National Institute for Health and Care Excellence

Final

# Colorectal cancer (update)

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

*NICE guideline NG151*

*Evidence reviews*

*January 2020*

*Final*

*Developed by the National Guideline Alliance part of 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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# Contents

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

| | |
|---|---|
| | • Treatment-related mortality<br>• Any grade 3 or 4 complications<br>• 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)<br><br>Multi-centre RCT<br><br>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<br>• Treatment-related mortality<br>• Grade 3 or 4 complications |

| Study | Population | Intervention/Comparison | Outcomes |
|---|---|---|---|
| **Comparison 1: CRS with HIPEC versus CRS +/- SACT** | | | |
| | | | |
| Verwaal 2003; Verwaal 2008<br><br>Single-centre RCT<br><br>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<br>• Treatment-related mortality |
| **Comparison 2: SACT versus supportive care** | | | |
| van Oudheusden 2015<br><br>Retrospective cohort study<br><br>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 that a referral to a nationally commissioned specialist centre where CRS with HIPEC could be considered should be discussed within a multidisciplinary team. 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 that offering chemotherapy and MDT discussion of referral to a nationally commissioned specialist centre should be 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 specilialist centre.

**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 offer 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. Currently in the UK there are only 3 nationally commissioned specialist CRS and HIPEC centres. If the demand exceeds the capacity of these centres, there may be a need to expand the current centres or develop new centres in the future.

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 nationally commissioned specialist centres offering CRS with HIPEC in the country, one in Basingstoke, one in Birmingham and one in Manchester. Even if a referral to a nationally commissioned specialist centre is done, the patient would only need to travel to the 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 the 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<br><br>Subgroups (analysed separately):<br>• Symptomatic or asymptomatic primary colorectal tumour<br>• Synchronous or metachronous metastases |
| Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s) | • Cytoreductive surgery (CRS)<br>• CRS with hyperthermic intraperitoneal chemotherapy (HIPEC)<br>• 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<br>• Best supportive care |
| Outcomes and prioritisation | **Critical:**<br>• Progression-free survival (MID: statistical significance)<br>• Overall survival (MID: statistical significance)<br>• Overall quality of life measured using validated scales (MID: published MIDs from literature, see below)<br><br>**Important:**<br>• Treatment-related mortality (MID: statistical significance)<br>• Any grade 3 or 4 complications (MID: statistical significance)<br>• Length of hospital stay (MID: statistical significance)<br><br>Quality of life MIDs from the literature:<br>• EORTC QLQ-C30: 5 points |

| | |
|---|---|
| | • EORTC QLQ-CR29: 5 points<br>• EORTC QLQ-CR38: 5 points<br>• EQ-5D: 0.09 using FACT-G quintiles<br>• FACT-C: 5 points<br>• FACT-G: 5 points<br>• SF-12: > 3.77 for the mental component summary and > 3.29 for the physical component summary<br>• 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<br>• RCTs<br>• Comparative observational studies will only be considered if eligible RCTs are not available |
| Other inclusion exclusion criteria | Inclusion:<br>• English-language<br>• All settings will be considered that consider medications and treatments available in the UK<br>• Studies published post 1995<br><br>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:<br>• Age<br>• Synchronous or metachronous<br>• 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.<br><br>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).<br>'GRADEpro' will be used to assess the quality of evidence for each outcome.<br><br>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<br>Limits (e.g. date, study design):<br>• Apply standard animal/non-English language exclusion |

| | |
|---|---|
| | • Limit to RCTs and systematic reviews in first instance, but download all results<br>• Dates: from 1995 |
| Identify if an update | Not an update |
| Author contacts | https://www.nice.org.uk/guidance/indevelopment/gid-ng10060<br>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<br><br>**Appraisal of methodological quality:**<br>The methodological quality of each study will be assessed using an appropriate checklist:<br>• ROBIS for systematic reviews<br>• Cochrane risk of bias tool for RCTs<br>• ROBINS-I for non-randomised studies<br>The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE.<br><br>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:**<br>Pairwise meta-analysis of randomised trials will be conducted where appropriate.<br>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.<br><br>**Minimally important differences**:<br>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.<br><br>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<br>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 4 metastatic 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 antitumo?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) |

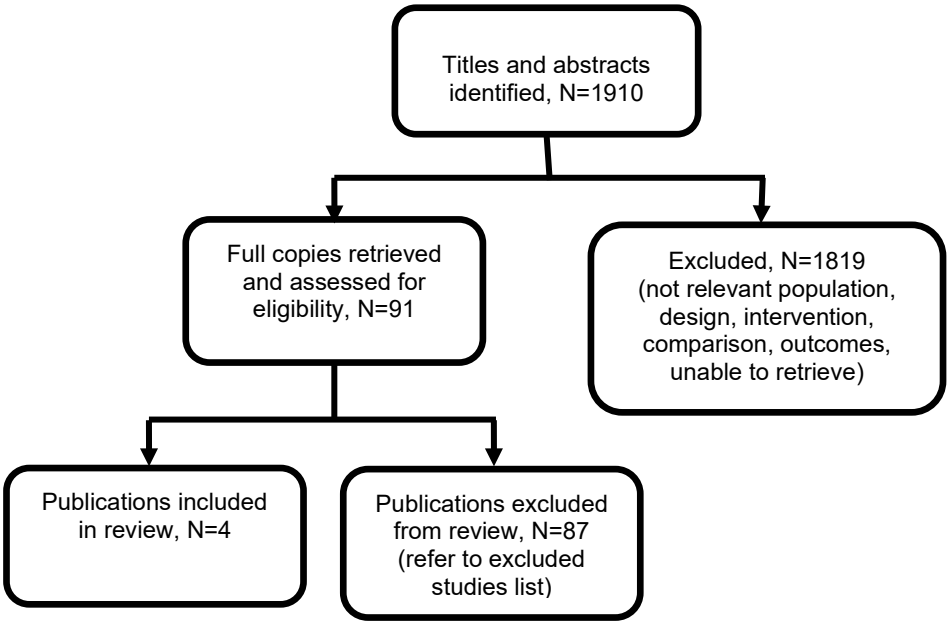
| # | Search |
|---|---|
| 22 | (SACT or chemotherap* or immunotherap* or biological agent* or biological therap*):ti,ab,kw (Word variations have been searched) |
| 23 | {or #13-#22} |
| 24 | #12 and #23 Publication Year from 1995 to 2018 |

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 intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7, Journal of Clincal Oncology, 36, LBA3503, 2018<br><br>**Ref Id** 930671<br><br>**Country/ies where the study was carried out** France<br><br>**Study type** Multi-centre RCT<br><br>**Aim of the study** The aim of the study was to assess the effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) | **Sample size** N= 265<br>CRS + HIPEC= 133<br>CRS alone= 132<br><br>**Characteristics** "Baseline characteristics were well balanced"<br><br>Median age, years= 60 (30-74)<br><br>**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 | **Interventions**<br>CRS+HIPEC+oxaliplatin vs CRS alone<br><br>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."<br><br>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**<br>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)<br>Allocation concealment: Not reported<br>Blinding: Not reported<br>Attrition: Not reported<br>Statistical analysis: Not reported<br>Follow up: 1 and 3 months after study therapy, every 3 months for 3 years, and then every 6 months for 2 years<br>Outcomes: Primary - 3 year overall survival. Secondary- 3 year recurrence free survival; morbidity from surgical complications | **Results**<br>Overall survival (median follow up 63.8 months), HR (CI), p-value 1.00 (0.73-1.37), 0.995<br><br>Post-operative mortality, n<br>CRS + HIPEC= 2/133<br>CRS alone= 2/132<br>60-day grade 3-5 morbidity, n<br>CRS + HIPEC= 32/133<br>CRS alone= 18/132 | **Limitations**<br>Risk of bias assessed using Cochrane risk of bias tool<br>Random sequence generation: Unclear (randomisation procedure not reported)<br>Allocation concealment: Low risk (not concealed, but unlikely to affect outcome assessment)<br>Blinding of participants and personnel: Low risk (open label, but unlikely to affect outcome assessment)<br>Blinding of outcome assessment: Low risk (unblinded, unlikely to affect outcome assessment)<br>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)<br>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 |
|---|---|---|---|---|---|
| on postoperative outcomes after cytoreductive surgery (CRS) for the treatment of peritoneal carcinomatosis of colorectal origin.<br><br>**Study dates** February 2008 to January 2014<br><br>**Source of funding** UNICANCER | ULN, alkaline phosphatase ≤ 3 times ULN, creatinine ≤ 1.25 times ULN, eligible for surgery.<br><br>**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<br><br>**Ref Id** 859167<br><br>**Country/ies where the study was carried out** | **Sample size**<br>N= 186<br>n systemic treatment= 92<br>n no systemic treatment= 94<br><br>**Characteristics**<br>Systemic treatment, n= 92<br>Male, n= 49<br>Age, years, < 70=62<br>Age, years, > 70=30<br>Tumour differentiation, n<br>Good=5<br>Moderate=52<br>Poor/undifferentiated=20<br>Unknown=15<br>Primary location, n<br>Left=41<br>Right=37<br>Rectum/rectosigmoid=9 | **Interventions** Systemic treatment versus no systemic treatment<br><br>Systemic treatment: Received chemotherapy in a palliative setting. 36/92 patients also received treatment including Bevacizumab<br><br>No systemic treatment: No treatment | **Details**<br>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.<br>Outcomes: Overall survival<br>Follow-up: Time from diagnosis of PC to death or end of follow | **Results**<br>Overall survival, HR (CI)<br>Chemotherapy only= 0.51 (0.35-0.73)<br>Chemotherapy + bevacizumab= 0.35 (0.22-0.56)<br>No treatment= reference<br>p-value= 0.10<br>Median overall survival, months (CI)<br>Chemotherapy only= 13.0 (9.5-16.0)<br>Chemotherapy + bevacizumab= 20.3 (13.7-29.3) | **Limitations**<br>Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions<br>Pre-intervention<br>Bias due to confounding: High risk of bias (differences in characteristics between groups at baseline)<br>Bias in selection of participants into the study: Low risk of bias<br>Bias in classification of interventions: Low risk of bias<br>Post-intervention<br>Bias due to deviations from |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Netherlands<br><br>**Study type**<br>Retrospective cohort study<br><br>**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.<br><br>**Study dates** 2003-2008 and 2010-2011<br><br>**Source of funding**<br>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. | Overlapping/NOS=5<br>Histology, n<br>Mucinous=26<br>Adenocarcinoma=64<br>Signet ring cell=2<br>Unknown=0<br>T-stage, n<br>T1/2=3<br>T3=68<br>T4=21<br>N-stage, n<br>N0=36<br>N1=35<br>N2=21<br>NX=0<br>M-status, n<br>PC only=32<br>PC+distant=60<br><br>No systemic treatment, n= 94<br>Male, n=40<br>Age, years, < 70=29<br>Age, years, > 70=65<br>Tumour differentiation, n<br>Good=4<br>Moderate=53<br>Poor/undifferentiated=23<br>Unknown=14<br>Primary location, n<br>Left=32<br>Right=46<br>Rectum/rectosigmoid=15<br>Overalpping/NOS=1<br>Histology, n<br>Mucinous=21<br>Adenocarcinoma=70<br>Signet ring cell=2<br>Unknown=1<br>T-stage, n<br>T1/2=6<br>T3=65<br>T4=23 | | up period (January 2014)<br>Statistical analysis: "Univariable 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." | No treatment= 3.4 (2.5-4.9)<br>p-value < 0.001 | intended interventions: Unclear risk of bias (The group of patients without comorbidities received Bevacizumab more often (42% versus. 30%, P = 0.07)<br>Bias due to missing data: Low risk of bias<br>Bias in measurement of outcomes: Low risk of bias<br>Bias in selection of the reported result: Low risk of bias<br><br>**Other information**<br>"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 |
|---|---|---|---|---|---|
| | N-stage, n<br>N0=29<br>N1=31<br>N2=32<br>NX=2<br>M-status, n<br>PC only=47<br>PC + distant=47<br><br>**Inclusion criteria** Patients with metachronous PC of colorectal origin who received systemic treatment in a palliative setting<br><br>**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**<br>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<br><br>**Ref Id** 859186 | **Sample size** N=105<br>CRS+HIPEC+SCT= 54<br>Standard= 51<br><br>**Characteristics**<br>CRS+HIPEC+SCT, n= 54<br>Male, n=34<br>Age, years, median (IQR)= 53 (28-69)<br>Performance status, n<br>Not recorded=15<br>0=30<br>1=9<br>2=0<br>Presentation at randomisation, n<br>Primary=30<br>Recurrent=24<br>Primary tumour, n<br>Appendix=7<br>Colon=41 | **Interventions**<br>CRS + HIPEC + SCT versus standard (surgery + SCT)<br>CRS+HIPEC+SCT:<br>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 | **Details**<br>Randomisation: performed centrally through a computer<br>Allocation concealment: Not reported<br>Blinding: Not reported<br>Attrition: one patient lost to follow up, intention to treat analysis used<br>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 | **Results**<br>Overall survival at 2 years, HR (CI), p-value<br>CRS+HIPEC+SCT= 0.55 (0.32-0.95), 0.032<br>Standard= reference<br><br>Overall survival, median follow up 21.6 months (event is overall survival)<br>CRS+HIPEC+SCT= 30/54 (55.6%)<br>Standard=20/51 (39.2%)<br>p-value not reported<br><br>Treatment-related mortality (30-day | **Limitations**<br>Risk of bias assessed using Cochrane risk of bias tool<br>Random sequence generation: Low risk of bias (computer generated)<br>Allocation concealment: Unclear risk of bias (not reported)<br>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)<br>Blinding of outcome assessment: Low risk of bias (blinding of outcome assessment not reported however outcome is not |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| **Country/ies where the study was carried out** Netherlands<br><br>**Study type** Single-centre RCT<br><br>**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.<br><br>**Study dates** February 1998 to August 2001<br><br>**Source of funding** Not reported | Rectum=6<br>Differentiation grade, n<br>Good=5<br>Moderate=33<br>Poor=15<br><br>Standard, n= 51<br>Male, n=24<br>Age, years, median (IQR)= 55 (29-70)<br>Performance status, n<br>Not recorded=19<br>0=23<br>1=7<br>2=2<br>Presentation at randomisation, n<br>Primary=28<br>Recurrent=23<br>Primary tumour, n<br>Appendix=11<br>Colon=34<br>Rectum=6<br>Differentiation grade, n<br>Good=3<br>Moderate=27<br>Poor=18<br><br>**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."<br><br>**Exclusion criteria** "Signs of distant metastases (liver, lung) on computed tomography (CT) scan of abdomen and chest x-ray were allowed. Patients had | removed. Reconstruction of gastrointestinal continuity was postponed until after the lavage, to prevent entrapment of tumour cells in suture lines."<br>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 | patients had to be entered."<br>Follow up: 2 years<br>Outcomes: Survival (time from randomisation to death from any cause) | mortality), n (for the 48 patients who underwent CRS followed by HIPEC in the experimental arm)<br>CRS+HIPEC+SCT= 4/48<br>Standard= 0/51<br><br>Median hospital stay, days, median (IQR) (for the 49 patients who underwent surgery in the experimental arm)<br>CRS+HIPEC+SCT= 29 (6-166)<br>Standard= not reported | likely to have been influenced by lack of blinding)<br>Incomplete outcome data: Unclear risk of bias (stated that one patient was lost to follow up but intention-to-treat analysis)<br>Selective reporting: Low risk of bias (all outcomes stated in Methods were reported in Results)<br>Other bias: None<br><br>**Other information**<br>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.<br>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 |
|---|---|---|---|---|---|
| | to be younger than 71 years and fit for major surgery (normal 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." | from the abdomen, and bowel continuity was 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"<br>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 | | | |

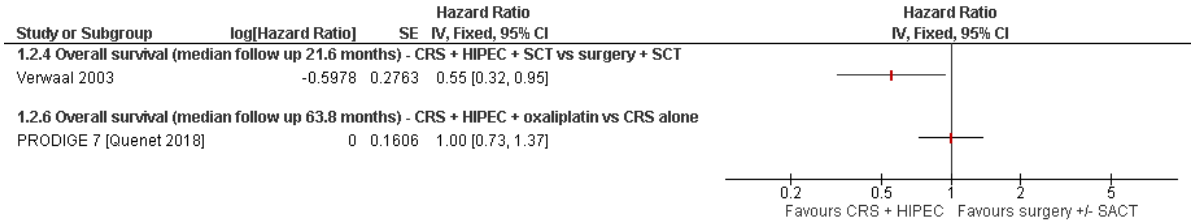
| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | | progression or intolerable toxicity." | | | |
| **Full citation**<br>Verwaal, V. J., Bruin, S., Boot, H., van Slooten, G., van Tinteren, H., 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer, Annals of Surgical Oncology, 15, 2426-32, 2008<br><br>**Ref Id** 493134<br><br>**Country/ies where the study was carried out**<br><br>**Study type** 8 year follow up of Verwaal 2003 trial. See Verwaal 2003 for study details.<br><br>**Aim of the study**<br><br>**Study dates**<br><br>**Source of funding** | **Sample size**<br><br>**Characteristics**<br>**Inclusion criteria**<br><br>**Exclusion criteria** | **Interventions** | **Details**<br>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.<br>Outcomes: disease specific survival (time from randomisation to death from any cause), progression free survival | **Results**<br>Progression free survival, months (median)<br>CRS+HIPEC+SCT= 12.6<br>Standard= 7.7<br>p-value= 0.020 | **Limitations**<br><br>**Other information**<br>"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 ‘‘cross-over’’." |

*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

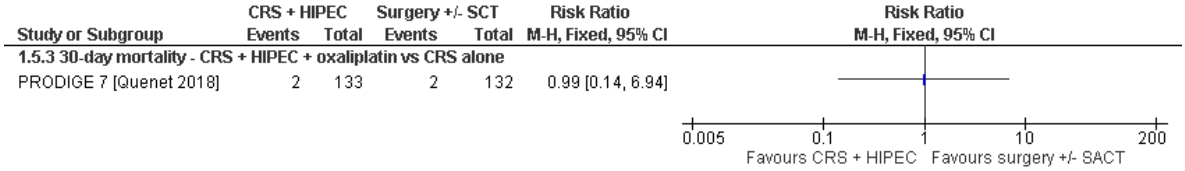
## Forest plots for review question: What is the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum?

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



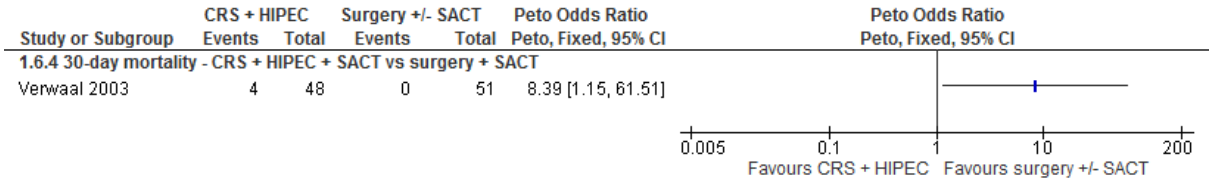

*CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; IV: inverse variance; SACT: systemic anti-cancer therapy; SE: standard error*

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



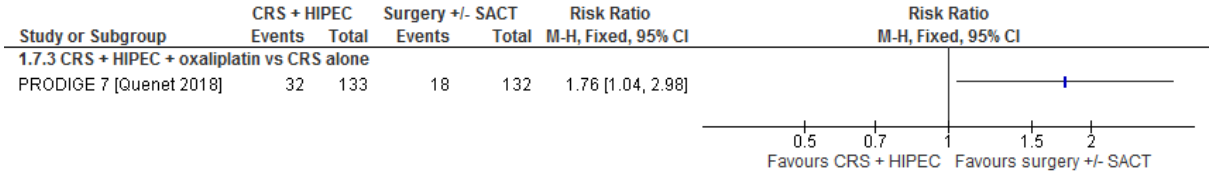

*CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; M-H: Mantel–Haenszel; SACT: systemic anti-cancer therapy*

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



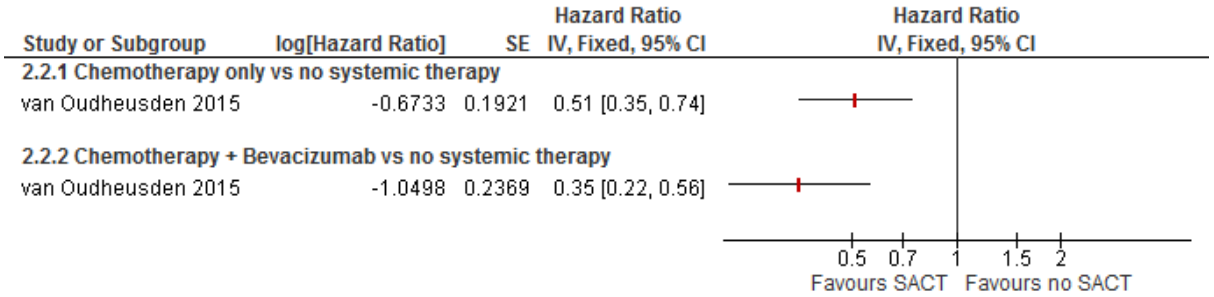

*CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; SACT: systemic anti-cancer therapy*

**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** | | | | | | | | | | | | |
| 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 |

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| Cashin, P. H., Graf, W., Nygren, P., Mahteme, H., Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: Prognosis and treatment of recurrences in a cohort study, European Journal of Surgical Oncology, 38, 509-515, 2012 | Comparison not relevant - CRS HIPEC versus CRS sequential postoperative intraperitoneal CT |
| 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 |

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| 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 |

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| 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 | Systematic review - studies assessed individually |

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| 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 | |
| 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 |

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| 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 | No case mix adjustments |

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| retrospective Peritoneal Surface Disease Severity Score (PSDSS) for Peritoneal Carcinomatosis of Colorectal Origin, BMC Cancer, 10, 689, 2010 | |
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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.