National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[D4] Local and systemic treatments for metastatic colorectal cancer isolated in the peritoneum

NICE guideline TBC

Evidence reviews

July 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

Contents

1

Optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum

This evidence review supports recommendation 1.5.9.

Review question

What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Introduction

Peritoneal carcinomatosis from colorectal cancer is the second-most common cause of death from colorectal cancer after liver metastases. Palliative systemic chemotherapy has commonly been used in an attempt to prolong survival for patients with peritoneal carcinomatosis. Efforts to achieve long-term survival have seen the combined use of cytoreductive surgery (CRS) to remove the metastases and heated intraperitoneal chemotherapy (HIPEC) to eradicate the residual disease. However, CRS with HIPEC is associated with high rates of morbidity and treatment-related mortality (Mehta 2016; Verwaal 2003). Therefore, the aim of this review was to determine the most effective combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the peritoneum that is potentially curable with local treatments such as CRS and HIPEC.

Summary of the protocol

Please see Table 1 for a summary of the population, intervention, comparison and outcomes (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with colorectal cancer with metastases isolated in the peritoneum. Subgroups: • Symptomatic or asymptomatic primary colorectal tumour • Synchronous or metachronous metastases
Intervention	• Cytoreductive surgery (CRS) • CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) • Systemic anti-cancer therapy (SACT) alone
Comparison	• Individual interventions or combinations of interventions compared to each other • Best supportive care
Outcomes	**Critical** • Progression-free survival • Overall survival • Overall quality of life **Important**

	• Treatment-related mortality • Any grade 3 or 4 complications • Length of hospital stay

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Two randomised controlled trials (RCTs) and 1 observational study (4 publications) were included in this review (PRODIGE 7 [Quenet 2016]; van Oudheusden 2015; Verwaal 2003 [Verwaal 2008]).

The included studies are summarised in Table 2.

One RCT compared CRS + HIPEC + oxaliplatin to CRS only (PRODIGE 7 [Quenet 2016]) and the other RCT compared CRS + HIPEC + SACT to surgery + SACT (Verwaal 2003; Verwaal 2008). The observational study compared chemotherapy (with or without Bevacizumab) to supportive care (van Oudheusden 2015).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention/Comparison	Outcomes
Comparison 1: CRS with HIPEC versus CRS +/- SACT			
PRODIGE 7 (Quenet 2016) Multi-centre RCT France	N=264 patients aged 18-70 with histopathologically confirmed colorectal cancer; peritoneal carcinoma extension ≤ 25 (Sugarbaker Index, determined intra operatively).	CRS + HIPEC + oxaliplatin versus CRS alone	• Overall survival • Treatment-related mortality • Grade 3 or 4 complications

Study	Population	Intervention/Comparison	Outcomes
Comparison 1: CRS with HIPEC versus CRS +/- SACT			
Verwaal 2003; Verwaal 2008 Single-centre RCT Netherlands	N=105 patients with histologically proven peritoneal metastases of colorectal adenocarcinoma or positive cytology of ascites.	CRS + HIPEC + SACT versus standard surgery and chemotherapy.	• Overall survival • Treatment-related mortality
Comparison 2: SACT versus supportive care			
van Oudheusden 2015 Retrospective cohort study Netherlands	N=186 patients with metachronous peritoneal carcinomatosis of colorectal origin.	Systemic treatment versus no systemic treatment.	• Overall survival

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; N: number; RCT: randomised controlled trial; SACT: systemic anti-cancer therapy

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Comparison 1: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) versus CRS +/- systemic anti-cancer therapy (SACT)

Critical outcomes

Progression-free survival

No evidence was identified to inform this outcome.

Overall survival

- Low quality evidence from 1 RCT (N=265; median follow-up 64 months) showed no clinically important difference in 5-year overall survival between those receiving CRS + HIPEC + oxaliplatin compared to those receiving CRS alone.
- Very low quality evidence from 1 RCT (N=105; median follow-up 22 months) showed a clinically important increase in 2 year overall survival between those receiving CRS + HIPEC + SACT compared to those receiving surgery + SACT.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Treatment-related mortality

- Low quality evidence from 1 RCT (N=265) showed no clinically important difference in 30-day treatment-related mortality between those receiving CRS + HIPEC + oxaliplatin compared to those receiving CRS alone.
- Very low quality evidence from 1 RCT (N=105) showed no clinically important difference in 30-day treatment-related mortality between those receiving CRS + HIPEC + SACT compared to those receiving surgery + SACT.

Any grade 3 or 4 complications

- Low quality evidence from 1 RCT (N=265) showed a clinically important increase in grade 3 or 4 complications between those receiving CRS + HIPEC + oxaliplatin compared to those receiving CRS alone.

Length of hospital stay

No evidence was identified to inform this outcome.

Comparison 2: Systemic anti-cancer therapy (SACT) versus supportive care

Critical outcomes

Progression free survival

No evidence was identified to inform this outcome.

Overall survival

- Very low quality evidence from 1 retrospective cohort study (N=186) showed a clinically important increase in 50-month overall survival between those receiving SACT (chemotherapy alone) compared to those receiving supportive care.
- Very low quality evidence from 1 retrospective cohort study (N=186) showed a clinically important increase in 50-month overall survival between those receiving SACT (chemotherapy + bevacizumab) compared to those receiving supportive care.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Treatment-related mortality

No evidence was identified to inform this outcome.

Any grade 3 or 4 complications

No evidence was identified to inform this outcome.

Length of hospital stay

No evidence was identified to inform this outcome.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Progression-free survival, overall survival, and overall quality of life were considered critical outcomes for decision making because progression of the metastases suggests ineffective treatment, potentially requiring further treatment and affecting overall survival. Quality of life was a critical outcome because of the impact that different treatment options can have on patients' functioning and the potential long term adverse effects.

Treatment-related mortality, grade 3 or 4 complications, and length of hospital stay were identified as important outcomes because they are indicative of the short-term side effects of treatment.

The quality of the evidence

Evidence was available from 1 RCT comparing CRS + HIPEC + SACT to surgery + SACT, 1 RCT comparing CRS + HIPEC + oxaliplatin to CRS only and 1 observational study which compared chemotherapy (with or without bevacizumab) to supportive care without any systemic therapy.

Evidence was available for overall survival, any grade 3 or 4 complications and treatment-related mortality. The evidence was assessed using GRADE and varied from very low to low quality. The quality of evidence was downgraded because of methodological limitations affecting the risk of bias and imprecision in the risk estimate.

Methodological limitations affecting the risk of bias were due to a lack of information regarding certain details such as randomisation, allocation methods, and outcomes measured. One study failed to report the number of patients randomised; another reported high levels of attrition; and another reported differences between the two groups at baseline.

Indirectness was also an issue as three studies included patients with appendiceal disease; and in two of these studies, protocol violations also occurred.

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes.

Benefits and harms

Despite the low quality of the evidence, it showed SACT to be beneficial in terms of overall survival. Offering SACT is also current practice. Based on the clinical evidence and their clinical expertise, the committee decided that SACT should be offered to patients with colorectal cancer with isolated peritoneal metastases.

Evidence for CRS and HIPEC were more mixed. In the PRODIGE 7 trial (Quenet 2018), overall survival rates for all patients were higher than expected (both arms received CRS), which the committee interpreted as evidence that high quality surgery is beneficial for survival outcomes. Additionally, the evidence indicated that there could be some benefit in overall survival for those whose treatment included CRS, HIPEC and SACT. Receiving active treatment, as opposed to supportive care increases the chance for survival. However. there are also risks of mortality and morbidity that are associated with surgical interventions.

The committee noted that the doses of oxaliplatin used in the PRODIGE 7 trial are much higher than those used in the UK and could explain the high level of toxicity in the treatment arm (CRS + HIPEC + oxaliplatin vs CRS alone). While lower doses of oxaliplatin are used in the UK, this drug still has a risk of severe toxicity. The committee were aware of non-randomised evidence (Prada-Villeverde 2014) that compared CRS + HIPEC (mitomycin C) versus CRS + HIPEC (oxaliplatin) that found that there was no statistically significant difference between groups in terms of median overall survival and that effectiveness of regimens with oxaliplatin was linked to the patient's Peritoneal Surface Disease Severity Score (PSDSS).

Based on the evidence and their clinical expertise, the committee decided to recommend referral to a specialist centre where CRS with HIPEC could be considered. The committee made the recommendation in line with the NICE interventional procedure guidance (IPG331) on cytoreductive surgery followed by HIPEC for peritoneal carcinomatosis,

The committee decided to recommend offering chemotherapy and referral to a specialist CRS centre in the same recommendation because these interventions should happen at the same time. That is, making a referral should not wait until chemotherapy has been given, and chemotherapy could be started before the person is reviewed in the HIPEC centre.

Currently in the UK there are only 3 specialist CRS and HIPEC centres.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The recommendation to offer SACT is not anticipated to have a significant resource impact as it is already standard practice to offer SACT to patients who are considered fit enough. The recommendation to consider referral to specialist centres has the potential to increase the number of referrals to specialist centres but this does not necessarily mean that more

procedures will take place because a significant proportion of patients with colorectal peritoneal metastases are not suitable for CRS with HIPEC. Therefore it was considered unlikely that the recommendation would have a significant resource impact.

In cost-effectiveness terms, the use of CRS and HIPEC would increase treatment costs but this may be offset, at least partially, by downstream cost savings associated with better disease control. Also if potential benefits in survival were realised then the interventions could be cost-effective in cost per QALY terms.

Other factors the committee took into account

The committee acknowledged the ongoing CAIRO 6 trial, which is assessing perioperative systemic therapy and cytoreductive surgery with HIPEC compared to upfront cytoreductive surgery with HIPEC alone for resectable colorectal peritoneal metastases. The results from this trial may provide evidence regarding optimal treatment strategies.

The committee recognised that there may be barriers to accessing specialist centres for some people who live far away from these centres due to the distance and difficulty or cost of transport. The option of receiving treatment in a centre far away from home and family could impact the decision that a patient makes about their care. There are currently 3 specialist centres offering CRS with HIPEC in the country, one in Basingstoke, one in Birmingham and one in Manchester. While the guideline recommends referring all people with metastatic colorectal cancer isolated in the peritoneum to the specialist centre for consideration of CRS with HIPEC, the patient would only need to travel to a specialist centre once the team in the specialist centre has reviewed the patient's records and deemed CRS with HIPEC is appropriate for them. Barriers to care in specialist centres for those living far away from these centres could be alleviated by ensuring transport is available to those who require assistance and suitable hostel type accommodation for relatives and carers is made available at major referral sites when daily visiting is not realistic because of the distance.

References

Mehta 2016

Mehta S, Gelli M and Agarwal D (2016) Complications of cytoreductive surgery and HIPEC in the treatment of peritoneal metastases. Indian Journal of Surgical Oncology 7(2): 225-229

Prada-Villaverde 2014

Prada-Villaverde A, Esquivel J, Lowy A, et al. (2014) The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with Mitomycin C versus Oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. Journal of Surgical Oncology 110(7): 779-785

PRODIGE 7 [Quenet 2018]

Quenet F, Dominique E, Lise R, et al. (2018) A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. Journal of Clinical Oncology 36: LBA3503

van Oudheusden 2015

van Oudheusden T, Razenberg L, van Gestel Y, et al. (2015) Systemic treatment of patients with metachronous peritoneal carcinomatosis of colorectal origin. Scientific Reports 21(5): 18632

Verwaal 2003

Verwaal V, Van Ruth S and De Bree E (2003) Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. Journal of Clinical Oncology 21(20): 3737-3743

Verwaal V, Bruin S, Boot H, et al. (2008) 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Annals of Surgical Oncology 15(9): 2426-32

Appendices

Appendix A – Review protocol

Review protocol for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Table 3: Review protocol for the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum

Field (based on PRISMA-P)	Content
Review question in guideline	What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?
Type of review question	Intervention
Objective of the review	To determine the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum.
Eligibility criteria – population/disease/condition/issue/domain	Adults with colorectal cancer with metastases isolated in the peritoneum Subgroups (analysed separately): • Symptomatic or asymptomatic primary colorectal tumour • Synchronous or metachronous metastases
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Cytoreductive surgery (CRS) • CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) • Systemic anti-cancer therapy (SACT) alone
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Individual interventions or combinations of interventions compared to each other • Best supportive care
Outcomes and prioritisation	**Critical:** • Progression-free survival (MID: statistical significance) • Overall survival (MID: statistical significance) • Overall quality of life measured using validated scales (MID: published MIDs from literature, see below) **Important:** • Treatment-related mortality (MID: statistical significance) • Any grade 3 or 4 complications (MID: statistical significance) • Length of hospital stay (MID: statistical significance) Quality of life MIDs from the literature: • EORTC QLQ-C30: 5 points

	• EORTC QLQ-CR29: 5 points • EORTC QLQ-CR38: 5 points • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points • FACT-G: 5 points • SF-12: > 3.77 for the mental component summary and > 3.29 for the physical component summary • SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Comparative observational studies will only be considered if eligible RCTs are not available
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post 1995 Studies conducted post 1995 will be considered for this review question because the guideline committee considered that some of the treatments were not commercially available before then.
Proposed sensitivity/sub-group analysis, or meta-regression	Observational studies should include multivariate analysis controlling for the following confounding factors: • Age • Synchronous or metachronous • Peritoneal cancer index
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion

	• Limit to RCTs and systematic reviews in first instance, but download all results • Dates: from 1995
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual **Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • ROBINS-I for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	**Synthesis of data:** Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. **Minimally important differences**: The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).

Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan 5 software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols; PROSPERO: International prospective register of systematic reviews; RCT: randomised controlled trial; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROBIS: a tool for assessing risk of bias in systematic reviews; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: What is the optimal combination 3 and sequence of local and systemic treatments in patients presenting with met- 4 astatic colorectal cancer isolated in the peritoneum?

5 Databases: Embase/Medline

6 Last searched on: 21/05/2018

#	Search
1	(exp colorectal cancer/ or exp colon tumour/ or exp rectum tumour/) use emez
2	exp colorectal neoplasms/ use ppez
3	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	Peritoneum metastasis/ use emez
6	peritoneal neoplasms/ use ppez
7	((peritoneum or peritoneal) adj3 (disseminat* or metasta* or migrat*)).tw.
8	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (peritoneum metasta* or peritoneal metasta* or peritoneal carcinom*)).tw.
9	or/5-7
10	4 and 9
11	10 or 8
12	cytoreductive surgery/ use emez or cytoreduction Surgical Procedures/ use ppez
13	surgery/ use emez or surgical procedures, operative/ use ppez or laparotomy/
14	(cytoreduc* or cyto-reduc* or CRS or debulk* or excis* or peritonectom* or operat* or resect* or surg*).tw.
15	or/12-14
16	exp antineoplastic agent/ use emez
17	exp antineoplastic agents/ use ppez
18	exp Antineoplastic Protocols/ use ppez
19	multimodality cancer therapy/ use emez
20	cancer therapy/ use emez
21	exp chemotherapy/ use emez
22	cancer combination chemotherapy/ use emez
23	Cancer Vaccines/ use ppez
24	cancer vaccine/ use emez
25	cancer immunotherapy/ use emez
26	exp antibodies, monoclonal/ use ppez or monoclonal antibody/ use emez
27	((anti canc* or anticanc* or anticancerogen* or anticarcinogen* or anti neoplas* or antineoplas* or anti tumo?r* or anti-tumo?r* or cytotoxic*) adj3 (agent* or drug* or protocol* or regimen* or treatment* or therap*)).tw.
28	(SACT or chemosaturat* or chemotherap* or immunotherap* or biological agent* or biological therap*).tw.
29	or/16-28
30	15 or 29
31	11 and 30
32	Letter/ use ppez
33	letter.pt. or letter/ use emez
34	note.pt.
35	editorial.pt.
36	Editorial/ use ppez
37	News/ use ppez
38	exp Historical Article/ use ppez
39	Anecdotes as Topic/ use ppez
40	Comment/ use ppez

#	Search
41	Case Report/ use ppez
42	case report/ or case study/ use emez
43	(letter or comment*).ti.
44	or/32-43
45	randomized controlled trial/ use ppez
46	randomized controlled trial/ use emez
47	random*.ti,ab.
48	or/45-47
49	44 not 48
50	animals/ not humans/ use ppez
51	animal/ not human/ use emez
52	nonhuman/ use emez
53	exp Animals, Laboratory/ use ppez
54	exp Animal Experimentation/ use ppez
55	exp Animal Experiment/ use emez
56	exp Experimental Animal/ use emez
57	exp Models, Animal/ use ppez
58	animal model/ use emez
59	exp Rodentia/ use ppez
60	exp Rodent/ use emez
61	(rat or rats or mouse or mice).ti.
62	or/49-61
63	31 not 62
64	limit 63 to (yr="1995 - current" and english language)
65	remove duplicates from 64

1 **Database: Cochrane Library**

2 Last searched on: 21/05/2018

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)):ti,ab,kw (Word variations have been searched)
3	#1 or #2
4	MeSH descriptor: [Peritoneal Neoplasms] explode all trees
5	MeSH descriptor: [Peritoneum] explode all trees
6	MeSH descriptor: [Neoplasm Metastasis] explode all trees
7	#5 and #6
8	((peritoneum or peritoneal) near/3 (disseminat* or metasta* or migrat*)):ti,ab,kw
9	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (peritoneum metasta* or peritoneal metasta* or peritoneal carcinom*)):ti,ab,kw
10	#4 or #7 or #8
11	#3 and #10
12	#11 or #9
13	MeSH descriptor: [Cytoreduction Surgical Procedures] this term only
14	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
15	MeSH descriptor: [Laparotomy] explode all trees
16	(cytoreduc* or cyto-reduc* or CRS or debulk* or excis* or peritonectom* or operat* or resect* or surg*):ti,ab,kw
17	MeSH descriptor: [Antineoplastic Agents] explode all trees
18	MeSH descriptor: [Antineoplastic Protocols] explode all trees
19	MeSH descriptor: [Cancer Vaccines] this term only
20	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
21	((anti canc* or anticanc* or anticarcinogen* or anti neoplas* or antineoplas* or cytotoxic*) near/3 (agent* or drug* or protocol* or regimen* or treatment* or therap*)):ti,ab,kw (Word variations have been searched)

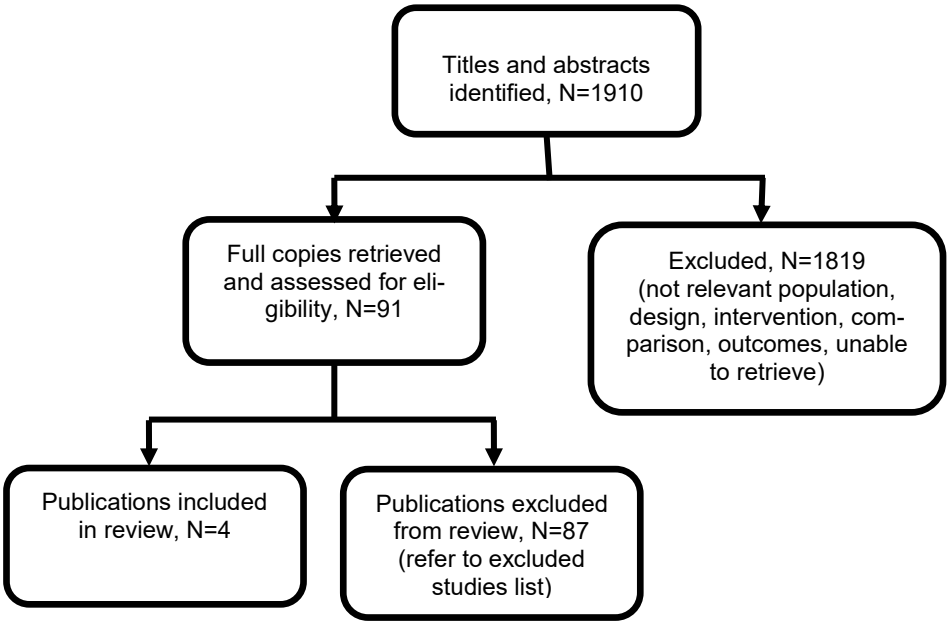
#	Search
22	(SACT or chemotherap* or immunotherap* or biological agent* or biological therap*):ti,ab,kw (Word variations have been searched)
23	{or #13-#22}
24	#12 and #23 Publication Year from 1995 to 2018

1

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation PRODIGE 7 F, Quenet; E, Dominique; R, Lise; G, Diane; G, Laurent; P, Marc; O, Facy; A, Catherine; et al, A UNICANCER phase III trial of hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7, Journal of Clincal Oncology, 36, LBA3503, 2018 **Ref Id** 930671 **Country/ies where the study was carried out** France **Study type** Multi-centre RCT **Aim of the study** The aim of the study was to assess the effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) on postoperative outcomes	**Sample size** N= 265 CRS + HIPEC= 133 CRS alone= 132 **Characteristics** "Baseline characteristics were well balanced" Median age, years= 60 (30-74) **Inclusion criteria** Adults aged 18-70 with histologically confirmed colorectal cancer, peritoneal carcinoma extension ≤ 25 (Sugarbaker Index) (determined intraoperatively), planning to receive standard systemic chemotherapy, chemotherapy for metastatic cancer should be initiated 3 months after surgery, macroscopically complete resection (R1) or surgical reduction of tumour to a residual thickness ≤ 1 mm (R2) is possible, WHO performance status 0-1, life expectancy > 12 weeks, ANC ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^{3,} total bilirubin ≤ 1.5 times upper limit of normal (ULN), AST and ALT ≤ 3 times ULN, alkaline phosphatase ≤ 3 times ULN, creatinine ≤	**Interventions** CRS+HIPEC+oxaliplatin vs CRS alone HIPEC: "Patients undergo surgery and receive standard systemic chemotherapy comprising leucovorin calcium IV followed by fluorouracil IV over 30 minutes. Systemic chemotherapy will continue for at least 6 months (before and after surgery). Patients also undergo CHIP comprising oxaliplatin intraperitoneally during surgery and hyperthermia for 30 minutes." Standard: "Patients undergo surgery and receive standard systemic chemotherapy comprising leucovorin calcium IV followed by fluorouracil IV over 30 minutes. Systemic chemotherapy will continue for at least 6 months (before and after surgery)."	**Details** Randomisation: Patients are stratified (1:) according to participating centre, residual tumuor status (R0/R1 vs R2 ≤ 1 mm), prior regimens of systemic chemotherapy (first vs ≥ second), and preoperative systemic chemotherapy for metastatic disease (yes vs no) Allocation concealment: Not reported Blinding: Not reported Attrition: Not reported Statistical analysis: Not reported Follow up: 1 and 3 months after study therapy, every 3 months for 3 years, and then every 6 months for 2 years Outcomes: Primary - 3 year overall survival. Secondary- 3 year recurrence free survival; morbidity from surgical complications	**Results** Overall survival (median follow up 63.8 months), HR (CI), p-value 1.00 (0.73-1.37), 0.995 Post-operative mortality, n CRS + HIPEC= 2/133 CRS alone= 2/132 60-day grade 3-5 morbidity, n CRS + HIPEC= 32/133 CRS alone= 18/132	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear (randomisation procedure not reported) Allocation concealment: Low risk (not concealed, but unlikely to affect outcome assessment) Blinding of participants and personnel: Low risk (open label, but unlikely to affect outcome assessment) Blinding of outcome assessment: Low risk (unblinded, unlikely to affect outcome assessment) Incomplete outcome data: Unclear risk (Stated that 264 patients were randomised, but then reported 265 patients in the Results, so a discrepancy in their reporting; Did not state how attrition was managed) Selective reporting: High risk (not all outcomes reported in Protocol reported in Abstract; full text not yet available)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
after cytoreductive surgery (CRS) for the treatment of peritoneal carcinomatosis of colorectal origin. **Study dates** February 2008 to January 2014 **Source of funding** UNICANCER	1.25 times ULN, eligible for surgery. **Exclusion criteria** No prior chemohyperthermia or concurrent participation in another study of first-line therapy for this cancer, extraperitoneal metastases, including liver and lung metastasis, carcinomatosis of other origin besides colorectal, in particular appendical carcinomatosis, peripheral neuropathy > grade 3, pregnant or nursing, other cancer in the past 5 years except basal cell skin cancer or carcinoma in situ of the cervix, inability to submit to follow-up medical testing for geographical, social, or psychological reasons.				Other bias: Full text of study not yet available.
Full citation van Oudheusden, T. R., Razenberg, L. G., van Gestel, Y. R., Creemers, G. J., Lemmens, V. E., de Hingh, I. H., Systemic treatment of patients with metachronous peritoneal carcinomatosis of colorectal origin, Scientific Reports, 5, 18632, 2015 **Ref Id** 859167 **Country/ies where the study was carried out** Netherlands	**Sample size** N= 186 n systemic treatment= 92 n no systemic treatment= 94 **Characteristics** Systemic treatment, n= 92 Male, n= 49 Age, years, < 70=62 Age, years, > 70=30 Tumour differentiation, n Good=5 Moderate=52 Poor/undifferentiated=20 Unknown=15 Primary location, n Left=41 Right=37 Rectum/rectosigmoid=9 Overlapping/NOS=5 Histology, n	**Interventions** Systemic treatment versus no systemic treatment Systemic treatment: Received chemotherapy in a palliative setting. 36/92 patients also received treatment including Bevacizumab No systemic treatment: No treatment	**Details** Data collection: Data was extracted from the Eindhoven Cancer Registry that collects data of patients with newly diagnosed cancer in the Southern part of the Netherlands. Data on metachronous metastases were additionally collected between 2010 and 2011 for all patients who were diagnosed with M0 colorectal cancer between 2003 and 2008 in the Dutch Eindhoven Cancer Registry. Outcomes: Overall survival Follow-up: Time from diagnosis of PC to death or end of follow up period (January 2014) Statistical analysis: "Univariable	**Results** Overall survival, HR (CI) Chemotherapy only= 0.51 (0.35-0.73) Chemotherapy + bevacizumab= 0.35 (0.22-0.56) No treatment= reference p-value= 0.10 Median overall survival, months (CI) Chemotherapy only= 13.0 (9.5-16.0) Chemotherapy + bevacizumab= 20.3 (13.7-29.3) No treatment= 3.4 (2.5-4.9) p-value < 0.001	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: High risk of bias (differences in characteristics between groups at baseline) Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Unclear risk of bias (The group of patients without comor-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Retrospective cohort study **Aim of the study** The aim of the study was to assess the use and effect of palliative systemic treating in patients with metachronous peritoneal carcinomatosis of colorectal origin. **Study dates** 2003-2008 and 2010-2011 **Source of funding** This study was funded by the Netherlands Organisation for Health Research and development (ZonMw), project numbers 152002012 and 152001022 and was supported by an unrestricted grant from Roche Pharmaceuticals.	Mucinous=26 Adenocarcinoma=64 Signet ring cell=2 Unknown=0 T-stage, n T1/2=3 T3=68 T4=21 N-stage, n N0=36 N1=35 N2=21 NX=0 M-status, n PC only=32 PC+distant=60 No systemic treatment, n= 94 Male, n=40 Age, years, < 70=29 Age, years, > 70=65 Tumour differentiation, n Good=4 Moderate=53 Poor/undifferentiated=23 Unknown=14 Primary location, n Left=32 Right=46 Rectum/rectosigmoid=15 Overalpping/NOS=1 Histology, n Mucinous=21 Adenocarcinoma=70 Signet ring cell=2 Unknown=1 T-stage, n T1/2=6 T3=65 T4=23 N-stage, n N0=29		and multivariable logistic regression analysis were used to identify predictors of treatment with Bevacizumab. Only variables with $p < 0.10$ in the univariate analysis were included in the multivariable analysis. The predictors were depicted as odds ratios with their 95% confidence intervals. The effect of systemic treatment on mortality was investigated using multivariable cox regression analyses and depicted as hazard ratios. Survival was determined using the Kaplan-Meier method and compared using a Log-rank test. All tests were two sided and p-value < 0.05 was considered to be significant."		bidities received Bevacizumab more often (42% versus. 30%, P = 0.07) Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information** "Moreover, a significant proportion of patients had also other distant metastases. It is therefore uncertain to what extent increased survival can be attributed to the treatment of the peritoneal deposits in these patients, especially so since the effectiveness of targeted therapies in non-peritoneal metastases is supported by stronger evidence"

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	N1=31 N2=32 NX=2 M-status, n PC only=47 PC + distant=47 **Inclusion criteria** Patients with metachronous PC of colorectal origin who received systemic treatment in a palliative setting **Exclusion criteria** Patients that underwent curative surgery for PC (CRS + HIPEC) or were receiving targeted therapy prior to PC diagnosis and those who did not undergo a curative primary tumour resection.				
Full citation Verwaal, V. J., Van Ruth, S., De Bree, E., Van Slooten, G. W., Van Tinteren, H., Boot, H., Zoetmulder, F. A. N., Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer, Journal of Clinical Oncology, 21, 3737-3743, 2003 **Ref Id** 859186 **Country/ies where the study was carried out**	**Sample size** N=105 CRS+HIPEC+SCT= 54 Standard= 51 **Characteristics** CRS+HIPEC+SCT, n= 54 Male, n=34 Age, years, median (IQR)= 53 (28-69) Performance status, n Not recorded=15 0=30 1=9 2=0 Presentation at randomisation, n Primary=30 Recurrent=24 Primary tumour, n Appendix=7 Colon=41 Rectum=6 Differentiation grade, n	**Interventions** CRS + HIPEC + SCT versus standard (surgery + SCT) CRS+HIPEC+SCT: CRS= "The objective of cytoreduction was to leave no macroscopic tumour behind, or at least to have limited residual tumour (2.5 mm in thickness). To achieve this, the stripping of the parietal peritoneum was carried out as described by Sugarbaker et al. Infiltrated viscera were resected if this was compatible with retaining function. Most often this concerned the rectum, parts of small bowel and colon, the gall bladder, parts of the stomach, and the spleen. The greater omentum was routinely removed. Reconstruction of gastrointestinal continuity was postponed	**Details** Randomisation: performed centrally through a computer Allocation concealment: Not reported Blinding: Not reported Attrition: one patient lost to follow up, intention to treat analysis used Statistical analysis: "The survival was estimated by the Kaplan-Meier method and tested with the log-rank test following the intention-to-treat principle. The analysis was planned at a median follow-up of 2 years to have 80% power to detect a 20% absolute difference in survival. To detect this difference, with P < .05 (two-tailed test), at least 100 patients had to be entered." Follow up: 2 years	**Results** Overall survival at 2 years, HR (CI), p-value CRS+HIPEC+SCT= 0.55 (0.32-0.95), 0.032 Standard= reference Overall survival, median follow up 21.6 months (event is overall survival) CRS+HIPEC+SCT= 30/54 (55.6%) Standard=20/51 (39.2%) p-value not reported Treatment-related mortality (30-day mortality), n (for the 48	**Limitations** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk of bias (computer generated) Allocation concealment: Unclear risk of bias (not reported) Blinding of participants and personnel: Low risk of bias (blinding of participants and personnel not possible, and outcome is not likely to be influenced by lack of blinding) Blinding of outcome assessment: Low risk of bias (blinding of outcome assessment not reported however outcome is not likely to have been influenced by lack of blinding)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Netherlands **Study type** Single-centre RCT **Aim of the study** The aim of the study was to assess the effectiveness of CRS with HIPEC compared to standard treatment for patients with peritoneal carcinomatosis of primary colorectal cancer. **Study dates** February 1998 to August 2001 **Source of funding** Not reported	Good=5 Moderate=33 Poor=15 Standard, n= 51 Male, n=24 Age, years, median (IQR)= 55 (29-70) Performance status, n Not recorded=19 0=23 1=7 2=2 Presentation at randomisation, n Primary=28 Recurrent=23 Primary tumour, n Appendix=11 Colon=34 Rectum=6 Differentiation grade, n Good=3 Moderate=27 Poor=18 **Inclusion criteria** "Patients with histologically proven peritoneal metastases of colorectal adenocarcinoma or positive cytology of ascites, who were diagnosed either at first presentation or at recurrence of colorectal adenocarcinoma." **Exclusion criteria** "Signs of distant metastases (liver, lung) on computed tomography (CT) scan of abdomen and chest x-ray were allowed. Patients had to be younger than 71 years and fit for major surgery (normal	until after the lavage, to prevent entrapment of tumour cells in suture lines." HIPEC - "To increase the volume of the abdominal cavity and to prevent spillage of lavage fluid, the skin of the laparotomy wound was pulled up against a retractor. A plastic sheet covered the laparotomy opening to reduce heat loss and to avoid drug spilling. A central aperture was made to allow manipulation to achieve optimal drug and heat distribution. The perfusion circuit consisted of a centrally placed inflow catheter, outflow catheters, placement in the pelvis below left and right diaphragm, a roller pump, and a heat exchanger. Temperature probes were attached to inflow and outflow catheters. Perfusion was started with a minimum of 3 L of isotonic dialysis fluid, at 1 to 2 L/min, and an inflow temperature of 41°C to 42°C. As soon as the temperature in the abdomen was stable above 40°C, MMC was added to the perfusate at a dose of 17.5 mg/m2 followed by 8.8 mg/m2 every 30 minutes. The total dose was limited to 70 mg at maximum. If the core temperature exceeded 39°C, the inflow temperature was reduced. After 90 minutes, the perfusion fluid was drained from the abdomen, and bowel continuity was	Outcomes: Survival (time from randomisation to death from any cause)	patients who underwent CRS followed by HIPEC in the experimental arm) CRS+HIPEC+SCT= 4/48 Standard= 0/51 Median hospital stay, days, median (IQR) (for the 49 patients who underwent surgery in the experimental arm) CRS+HIPEC+SCT= 29 (6-166) Standard= not reported	Incomplete outcome data: Unclear risk of bias (stated that one patient was lost to follow up but intention-to-treat analysis) Selective reporting: Low risk of bias (all outcomes stated in Methods were reported in Results) Other bias: None **Other information** 7/51 patients in the standard arm never started SCT due to withdrawing consent or severe disease progression. 12/38 patients who started SCT in the standard arm stopped because of disease progression, toxicity or were still on treatment. 5/54 patients in the CRT+HIPEC+SCT arm did undergo CRT followed by HIPEC due to death before surgery, development of liver or lung metastases, withdrawing consent or the detection of primary lung cancer. 14/54 patients never started adjuvant chemotherapy after cytoreduction followed by HIPEC.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	bone marrow indices, and normal renal and liver functions). Initially, patients who had received fluorouracil (FU) within 12 months before random assignment were excluded. In the first year of the study, an amendment to the protocol was made to allow inclusion of these patients."	restored. A temporary colostomy was made in most cases if the rectum was resected. A draining gastrostomy and transgastric jejunal feeding tube were inserted. The outflow catheters were used for postoperative drainage of the abdomen cavity" Standard: "Surgery was only performed in cases of symptoms of intestinal obstruction, and consisted of either bypass or stoma surgery. Often, this type of surgery had already been performed before referral for random assignment. Patients started chemotherapy immediately after random assignment or after recovery from surgery. Chemotherapy was given in the local setting, usually by the patients' own medical oncologist, and consisted of FU (intravenous [IV] push-dose of 400 mg/m^2) and leucovorin (IV 80 mg/m^2) on an outpatient basis (modified Laufman regimen25). Treatment was given weekly for 26 weeks, or until progression, death, or unacceptable toxicity. Patients who had already been treated with FU within 12 months before random assignment were treated with irinotecan (350 mg/m^2) at 3 weekly intervals for 6 months or until progression or intolerable toxicity."			
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

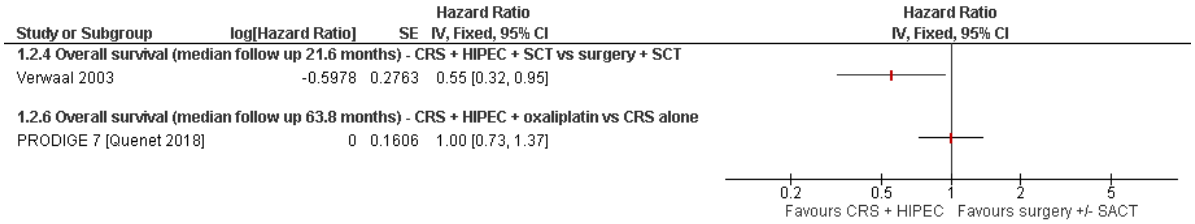
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Verwaal, V. J., Bruin, S., Boot, H., van Slooten, G., van Tinteren, H., 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer, Annals of Surgical Oncology, 15, 2426-32, 2008 **Ref Id** 493134 **Country/ies where the study was carried out** **Study type** 8 year follow up of Verwaal 2003 trial. See Verwaal 2003 for study details. **Aim of the study** **Study dates** **Source of funding**	**Characteristics** **Inclusion criteria** **Exclusion criteria**		Follow up: All patients were seen at the outpatient clinic once every 3 months for 2 years, every 6 months until 5 years after the randomization and once a year thereafter. Outcomes: disease specific survival (time from randomisation to death from any cause), progression free survival	Progression free survival, months (median) CRS+HIPEC+SCT= 12.6 Standard= 7.7 p-value= 0.020	**Other information** "During the followup, one patient was crossed over from the control arm to the HIPEC arm due to recurrence of the disease. This was at 30 months after randomization. For survival, this patient was censored at the moment of the ‘‘crossover’’."

ALT: Alanine transaminase; ANC: absolute neutrophil count; AST: aspartate transaminase; CHIP: intraperitoneal chemohyperthermia; CI: confidence interval; CRS: cytoreductive surgery; CT; computed tomography; FU: Fluorouracil/5-FU; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; IQR: interquartile range; IV: intravenous; MMC: mitomycin C; N: number; NOS: not otherwise specified; PC: peritoneal carcinomatosis; R0: complete resection: R1: microscopic tumour tissue present at resection margin; R2: macroscopic tumour tissue present at resection margin; RCT: randomised controlled trial; ROBINS-I: a tool for assessing risk of bias in non-randomised studies; SCT: systemic chemotherapy/systemic anti-cancer therapy; ULN: upper limit of normal; WHO: World Health Organization

Appendix E – Forest plots

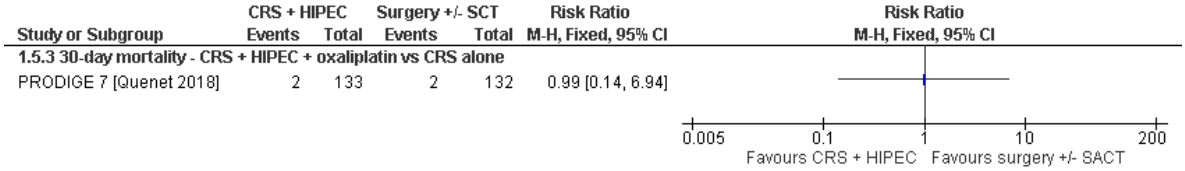
Forest plots for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Figure 2: Comparison 1 – cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) versus CRS +/- systemic anti-cancer therapy (SACT) – overall survival



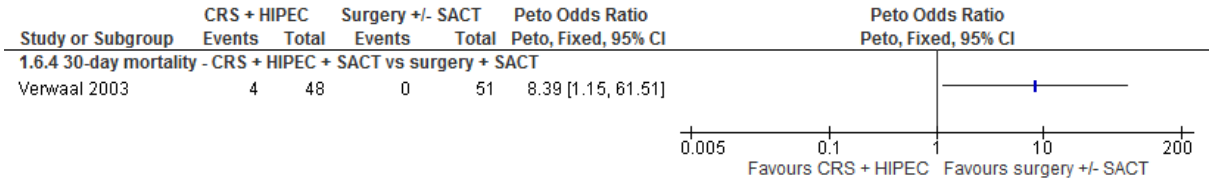
CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; IV: inverse variance; SACT: systemic anti-cancer therapy; SE: standard error

Figure 3: Comparison 1 – cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) versus CRS +/- systemic anti-cancer therapy (SACT) – treatment-related mortality



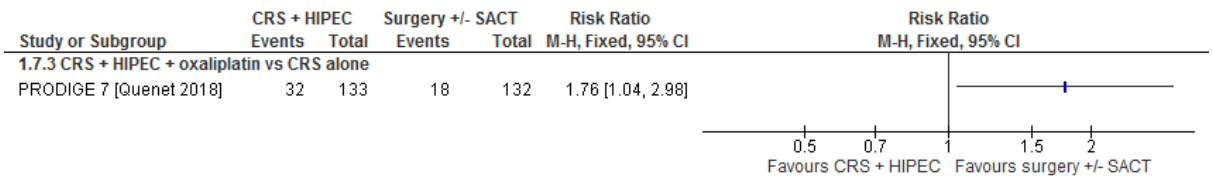
CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; M-H: Mantel–Haenszel; SACT: systemic anti-cancer therapy

Figure 4: Comparison 1 – cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) versus CRS +/- systemic anti-cancer therapy (SACT) – treatment-related mortality



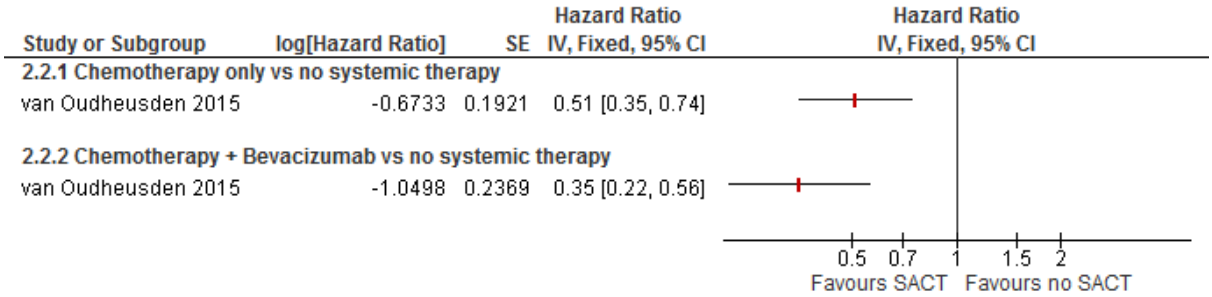
CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; SACT: systemic anti-cancer therapy

Figure 5: Comparison 1 – cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) versus CRS +/- systemic anti-cancer therapy (SACT) – grade 3 or 4 complications



CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; M-H: Mantel–Haenszel; SACT: systemic anti-cancer therapy

Figure 6: Comparison 2 – systemic anti-cancer therapy (SACT) versus supportive care – overall survival



CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; IV: inverse variance; SACT: systemic anti-cancer therapy; SE: standard error

Appendix F – GRADE tables

GRADE tables for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Table 5: Clinical evidence profile for profile for comparison 1: cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) + SACT versus CRS +/- systemic anti-cancer therapy (SACT)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRS + HIPEC + SACT	CRS +/- SACT	Relative (95% CI)	Absolute	Quality	Importance
Progression-free survival												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (median follow up of 21.6 months), event is death from any cause - CRS + HIPEC + SACT versus surgery + SACT												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	serious[2]	serious[3]	none	24/54 (44.4%)	31/51 (60.7%)	HR 0.55 (0.32 to 0.95)	At 2 years surgery + SACT 60.7%[a], CRS + HIPEC + SACT 76.0% (62.2% to 85.2%)	VERY LOW	CRITICAL
Overall survival (median follow up 63.8 months), event is death from any cause – CRS + HIPEC + oxaliplatin vs CRS alone												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	133	132	HR 1.00 (0.73 to 1.37)	Not calculable[5]	LOW	CRITICAL
Overall quality of life												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
30-day treatment-related mortality - CRS + HIPEC + oxaliplatin versus CRS alone												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRS + HIPEC + SACT	CRS +/- SACT	Relative (95% CI)	Absolute		
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	2/133 (1.5%)	2/132 (1.5%)	RR 0.99 (0.14 to 6.94)	990 fewer per 1000 (from 2410 fewer to 4390 more)	LOW	IMPORTANT
30-day treatment-related mortality - CRS + HIPEC + SACT versus surgery + SACT												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	serious[2]	serious[3]	none	4/48 (8.3%)	0/51 (0%)	Peto OR 8.39 (1.15 to 61.51)	-	VERY LOW	IMPORTANT
Grade 3 or 4 complications - CRS + HIPEC + oxaliplatin versus CRS alone												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	32/133 (24.1%)	18/132 (13.6%)	RR 1.76 (1.04 to 2.98)	136 fewer per 1000 (from 136 fewer to 136 more)	LOW	IMPORTANT

CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; OR: odds ratio; RR: relative risk; SACT: systemic anti-cancer therapy
1 7/51 patients (14%) in standard arm never started SCT; 12/38 in standard arm did not complete SCT; 5/54 in treatment arm complete CRS + HIPEC; 14/54 never started adjuvant CT after CRS + HIPEC (Verwaal 2003)
2 Quality of evidence was downgraded by 1 due to 18/105 (17%) patients having appendiceal disease (Verwaal 2003)
3 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (< 300 events for dichotomous outcomes or < 400 participants for continuous outcomes).
4 Quality of evidence was downgraded by 1 because the study did not report the event rates (PRODIGE 7)
5 The absolute effect was not calculable because the study did not report the event rates (PRODIGE 7)
a The absolute risk at 2 years in the control group taken from Verwaal 2003

Table 6: Clinical evidence profile for comparison 2: Systemic anti-cancer therapy (SACT) versus supportive care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SACT	Supportive care	Relative (95% CI)	Absolute		
Progression free survival												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SACT	Supportive care	Relative (95% CI)	Absolute	Quality	Importance
50-month overall survival, event is death from any cause, controlled for sex, age, comorbidity, primary tumour location and systemic therapy - Chemotherapy only versus no systemic therapy												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	49/56 (87.5%)	90/94 (95.7%)	HR 0.51 (0.35 to 0.74)	At 50 months no systemic treatment 4.3%[a], CT only 20.1% (9.7% to 33.2%)	VERY LOW	CRITICAL
50-month overall survival, event is death from any cause, controlled for sex, age, comorbidity, primary tumour location and systemic therapy - Chemotherapy + bevacizumab versus no systemic therapy												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31/36 (86.1%)	90/94 (95.7%)	HR 0.35 (0.22 to 0.56)	At 50 months no systemic treatment 4.3%[a], CT + Bevacizumab 33.2% (17.2% to 50%)	VERY LOW	CRITICAL
Overall quality of life												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Treatment-related mortality												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Any grade 3/4 complications												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Length of hospital stay												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SACT	Supportive care	Relative (95% CI)	Absolute		
0	no evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; CT: chemotherapy; HR: hazard ratio; SACT: systemic anti-cancer therapy
1 Quality of evidence was downgraded by 1 as differences in characteristics between groups at baseline, deviations from intended protocol (van Oudheusden 2015)
2 Quality of evidence downgraded by 1 due to proportion of patients having other distant metastases (van Oudheusden 2015)
3 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (< 300 events for dichotomous outcomes or < 400 participants for continuous outcomes)
a The absolute risk at 50 months in the control group taken from van Oudheusden (2015)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical studies for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Akbarov, E. T., Navruzov, S. N., Abdujapparov, S. B., Hakimov, A. M., Khudayarov, S. S., Islamov, K. J., Babakulob, H. B., Turaev, G. Kh, Use targeted therapy with endolymphatic chemotherapy in peritoneal carcinomatosis of colorectal cancer, Annals of Oncology, Conference, 2009	Full text is an abstract
Baratti, D., Kusamura, S., Iusco, D., Bonomi, S., Grassi, A., Virzi, S., Leo, E., Deraco, M., Postoperative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: A two-center study of 101 patients, Diseases of the Colon and Rectum, 57, 858-868, 2014	Cohort study design not relevant; RCT evidence available
Baratti, D., Kusamura, S., Pietrantonio, F., Guaglio, M., Niger, M., Deraco, M., Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review, Critical Reviews in Oncology/Hematology, 100, 209-222, 2016	Systematic review - studies assessed individually
Bloemendaal, A. L. A., Verwaal, V. J., van Ruth, S., Boot, H., Zoetmulder, F. A. N., Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: A prospective study, European Journal of Surgical Oncology, 31, 1145-1151, 2005	Not comparative - analyses the control arm from Verwaal 2003
Braam, H. J., Boerma, D., Wiezer, M. J., van Ramshorst, B., Hyperthermic intraperitoneal chemotherapy during primary tumour resection limits extent of bowel resection compared to two-stage treatment, European Journal of Surgical Oncology, 39, 988-93, 2013	Comparison not relevant - one-stage primary tumour resection HIPEC versus two-stage procedure
Cao, C., Yan, T. D., Black, D., Morris, D. L., A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin, Annals of Surgical Oncology, 16, 2152-65, 2009	Systematic review - studies assessed individually
Cashin, P. H., Mahteme, H., Spang, N., Syk, I., Frodin, J. E., Torkzad, M., Glimelius, B., Graf, W., Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: A randomised trial, European Journal of Cancer, 53, 155-162, 2016	Intervention not relevant, did not include HIPEC
Cashin, P. H., Mahteme, H., Syk, I., Frodin, J. E., Glimelius, B., Graf, W., Quality of life and cost effectiveness in a randomized trial of patients with colorectal cancer and peritoneal metastases, European Journal of Surgical Oncology., 2018	Intervention not relevant, did not include HIPEC
Cashin, P. H., Graf, W., Nygren, P., Mahteme, H., Patient selection for cytoreductive surgery in colorectal peritoneal carcinomatosis using serum tumour markers: An observational cohort study, Annals of Surgery, 256, 1078-1083, 2012	Cohort study design not relevant; RCT evidence available
Cashin, P. H., Graf, W., Nygren, P., Mahteme, H., Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: Prognosis and treatment of recurrences in	Comparison not relevant - CRS HIPEC versus CRS sequential postoperative intraperitoneal CT

a cohort study, European Journal of Surgical Oncology, 38, 509-515, 2012	
Cashin, P. H., Graf, W., Nygren, P., Mahteme, H., Intraoperative hyperthermic versus postoperative normothermic intraperitoneal chemotherapy for colonic peritoneal carcinomatosis: A case-control study, Annals of Oncology, 23, 647-652, 2012	Comparison not relevant - HIPEC versus normothermic sequential postoperative intraperitoneal chemotherapy (SPIC)
Cavaliere, F., Perri, P., Di Filippo, F., Giannarelli, D., Botti, C., Cosimelli, M., Tedesco, M., Principi, F., Laurenzi, L., Cavaliere, R., Treatment of peritoneal carcinomatosis with intent to cure, Journal of Surgical Oncology, 74, 41-4, 2000	Not comparative
Ceelen, W., Van Nieuwenhove, Y., Putte, D. V., Pattyn, P., Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and hyperthermic intraperitoneal chemoperfusion (HIPEC) for colorectal carcinomatosis, Annals of Surgical Oncology, 21, 3023-3028, 2014	Not comparative
Chia, C. S., Seshadri, R. A., Kepenekian, V., Vaudoyer, D., Passot, G., Glehen, O., Survival outcomes after Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from gastric cancer: A systematic review, Pleura and Peritoneum, 1, 67-77, 2016	Population not relevant - patients had gastric cancer
Chua, T. C., Morris, D. L., Saxena, A., Esquivel, J., Liauw, W., Doerfer, J., Germer, C. T., Kerscher, A. G., Pelz, J. O. W., Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: A multicenter study, Annals of Surgical Oncology, 18, 1560-1567, 2011	Cohort study design not relevant; RCT evidence available
Chua, T. C., Quinn, L. E., Zhao, J., Morris, D. L., Iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent peritoneal metastases, Journal of Surgical Oncology, 108, 81-88, 2013	Comparison not relevant - primary CRS versus iterative CRS
Devilee, R, Simkens, G, Oudheusden, T, Rutten, H, Creemers, G, Tije, B, Nieuwenhuijzen, G, Hingh, I, Timing of systemic treatment in patients undergoing cytoreductive surgery and HIPEC for peritoneal metastases of colorectal origin, Annals of surgical oncology., 23, S80-s81, 2016	Full text is an abstract
Devilee, R. A., Simkens, G. A., van Oudheusden, T. R., Rutten, H. J., Creemers, G. J., ten Tije, A. J., de Hingh, I. H., Increased Survival of Patients with Synchronous Colorectal Peritoneal Metastases Receiving Preoperative Chemotherapy Before Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy, Annals of Surgical Oncology, 23, 2841-2848, 2016	Cohort study design not relevant; RCT evidence available
Elias, D., Delperro, J. R., Sideris, L., Benhamou, E., Pocard, M., Baton, O., Giovannini, M., Lasser, P., Treatment of peritoneal carcinomatosis from colorectal cancer: Impact of complete cytoreductive surgery and difficulties in conducting randomized trials, Annals of Surgical Oncology, 11, 518-521, 2004	Intervention not relevant, did not include HIPEC
Elias, D., Blot, F., Elotmany, A., Antoun, S., Lasser, P., Boige, V., Rougier, P., Ducreux, M., Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy, Cancer, 92, 71-76, 2001	Cohort study design not relevant; RCT evidence available
Elias, D., Gilly, F., Boutitie, F., Quenet, F., Bereder, J. M., Mansvelt, B., Lorimier, G., Dube, P., Glehen, O., Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: Retrospective analysis of 523 patients from a multicentric french study, Journal of Clinical Oncology, 28, 63-68, 2010	Cohort study design not relevant; RCT evidence available

Elias, D., Lefevre, J. H., Chevalier, J., Brouquet, A., Marchal, F., Classe, J. M., Ferron, G., Guilloit, J. M., Meeus, P., Goere, D., Bonastre, J., Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin, Journal of Clinical Oncology, 27, 681-685, 2009	Cohort study design not relevant; RCT evidence available
Elias, D., Pocard, M., Goere, D., HIPEC with oxaliplatin in the treatment of peritoneal carcinomatosis of colorectal origin, Cancer treatment and research, 134, 303-318, 2007	Summaries of previously completed cohort studies and trials
Esquivel, J., Lowy, A. M., Markman, M., Chua, T., Pelz, J., Baratti, D., Baumgartner, J. M., Berri, R., Bretcha-Boix, P., Deraco, M., Flores-Ayala, G., Glehen, O., Gomez-Portilla, A., Gonzalez-Moreno, S., Goodman, M., Halkia, E., Kusamura, S., Moller, M., Passot, G., Pocard, M., Salti, G., Sardi, A., Senthil, M., Spilioitis, J., Torres-Melero, J., Turaga, K., Trout, R., The American Society of Peritoneal Surface Malignancies (ASPSM) Multiinstitution Evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1,013 Patients with Colorectal Cancer with Peritoneal Carcinomatosis, Annals of Surgical Oncology, 21, 4195-4201, 2014	Cohort study design not relevant; RCT evidence available
Eveno, C., Passot, G., Goere, D., Soyer, P., Gayat, E., Glehen, O., Elias, D., Pocard, M., Bevacizumab doubles the early postoperative complication rate after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal origin, Annals of Surgical Oncology, 21, 1792-1800, 2014	Cohort study design not relevant; RCT evidence available
Eveno, C., Pocard, M., Randomized controlled trials evaluating Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in prevention and therapy of peritoneal metastasis: A Systematic review, Pleura and Peritoneum, 1, 169-182, 2016	Systematic review - studies assessed individually
Franko, J., Ibrahim, Z., Gusani, N. J., Holtzman, M. P., Bartlett, D. L., Zeh, Iii H. J., Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis, Cancer, 116, 3756-3762, 2010	Cohort study design not relevant; RCT evidence available
Franko, J., Shi, Q., Goldman, C. D., Pockaj, B. A., Nelson, G. D., Goldberg, R. M., Pitot, H. C., Grothey, A., Alberts, S. R., Sargent, D. J., Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: A pooled analysis of North Central Cancer Treatment Group phase III trials N9741 and N9841, Journal of Clinical Oncology, 30, 263-267, 2012	Comparison not relevant - patients with peritoneal carcinomatosis CRC (pcCRC) versus non-pcCRC
Franko, J., Shi, Q., Meyers, J. P., Maughan, T. S., Adams, R. A., Seymour, M. T., Saltz, L., Punt, C. J. A., Koopman, M., Tournigand, C., Tebbutt, N. C., Diaz-Rubio, E., Souglakos, J., Falcone, A., Chibaudel, B., Heinemann, V., Moen, J., De Gramont, A., Sargent, D. J., Grothey, A., Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database, The Lancet Oncology, 17, 1709-1719, 2016	< 25% of patients in each included trial had peritoneal metastases
Gervais, M. K., Dube, P., McConnell, Y., Drolet, P., Mitchell, A., Sideris, L., Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with oxaliplatin for peritoneal carcinomatosis arising from colorectal cancer, Journal of Surgical Oncology, 108, 438-443, 2013	Cohort study design not relevant; RCT evidence available

Glehen, O., Cotte, E., Schreiber, V., Sayag-Beaujard, A. C., Vignal, J., Gilly, F. N., Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin, British Journal of Surgery, 91, 747-754, 2004	Cohort study design not relevant; RCT evidence available
Glehen, O., Kwiatkowski, F., Sugarbaker, P. H., Elias, D., Levine, E. A., De Simone, M., Barone, R., Yonemura, Y., Cavaliere, F., Quenet, F., Gutman, M., Tentes, A. A. K., Lorimier, G., Bernard, J. L., Bereder, J. M., Porcheron, J., Gomez-Portilla, A., Shen, P., Deraco, M., Rat, P., Gilly, F. N., Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy for the Management of Peritoneal Carcinomatosis from Colorectal Cancer: A Multi-Institutional Study, Journal of Clinical Oncology, 22, 3284-3292, 2004	Cohort study design not relevant; RCT evidence available
Glockzin, G., Gerken, M., Lang, S. A., Klinkhammer-Schalke, M., Piso, P., Schlitt, H. J., Oxaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastasis from appendiceal and colorectal cancer: A retrospective analysis, BMC Cancer, 14 (1) (no pagination), 2014	Cohort study design not relevant; RCT evidence available
Glockzin, G., von Breitenbuch, P., Schlitt, H. J., Piso, P., Treatment-related morbidity and toxicity of CRS and oxaliplatin-based HIPEC compared to a mitomycin and doxorubicin-based HIPEC protocol in patients with peritoneal carcinomatosis: a matched-pair analysis, Journal of Surgical Oncology, 107, 574-8, 2013	Cohort study design not relevant; RCT evidence available
Goere, D., Souadka, A., Faron, M., Cloutier, A. S., Viana, B., Honore, C., Dumont, F., Elias, D., Extent of Colorectal Peritoneal Carcinomatosis: Attempt to Define a Threshold Above Which HIPEC Does Not Offer Survival Benefit: A Comparative Study, Annals of Surgical Oncology, 22, 2958-2964, 2015	Cohort study design not relevant; RCT evidence available
Grass, F., Vuagniaux, A., Teixeira-Farinha, H., Lehmann, K., Demartines, N., Hubner, M., Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis, British Journal of Surgery, 104, 669-678, 2017	Intervention not relevant - pressurized intraperitoneal aerosol chemotherapy
He, T., Chen, Z., Xing, C., Cytoreductive surgery combined with intraperitoneal chemotherapy in the treatment of colorectal peritoneal metastasis: A meta-analysis, International Journal of Clinical and Experimental Medicine, 9, 20562-20570, 2016	Systematic review - studies assessed individually
Hompes, D., D'Hoore, A., Wolthuis, A., Fieuws, S., Mirck, B., Bruin, S., Verwaal, V., The of Oxaliplatin or Mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: A comparative study, Journal of Surgical Oncology, 109, 527-532, 2014	Cohort study design not relevant; RCT evidence available
Huang, C. Q., Feng, J. P., Yang, X. J., Li, Y., Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from colorectal cancer: A case-control study from a Chinese center, Journal of Surgical Oncology, 109, 730-739, 2014	Cohort study design not relevant; RCT evidence available
Huang, C. Q., Min, Y., Wang, S. Y., Yang, X. J., Liu, Y., Xiong, B., Yonemura, Y., Li, Y., Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for peritoneal carcinomatosis from colorectal cancer: A systematic review and meta-analysis of current evidence, Oncotarget, 8, 55657-55683, 2017	Systematic review - studies assessed individually

Huang, C. Q., Yang, X. J., Yu, Y., Wu, H. T., Liu, Y., Yonemura, Y., Li, Y., Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for patients with peritoneal carcinomatosis from colorectal cancer: A phase II study from a Chinese Center, PLoS ONE, 9 (9) (no pagination), 2014	Not comparative
Klaver, C. E. L., Groenen, H., Morton, D. G., Laurberg, S., Bemelman, W. A., Tanis, P. J., Recommendations and consensus on the treatment of peritoneal metastases of colorectal origin: a systematic review of national and international guidelines, Colorectal Disease, 19, 224-236, 2017	Study design not relevant - systematic review of guidelines
Klaver, Y. L. B., Leenders, B. J. M., Creemers, G. J., Rutten, H. J. T., Verwaal, V. J., Lemmens, V. E. P. P., De Hingh, I. H. J. T., Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin, American Journal of Clinical Oncology: Cancer Clinical Trials, 36, 157-161, 2013	Comparison not relevant - compares different systemic treatments
Kobayashi, H., Kotake, K., Sugihara, K., Outcomes of surgery without HIPEC for synchronous peritoneal metastasis from colorectal cancer: Data from a multi-center registry, International Journal of Clinical Oncology, 19, 98-105, 2014	Cohort study design not relevant; RCT evidence available
Kobayashi, H., Kotake, K., Sugihara, K., Impact of surgical resection of synchronous peritoneal metastasis from colorectal cancer: A propensity scorematched analysis, Diseases of the Colon and Rectum, 61 (5), e226, 2018	Full text is an abstract
Kok, N. F., de Hingh, I. H., Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal metastases of colorectal origin, The British journal of surgery, 104, 313-315, 2017	Cohort study design not relevant; RCT evidence available
Kuijpers, A. M., Mehta, A. M., Boot, H., Van leerdam, M. E., Hauptmann, M., Aalbers, A. G., Verwaal, V. J., Perioperative systemic chemotherapy in peritoneal carcinomatosis of lymph node positive colorectal cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, Annals of Oncology, 25, 864-869, 2014	Cohort study design not relevant; RCT evidence available
Lam, J. Y., McConnell, Y. J., Rivard, J. D., Temple, W. J., Mack, L. A., Hyperthermic intraperitoneal chemotherapy + early postoperative intraperitoneal chemotherapy versus hyperthermic intraperitoneal chemotherapy alone: assessment of survival outcomes for colorectal and high-grade appendiceal peritoneal carcinomatosis, American Journal of Surgery, 210, 424-30, 2015	Comparison not relevant - HIPEC EPIC versus HIPEC alone
Lee, L., Alie-Cusson, F., Dube, P., Sideris, L., Postoperative complications affect long-term outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis, Journal of Surgical Oncology, 116, 236-243, 2017	Cohort study design not relevant; RCT evidence available
Maciver, A. H., Lee, N., Skitzki, J. J., Boland, P. M., Francescutti, V., Cytoreduction and hyperthermic intraperitoneal chemotherapy (CS/HIPEC) in colorectal cancer: Evidence-based review of patient selection and treatment algorithms, European Journal of Surgical Oncology, 43, 1028-1039, 2017	Narrative review
Maggiori, L., Goere, D., Viana, B., Tzanis, D., Dumont, F., Honore, C., Eveno, C., Elias, D., Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent?: A case-control study, Annals of Surgery, 258, 116-121, 2013	Cohort study design not relevant; RCT evidence available

Mahteme, H., Hansson, J., Berglund,, Pahlman, L., Glimelius, B., Nygren, P., Graf, W., Improved survival in patients with peritoneal metastases from colorectal cancer: A preliminary study, British Journal of Cancer, 90, 403-407, 2004	Population not relevant, only 8/18 patients had peritoneal metastases
Maillet, M., Glehen, O., Lambert, J., Goere, D., Pocard, M., Msika, S., Passot, G., Elias, D., Eveno, C., Sabate, J. M., Lourenco, N., Andre, T., Gornet, J. M., Early Postoperative Chemotherapy After Complete Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy for Isolated Peritoneal Carcinomatosis of Colon Cancer: A Multicenter Study, Annals of Surgical Oncology, 23, 863-869, 2016	Cohort study design not relevant; RCT evidence available
McConnell, Y. J., Mack, L. A., Francis, W. P., Ho, T., Temple, W. J., HIPEC+EPIC versus HIPEC-alone: differences in major complications following cytoreduction surgery for peritoneal malignancy, Journal of Surgical Oncology, 107, 591-6, 2013	Comparison not relevant - HIPEC EPIC versus HIPEC alone
Mirnezami, R., Mehta, A. M., Chandrakumaran, K., Cecil, T., Moran, B. J., Carr, N., Verwaal, V. J., Mohamed, F., Mirnezami, A. H., Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone, British Journal of Cancer, 111, 1500-1508, 2014	Systematic review; studies assessed individually
Mirnezami, R., Moran, B. J., Harvey, K., Cecil, T., Chandrakumaran, K., Carr, N., Mohamed, F., Mirnezami, A. H., Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal metastases, World Journal of Gastroenterology, 20, 14018-32, 2014	Systematic review - studies assessed individually
Nadler, A., McCart, J. A., Govindarajan, A., Peritoneal Carcinomatosis from Colon Cancer: A Systematic Review of the Data for Cytoreduction and Intraperitoneal Chemotherapy, Clinics in Colon & Rectal Surgery, 28, 234-46, 2015	Systematic review - studies assessed individually
Park, S. Y., Choi, G. S., Park, J. S., Kim, H. J., Yang, C. S., Kim, J. G., Kang, B. W., Efficacy of Early Postoperative Intraperitoneal Chemotherapy After Complete Surgical Resection of Peritoneal Metastasis from Colorectal Cancer: A Case-Control Study from a Single Center, Annals of Surgical Oncology, 23, 2266-2273, 2016	Cohort study design not relevant; RCT evidence available
Passot, G., Vaudoyer, D., Cotte, E., You, B., Isaac, S., Noel Gilly, F., Mohamed, F., Glehen, O., Progression following neoadjuvant systemic chemotherapy may not be a contraindication to a curative approach for colorectal carcinomatosis, Annals of Surgery, 256, 125-129, 2012	Cohort study design not relevant; RCT evidence available
Passot, G., You, B., Boschetti, G., Fontaine, J., Isaac, S., Decullier, E., Maurice, C., Vaudoyer, D., Gilly, F. N., Cotte, E., Glehen, O., Pathological response to neoadjuvant chemotherapy: A new prognosis tool for the curative management of peritoneal colorectal carcinomatosis, Annals of Surgical Oncology, 21, 2608-2614, 2014	Cohort study design not relevant; RCT evidence available
Pelz, J. O. W., Chua, T. C., Esquivel, J., Stojadinovic, A., Doerfer, J., Morris, D. L., Maeder, U., Germer, C., Kerscher, A. G., Evaluation of Best Supportive Care and Systemic Chemotherapy as Treatment Stratified according to the retrospective Peritoneal Surface Disease Severity Score (PSDSS) for Peritoneal Carcinomatosis of Colorectal Origin, BMC Cancer, 10, 689, 2010	No case mix adjustments
Pestieau, S. R., Sugarbaker, P. H., Ota, D. M., Treatment of primary colon cancer with peritoneal carcinomatosis: Comparison of concomitant versus. delayed management, Diseases of the Colon and Rectum, 43, 1341-1348, 2000	Cohort study design not relevant; RCT evidence available

Piso, P., Koller, M., Arnold, D., J. Schlitt H, Glockzin, G., Multimodality treatment of colorectal peritoneal metastasis with perioperative systemic chemotherapy, cytoreductive surgery (CRS), and HIPEC: First safety results of the COMBATAC trial, Journal of Clinical Oncology. Conference, 32, 2014	Full text is an abstract; not comparative
Prada-Villaverde, A., Esquivel, J., Lowy, A. M., Markman, M., Chua, T., Pelz, J., Baratti, D., Baumgartner, J. M., Berri, R., Bretcha-Boix, P., Deraco, M., Flores-Ayala, G., Glehen, O., Gomez-Portilla, A., Gonzalez-Moreno, S., Goodman, M., Halkia, E., Kusamura, S., Moller, M., Passot, G., Pocard, M., Salti, G., Sardi, A., Senthil, M., Spiliotis, J., Torres-Melero, J., Turaga, K., Trout, R., The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with Mitomycin C versus Oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery, Journal of Surgical Oncology, 110, 779-785, 2014	Cohort study design not relevant; RCT evidence available
Rivard, J. D., McConnell, Y. J., Temple, W. J., Mack, L. A., Cytoreduction and heated intraperitoneal chemotherapy for colorectal cancer: Are we excluding patients who may benefit?, Journal of Surgical Oncology, 109, 104-109, 2014	Not comparative
Rovers, K. P., Simkens, G. A., Punt, C. J., van Dieren, S., Tanis, P. J., de Hingh, I. H., Perioperative systemic therapy for resectable colorectal peritoneal metastases: Sufficient evidence for its widespread use? A critical systematic review, Critical Reviews in Oncology/Hematology, 114, 53-62, 2017	Systematic review - studies assessed individually
Sammartino, P., Sibio, S., Biacchi, D., Cardi, M., Accarpio, F., Mingazzini, P., Rosati, M. S., Cornali, T., Di Giorgio, A., Prevention of peritoneal metastases from colon cancer in high-risk patients: Preliminary results of surgery plus prophylactic HIPEC, Gastroenterology Research and Practice, (no pagination), 2012	Cohort study design not relevant; RCT evidence available
Sammartino, P., Sibio, S., Biacchi, D., Cardi, M., Mingazzini, P., Rosati, M. S., Cornali, T., Sollazzo, B., Atta, J. M., Di Giorgio, A., Long-term results after proactive management for locoregional control in patients with colonic cancer at high risk of peritoneal metastases, International Journal of Colorectal Disease, 29, 1081-1089, 2014	Cohort study design not relevant; RCT evidence available
Scaringi, S., Leo, F., Canonico, G., Batignani, G., Ficari, F., Tonelli, F., The role of cytoreductive surgery alone for the treatment of peritoneal carcinomatosis of colorectal origin. A retrospective analysis with regard to multimodal treatments, Hepato-Gastroenterology, 56, 650-655, 2009	Not comparative
Shen, P., Stewart, Iv J. H., Levine, E. A., Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Surface Malignancy: Overview and Rationale, Current Problems in Cancer, 33, 125-141, 2009	Narrative review
Shen, P., Stewart, J. H, Levine, E. A., The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer with peritoneal surface disease, Current Problems in Cancer, 33, 154-67, 2009	Not comparative
Ung, L., C. Chua T, L. Morris D, Peritoneal metastases of lower gastrointestinal tract origin: A comparative study of patient outcomes following cytoreduction and intraperitoneal chemotherapy, Journal of Cancer Research and Clinical Oncology, 139, 1899-1908, 2013	Cohort study design not relevant; RCT evidence available
Ung, L., Chua, T. C., Morris, D. L., Cure for peritoneal metastases? An evidence-based review, ANZ Journal of Surgery, 83, 821-826, 2013	Narrative review

Vaira, M., Cioppa, T., D'Amico, S., De Marco, G., D'Alessandro, M., Fiorentini, G., De Simone, M., Treatment of Peritoneal carcinomatosis from colonic cancer by cytoreduction, peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC). Experience of ten years, In Vivo, 24, 79-84, 2010	Cohort study design not relevant; RCT evidence available
Vallicelli, C., Cavaliere, D., Catena, F., Coccolini, F., Ansaloni, L., Poiasina, E., Abongwa, H. K., De Simone, B., Alberici, L., Framarini, M., Verdecchia, G. M., Management of peritoneal carcinomatosis from colorectal cancer: review of the literature, International Journal of Colorectal Disease, 29, 895-8, 2014	Narrative review
van Oudheusden, T. R., Braam, H. J., Nienhuijs, S. W., Wiezer, M. J., van Ramshorst, B., Luyer, M. D., Lemmens, V. E., de Hingh, I. H., Cytoreduction and hyperthermic intraperitoneal chemotherapy: a feasible and effective option for colorectal cancer patients after emergency surgery in the presence of peritoneal carcinomatosis, Annals of Surgical Oncology, 21, 2621-6, 2014	Cohort study design not relevant; RCT evidence available
Van Oudheusden, T. R., Nienhuijs, S. W., Luyer, M. D., Nieuwenhuijzen, G. A., Lemmens, V. E., Rutten, H. J., De Hingh, I. H., Incidence and treatment of recurrent disease after cytoreductive surgery and intraperitoneal chemotherapy for peritoneally metastasized colorectal cancer: A systematic review, European Journal of Surgical Oncology, 41, 1269-1277, 2015	Systematic review - studies assessed individually
Verwaal, V. J., Cytoreduction and HIPEC for peritoneal carcinomatosis from colorectal origin: The Amsterdam experience, Acta Chirurgica Belgica, 106, 283-284, 2006	Editorial
Verwaal, V. J., Results of cytoreduction followed by HIPEC in carcinomatosis of colorectal origin, Cancer Treatment & Research, 134, 291-301, 2007	Narrative review
Verzijden, Jcm, Klaver, Ylb, de, Hingh Ignace Hjt, Bleichrodt, Rp, Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis in patients with colorectal cancer, Cochrane Database of Systematic Reviews, 2010	Protocol
Waite, K., Youssef, H., The Role of Neoadjuvant and Adjuvant Systemic Chemotherapy with Cytoreductive Surgery and Heated Intraperitoneal Chemotherapy for Colorectal Peritoneal Metastases: A Systematic Review, Annals of Surgical Oncology, 24, 705-720, 2017	Systematic review - studies assessed individually
Wu, W., Yan, S., Liao, X., Xiao, H., Fu, Z., Chen, L., Mou, J., Yu, H., Zhao, L., Liu, X., Curative versus palliative treatments for colorectal cancer with peritoneal carcinomatosis: A systematic review and metaanalysis, Oncotarget, 8, 113202-113212, 2017	Systematic review - studies assessed individually
Yan, T. D., Black, D., Savady, R., Sugarbaker, P. H., Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma, Journal of Clinical Oncology, 24, 4011-4019, 2006	Systematic review - studies assessed individually
Yuan, H., Zheng, B., Tu, S., Clinical research of intraperitoneal implantation of sustained-release 5-fluorouracil in advanced colorectal cancer, World Journal of Surgical Oncology, 13, 320, 2015	Population not relevant - mixed population with peritoneal, liver and other liver metastases. Intervention not relevant - not HIPEC
Zani, S., Papalezova, K., Stinnett, S., Tyler, D., Hsu, D., Blazer, Iii D. G., Modest advances in survival for patients with colorectal-associated peritoneal carcinomatosis in the era of modern chemotherapy, Journal of Surgical Oncology, 107, 307-311, 2013	Comparison not relevant - received CT pre or post 2003

Zhu, Y., Hanna, N., Boutros, C., Alexander Jr, H. R., Assessment of clinical benefit and quality of life in patients undergoing cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) for management of peritoneal metastases, Journal of Gastrointestinal Oncology, 4, 62-71, 2013	Narrative review

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Appendix L – Research recommendations

Research recommendations for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

No research recommendations were made for this review question.