecan* or capecitabin* or panitumumab* or bevacizumab* or cetuximab* or regorafenib* or FOLFIRI* or FOLFOX* or CapeOX* or FLOX* or XELOX*).mp.
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp time/
22. exp time to treatment/
23. exp early intervention/
24. ((time or delay* or immediate or initial or expectancy or primary or early or deferred or deferral) and chemo*).m_titl.
25. 21 or 22 or 23 or 24
26. 3 or 7 and 20 and 25
27. CROSSOVER PROCEDURE.sh.
28. DOUBLE-BLIND PROCEDURE.sh.
29. SINGLE-BLIND PROCEDURE.sh.
30. (crossover* or cross over*).ti,ab.
31. placebo*.ti,ab.
32. (doubl* adj blind*).ti,ab.
33. allocat*.ti,ab.
34. trial.ti.
35. RANDOMIZED CONTROLLED TRIAL.sh.
36. random*.ti,ab.
37. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
39. 37 not 38
40. 26 and 39

Appendix 5. Criteria for judging risk of bias in the 'Risk of bias' assessment tool

Random sequence generation

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence

Criteria for a judgement of low risk of bias	<p>The investigators described a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> • referring to a random number table; • using a computer random number generator; • coin tossing; • shuffling cards or envelopes; • throwing dice; • drawing of lots; • minimisation.*
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(Continued)

*Minimisation may be implemented without a random element; this is considered to be equivalent to being random.

Criteria for the judgement of high risk of bias	<p>The investigators described a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> • sequence generated by odd or even date of birth; • sequence generated by some rule, based on date (or day) of admission; • sequence generated by some rule, based on hospital or clinic record number. <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned above, and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example:</p> <ul style="list-style-type: none"> • allocation by judgement of the clinician; • allocation by preference of the participant; • allocation based on the results of a laboratory test or a series of tests; • allocation by availability of the intervention.
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Criteria for the judgement of unclear risk of bias	Insufficient information about the sequence generation process to permit judgement of low risk or high risk
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Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocation prior to assignment

Criteria for a judgement of low risk of bias	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation.</p> <ul style="list-style-type: none"> • Central allocation (including telephone, web-based, and pharmacy-controlled randomisation) • Sequentially-numbered drug containers of identical appearance • Sequentially-numbered, opaque, sealed envelopes
Criteria for the judgement of high risk of bias.	<p>Participants or investigators enrolling participants could possibly foresee assignments, and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> • using an open random allocation schedule (e.g. a list of random numbers); • assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed, nonopaque, or not sequentially numbered); • alternation or rotation; • date of birth; • case record number; • any other explicitly unconcealed procedure.
Criteria for the judgement of unclear risk of bias.	Insufficient information to permit judgement of low risk or high risk. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definite judgement – for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Criteria for a judgement of low risk of bias	<p>Any one of the following.</p> <ul style="list-style-type: none"> • No blinding, or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
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(Continued)

	<ul style="list-style-type: none"> Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of high risk of bias	Any one of the following. <ul style="list-style-type: none"> No blinding, or incomplete blinding, and the outcome was likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.
Criteria for the judgement of unclear risk of bias	Any one of the following. <ul style="list-style-type: none"> Insufficient information to permit judgement of low risk or high risk. The study did not address this outcome.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors

Criteria for a judgement of low risk of bias.	Any one of the following. <ul style="list-style-type: none"> No blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of high risk of bias.	Any one of the following. <ul style="list-style-type: none"> No blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.
Criteria for the judgement of unclear risk of bias.	Any one of the following. <ul style="list-style-type: none"> Insufficient information to permit judgement of low risk or high risk. The study did not address this outcome.

Incomplete outcome data

Attrition bias due to amount, nature, or handling of incomplete outcome data

Criteria for a judgement of low risk of bias	Any one of the following. <ul style="list-style-type: none"> No missing outcome data. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods.
Criteria for the judgement of high risk of bias	Any one of the following. <ul style="list-style-type: none"> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.

(Continued)

- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Criteria for the judgement of unclear risk of bias

Any one of the following.

- Insufficient reporting of attrition or exclusions to permit judgement of low risk or high risk (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

Selective reporting

Reporting bias due to selective outcome reporting

Criteria for a judgement of low risk of bias

Any of the following.

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available, but it is clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

Criteria for the judgement of high risk of bias.

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes was reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review were reported incompletely, so that they could not be entered in a meta-analysis.
- The study report failed to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for the judgement of unclear risk of bias.

Insufficient information to permit judgement of low risk or high risk. It is likely that the majority of studies will fall into this category.

Other bias

Bias due to problems not covered elsewhere in the table

Criteria for a judgement of low risk of bias

The study appeared to be free of any sources of bias.

Criteria for the judgement of high risk of bias

There was at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Criteria for the judgement of unclear risk of bias

There may be a risk of bias, but there was either:

- insufficient information to assess whether an important risk of bias existed; or

(Continued)

- insufficient rationale or evidence that an identified problem would introduce bias.
-

CONTRIBUTIONS OF AUTHORS

- Yvette Claassen (YC): Draft the protocol; select trials to include; extract data from trials; interpretation of data; draft the final review
- Maxime van der Valk (MV): Select trials to include; extract data from trials; interpretation of data; draft the final review
- Anne Breugom (AB): Draft the protocol; select trials to include; co-authoring the final review
- Martine Frouws (MF): Co-authoring draft of the protocol; co-authoring final review
- Esther Bastiaannet (EB): Designing the review; co-ordinating the review; interpretation of data; comments and general advice on the protocol and review
- Gerrit-Jan Liefers (GL): Comments and general advice on the review
- Cornelis van de Velde (CV): Comments and general advice on the review
- Ellen Kapiteijn (EK): Co-ordinating the review; interpretation of data; comments and general advice on the protocol and review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- No sources of support supplied, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had planned to perform subgroup and sensitivity analyses. However, due to the very limited number of included studies, these analyses were not possible.

INDEX TERMS

Medical Subject Headings (MeSH)

*Time-to-Treatment; Antineoplastic Agents [adverse effects] [*therapeutic use]; Asymptomatic Diseases [*therapy]; Colonic Neoplasms [*drug therapy] [*mortality] [pathology]; Confidence Intervals; Diarrhea [chemically induced]; Drug Administration Schedule; Nausea [chemically induced]; Palliative Care [*statistics & numerical data]; Proportional Hazards Models; Randomized Controlled Trials as Topic; Rectal Neoplasms [*drug therapy] [*mortality] [pathology]; Stomatitis [chemically induced]; Survival Analysis; Vomiting [chemically induced]

MeSH check words

Humans