NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Peritoneal carcinomatosis is cancer that has spread from other parts of the body to the lining of the abdominal cavity (peritoneum). This may lead to bowel obstruction, accumulation of fluid and pain.

There are 2 parts to this procedure which is done under general anaesthesia. The first part is cytoreductive surgery, which removes all the visible cancer. The second part is chemotherapy during the surgery (intraoperative). The abdominal cavity is filled with heated (hyperthermic) chemotherapy fluid to reach any cancer cells the surgery may have missed. This fluid is drained at the end of the procedure. The aim is to reduce symptoms and improve quality of life.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2019.

Procedure name

- Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Professional societies

- Association of Cancer Surgeons (ACP)
- Association of Coloproctology of Great Britain and Ireland
- British Association of Surgical Oncology (BASO)
- British Gynaecological Cancer Society (BGCS)
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS)
- Faculty of Clinical Oncology (FCO)
- British Society of Gastroenterology
- Royal College of Surgeons Edinburgh
- Royal College of Surgeons of England

- The Royal College of Physicians and Surgeons of Glasgow.

Description of the procedure

Indications and current treatment

Peritoneal metastases commonly result from the regional spread of gastrointestinal, gynaecological and other malignancies. Peritoneal carcinomatosis is an advanced form of cancer associated with short survival and poor quality of life. It may lead to bowel obstruction, fluid build-up in the peritoneal cavity and pain.

There is no curative treatment. Current standard treatment is short-term palliation of complications such as bowel obstruction using systemic chemotherapy alone (or with surgery), closed peritoneal instillation of chemotherapy, or surgery alone.

What the procedure involves

Cytoreduction surgery is done to remove all macroscopic tumours within the peritoneal cavity. Hyperthermic intraoperative peritoneal chemotherapy is then used to distribute a chemotherapeutic drug uniformly to all surfaces of the intra-abdominal cavity and to increase drug penetration. This is done to treat any remaining microscopic traces of the cancer. The aim is to reduce symptoms, extend survival and improve quality of life.

Using general anaesthesia, a laparotomy is done and all macroscopic tumour is removed, with resection of involved organs and stripping of the tumour from the surface of some organs and peritoneum. The surgery, which is extensive and complex is followed by perfusion of the abdominal cavity for 30 to 120 minutes with a heated (between 40 and 48°C) chemotherapy solution (such as Mitomycin C or cisplatin). The fluid is then drained from the abdominal cavity before it is closed. This part of the procedure is generally called HIPEC (hyperthermic intraperitoneal chemotherapy), but in the past has been known as HIIC (heated intraoperative intraperitoneal chemotherapy), IPCH (intraperitoneal chemotherapy) and IPHC (intraperitoneal hyperthermic chemotherapy).

A further course of systemic or early postoperative intraperitoneal chemotherapy (EPIC) may be administered for 4 to 5 days following the procedure.

The surgery is extensive and may include:

- removal of the right hemicolon, spleen, gall bladder, parts of the stomach, greater omentum and lesser omentum

- stripping of the peritoneum from the pelvis and diaphragm
- stripping of tumour from the surface of the liver
- removal of the uterus and ovaries in women
- removal of the rectum in some cases.

Efficacy summary

Peritoneal carcinomatosis from gynaecological cancers (derived from ovarian and endometrial cancers)

Overall survival

A systematic review of 1,168 patients (in 16 studies) with recurrent ovarian cancer having cytoreduction surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) reported that overall survival ranged between 26.7 and 30 months. Median overall survival across 6 studies ranged from 25.7 to 45.7 months. A randomised controlled trial (RCT) (Spiliotis 2015) included in the systematic review reported that overall mean survival in the CRS and HIPEC group was significantly longer than for CRS and chemotherapy (26.7 months compared with 13.4 months, p=0.006). Also, for platinum sensitive patients in the RCT, a statistically significant difference in mean overall survival was seen for CRS and HIPEC compared with non-HIPEC groups (26.8 months compared with 15.2 months, p=0.035). A non-statistically significant difference was seen in the platinum resistant patients who had CRS and HIPEC.[1]

An RCT of 245 patients comparing CRS plus HIPEC (n=123) with CRS alone (n=122) for treatment of advanced ovarian cancer reported that CRS plus HIPEC resulted in longer median overall survival by 11.8 months than CRS alone (CRS plus HIPEC group 45.7 months compared with CRS alone 33.9 months). At a median follow-up of 4.7 years, 50% (61/123) of patients in the CRS plus HIPEC group and 62% (76/122) of patients in the CRS alone group had died (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.48 to 0.94; p=0.02).[4]

A meta-analysis of 1,608 patients from 26 studies on CRS and HIPEC in patients with advanced epithelial ovarian cancer (n=534) and recurrent ovarian cancer (n=1,074) reported a median overall survival of 63 months in advanced cancer and 39 months in recurrent cancer.[2]

A systematic review of 895 patients (in 19 studies) with ovarian cancer who had CRS and HIPEC reported an overall median survival range of 25 to 64 months (in 13 studies)[3].

A systematic review of 68 patients (in 8 studies) with peritoneal carcinomatosis from endometrial cancer who had CRS and HIPEC reported that median overall survival ranged from 12 to 33 months.[5]

5-year survival

The systematic review of 895 patients (in 19 studies) with ovarian cancer reported a 5-year survival range of 12 to 66% (in 9 studies)[3].

The systematic review of 1,168 patients (in 16 studies) with recurrent ovarian cancer having CRS and HIPEC reported 5-year survival rates higher than 50% in the HIPEC group (in 4 case control studies), which was significantly higher than rates in patients who had CRS and chemotherapy.[1]

The meta-analysis of 1,608 patients from 26 studies on CRS and HIPEC in patients with advanced epithelial ovarian cancer (n=534) and recurrent ovarian cancer (n=1,074) reported that 5-year survival was 40% (95% CI 37.8 to 41.7). For recurrent cancer, 5-year overall survival was 32% (95% CI 30.3 to 33.7). Optimal cytoreduction was achieved in 79% of patients with advanced cancer and 77% of patients with recurrent cancer.[2]

Disease-free survival

The systematic review of 1,168 patients (in 16 studies) with recurrent ovarian cancer who had CRS and HIPEC reported that disease-free survival (in 11 studies) varied between 8.5 and 48 months. Four case control studies in the systematic review reported a benefit for patients who had HIPEC compared with non-HIPEC.[1]

The systematic review of 68 patients (in 8 studies) with peritoneal carcinomatosis from endometrial cancer who had CRS and HIPEC reported that median disease-free survival ranged from 7 to 18 months.[5]

Recurrence-free survival

The RCT of 245 patients comparing CRS plus HIPEC (n=123) with CRS alone (n=122) for treatment of advanced ovarian cancer reported that CRS plus HIPEC resulted in longer median recurrence-free survival by 3.5 months (CRS plus HIPEC 14.2 months, compared with CRS alone 10.7 months). In the intention to treat analysis, disease recurrence or death occurred in 81% (99/122) of patients who had CRS plus HIPEC and in 89% (110/123) of patients who had CRS alone (HR 0.66, 95% CI 0.50 to 0.87; p=0.003)[4].

Peritoneal carcinomatosis from gastric cancer

Overall survival

A systematic review and meta-analysis of 620 patients (14 studies) with peritoneal carcinomatosis from gastric cancer who had CRS and HIPEC reported that the overall survival rate was higher, but not statistically significant, for the CRS and HIPEC group compared with the control group at 1-year follow up (risk ratio [RR]=0.67, 95% CI 0.52 to 0.86), 2-year follow up (RR=0.87, 95% CI 0.73 to 1.04, p=0.12) and 3-year follow-up (RR=0.99, 95% CI 0.93 to 1.06, p=0.85).[5] The median survival rate also showed a statistically-significant increase for CRS and HIPEC group compared with the control group (11.1 months compared with 7.1 months; weighted mean difference [WMD]=4.04, 95% CI 2.40 to 5.67, p=0.001). This was consistent in RCTs and high-quality nonrandomised controlled trials (NRCTs). Comparing CRS and HIPEC with systemic chemotherapy alone did not show a statistically-significant difference between groups (WMD=2.95, 95% CI 0.92 to 6.83, p=0.14).[6]

A systematic review of 1,578 patients (17 studies) with peritoneal carcinomatosis from gastric cancer who had CRS and HIPEC reported that the medial overall survival ranged from 6.6 months to 15.8 months. The 5-year overall survival ranged from 6% to 31%. Three comparative studies (including 1 RCT) in the systematic review reported that overall survival in the HIPEC group was better than the control surgery group. In patients with complete cytoreduction (11 studies), the median overall survival ranged from 11.2 to 43.4 months and the 5-year overall survival was 13% to 23% (in 2 studies).[7]

Overall survival rate by extent of peritoneal carcinomatosis

The systematic review and meta-analysis of 620 patients (14 studies) with peritoneal carcinomatosis reported that in studies of patients with limited peritoneal dissemination, no statistically-significant differences in survival rates were found between the CRS plus HIPEC group and the control group at 1-year follow up (RR=0.62, 95% CI 0.35 to 1.12, p=0.11), 2-year (RR=0.75, 95% CI 0.50 to 1.14, p=0.18) and 3-year follow-up (RR=0.78, 95% CI 0.57 to 1.06, p=0.11). In studies reporting data on patients with extensive peritoneal dissemination, no significant differences were reported in survival rates at 1-year follow up (RR=0.84, 95% CI 0.64 to1.11, p=0.22) and 2-year follow up (RR=0.94, 95% CI 0.77 to 1.13, p=0.51) between groups.[6]

Overall survival rate by the peritoneal cancer index

The systematic review and meta-analysis of 620 patients (14 studies) with peritoneal carcinomatosis reported that in 2 studies with low peritoneal cancer index (PCI) (less than 20 points), the median survival was not significantly different between the CRS plus HIPEC group and the control group

(11.57 months in the HIPEC group compared with 8.6 months in the control group, WMD=2.97, 95% CI 0.62 to 6.57, p=0.11). But in 1 study with high PCI (more than 20 points) the median survival was statistically significantly different between groups (13.5 months in the HIPEC group compared with 3 months in the control group, p=0.012).[6]

Peritoneal carcinomatosis from colorectal cancer

Overall survival

A systematic review and meta-analysis of 10,036 patients (in 76 studies including 15 controlled and 61 non-controlled studies) who had treatments for peritoneal carcinomatosis from colorectal cancer reported that the mean overall survival rate for CRS plus HIPEC was 29.2 (±11.3) months. Meta-analysis of 15 controlled studies (including 3,179 patients) reported that the mean overall survival for the CRS plus HIPEC treatment group was 34.3 (±14.8) months and the traditional therapy group was 18.8 (±8.8) months. The summarised hazard ratio for overall survival was 2.67 (95% CI 2.21 to 3.23, I^2=0%, p <0.00001).[8]

A systematic review and meta-analysis of 1,308 patients (in 9 studies) who had CRS plus HIPEC for peritoneal metastases from colon or rectum, reported that the CRS plus HIPEC treatment achieved longer overall survival for patients with peritoneal metastases from colonic origin (n=621) compared with those from rectal origin (n=113), with overall survival mean difference of 24.5 months (95% CI 14.70 to 34.28; p<0.00001; I^2=98%). It also reported that the pooled hazard ratio for disease-related death in rectal peritoneal metastases (n=532) was 1.62 (95% CI 1.01 to 2.59; p=0.05; I^2=25%) compared with colonic peritoneal metastases (n=42).[9]

5-year survival

The systematic review and meta-analysis of 10,036 patients who had treatments for peritoneal carcinomatosis from colorectal cancer reported that the 5-year survival rate was 27.5% (±14.1). Meta-analysis of 15 controlled studies (with 3,179 patients) reported that 5-year survival for the CRS plus HIPEC group was 40% (±11.5) compared with 18% (±14.1) for the traditional therapy group.[8]

Disease-free survival

In the systematic review and meta-analysis of 76 studies (with 10,036 patients who had CRS plus HIPEC for peritoneal carcinomatosis from colorectal cancer), meta-analysis of 15 controlled studies with 3,179 patients reported that the mean disease-free survival or recurrence-free survival was 15.9 (±7.7) months.[7]

The systematic review and meta-analysis of 1,308 patients (in 9 studies) who had CRS plus HIPEC for peritoneal metastases from colon or rectum, reported that CRS plus HIPEC gave longer disease-free survival for patients with colonic origin peritoneal metastases (n=463) compared with those from rectal origin (n=86), with a mean difference of 7.8 months (95%CI 1.37 to 14.13; p=0.02; I^2=95%).[9]

Quality of life for peritoneal carcinomatosis of various origins

A systematic review and meta-analysis of 15 studies (1,583 patients) assessing the effect of CRS and HIPEC on health-related quality of life (HRQOL) in patients with peritoneal carcinomatosis compared pre-operative disease specific HRQOL scores with post-operative scores at 1-year follow-up (in 8 studies). The pooled effect of combined post-operative functional assessment of cancer therapy (FACT-C) and European organisation of research and treatment (ERTOC) quality of life questionnaire scores were significantly improved from baseline on overall health status (mean difference [MD] 0.28, 95% CI -0.52 to 0.29; p=0.001). Subgroup analyses showed statistically significant improvement in emotional health (MD 0.38, 95% CI 0.15 to 0.60; p=0.001). Physical health (MD 0.03, 95% CI -0.24 to 0.30; p=0.83), social health (MD -0.06, 95% CI -0.23 to 0.11; p=0.48) and functional health (MD 0.21, 95% CI -0.14 to 0.55; p=0.24) remained at similar levels with no significant difference.[10]

Qualitative analysis shows that HRQOL declined within 3 to 4 months and reached a comparable or better level after 1 year, and improved up to 5 years for overall general health (on SF-36 and FACT-C) and physical health domains. Physical health declined within the first 3 months and improved to baseline levels between 6 months and 3 years. There was little effect on social health. Functional status was at pre-operative levels and was maintained up to 5 years. Emotional health initially decreased because of morbidity but improved within 3 months. Activities of daily living and satisfaction levels were high. Comparing overall HRQOL to a reference population gives inconclusive results. Physical health, social health and functional heath domains were comparable or worse from 1 to 4 years, and emotional health declined in the long term.[10]

The RCT of 245 patients comparing CRS plus HIPEC (n=123) with CRS alone (n=122) for advanced ovarian cancer reported that quality of life outcomes did not differ significantly between the 2 groups.[4]

Safety summary

Peritoneal carcinomatosis from gynaecological cancers (ovarian and endometrial derived peritoneal carcinomatosis)

Postoperative mortality

A systematic review of 895 patients (in 19 studies) with ovarian cancer who had cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) reported a mortality range of 0 to 10% (in 16 studies)[3].

A meta-analysis of 1,608 patients (from 26 studies) with ovarian cancer who had CRS and HIPEC reported that the perioperative mortality rate was 1% (range 0 to 4%) for advanced ovarian cancer (13 studies) and 3% (range 0 to 10%) for recurrent ovarian cancer (13 studies).[2]

A systematic review of 1,168 patients (in 16 studies) with recurrent ovarian cancer having CRS and HIPEC reported that procedure-related mortality was 5% in 1 study (n=3, caused by an anastomotic leak, severe pneumonia and sepsis)[1].

A systematic review of 68 patients (in 8 studies) with peritoneal carcinomatosis from endometrial cancer who had CRS and HIPEC reported that treatment associated mortality was 1% (1/63)[5].

Postoperative morbidity

The systematic review of 895 patients with ovarian cancer reported a grade 1 complication (no intervention necessary) rate of 0 to 70% (12 studies), grade 2 complication (medical treatment required) rate of 1 to 50% (12 studies), grade 3 complication (intensive intervention such as radiology required) rate of 0 to 40% (13 studies) and grade 4 complication (that needed return to operating theatre or intensive care unit) rate of 0 to 15% (14 studies)[3].

The systematic review of 1,168 patients (in 16 studies) with recurrent ovarian cancer reported morbidity rates (assessed using CTCAE in 6 studies or Clavien Dindo classification in 3 studies) between 12 and 100%. One study that compared HIPEC and non-HIPEC groups reported no difference in overall morbidity between the 2 groups (23% in the non-HIPEC group, 14% rated grade 3 to 4; 28% in the HIPEC group, 21% rated grade 3 to 4). Another study reported mainly grade 1 to 2 morbidity, with similar rates in the HIPEC (29%) and non-HIPEC (25%) groups[1].

The most frequent events were bone marrow depression, gastrointestinal fistulation, anaemia, renal failure or acute kidney injury. Other adverse events included pleural effusion, post-operative bleeding, abdominal abscess, urinary tract infection, leucopenia, thrombocytopenia, neutropenia, lymphocyst needing drainage, infected central catheter, transient haematological toxicity, transient confusional syndrome, prolonged ileus, wound infection, abdominal collection and pancreatic leak, unilateral ureteric injury, sepsis and electrolyte imbalance.

Reoperation was needed for ureteric necrosis, staple line bleeding and thoracic empyema[1].

The systematic review of 68 patients (in 8 studies) with peritoneal carcinomatosis from endometrial cancer reported that adverse events grade 1 or 2 were observed in 33% (23/63) of patients, grade 3 in 19% (12/63) of patients and grade 4 in 10% (6/63) of patients[5].

A RCT of 245 patients comparing CRS plus HIPEC (n=123) with CRS alone (n=122) for treatment of advanced ovarian cancer reported that the incidence of postoperative complications (including grade 3 or 4 adverse events) did not differ significantly between the 2 groups (CRS plus HIPEC 27% compared with CRS alone 25%, p=0.76).[4]

Peritoneal carcinomatosis from gastric cancers

Postoperative mortality

In a systematic review of 1,578 patients (in 17 studies) who had CRS and HIPEC for peritoneal carcinomatosis from gastric cancer the mortality rate (in 12 studies) ranged from 0 to 7%. Another systematic review included in this study reported a mortality rate of 5%[7].

Postoperative morbidity

A systematic review and meta-analysis of 620 patients (14 studies) with peritoneal carcinomatosis from gastric cancer reported a statistically significantly higher risk of developing postoperative complications in the HIPEC group compared with the control group (RR=2.15, 95% CI 1.29 to 3.58, p<0.01) and this was consistent among RCTs (RR=2.88, 95% CI 1.04 to 7.97, p=0.04) and NRCTs (RR=1.86, 95% CI 1.04 to 3.33, p=0.04). HIPEC is related to a high risk of developing respiratory failure (RR=3.67, 95% CI 2.02 to 6.67, p<0.001) and renal dysfunction (RR=4.46, 95% CI 1.42 to 13.99, p=0.01) and it is related to systemic drugs toxicity. Analysis of the anastomotic leakage data did not show a statistically significant difference in rates between the groups (p=0.42)[6].

In the systematic review of 1,578 patients (17 studies) on CRS and HIPEC for peritoneal carcinomatosis from gastric cancer the morbidity rate (in 14 studies) ranged from 3% to 52%. Another systematic review included in this study reported a morbidity rate of 22%[7].

Peritoneal carcinomatosis from colorectal cancers

Mortality

In the systematic review and meta-analysis of 10,036 patients (in all 76 studies) with peritoneal carcinomatosis from colorectal cancer, the mortality rate for CSR plus HIPEC was 3% (±2.9). Meta-analysis of 15 controlled studies (3,179 patients) reported that the mean mortality rate for the CSR plus HIPEC group was 4% (±3.7) compared with 6% (±4.2) for the traditional treatment group (not statistically significant)[8].

Morbidity

In the systematic review and meta-analysis of 10,036 patients (in all 76 studies) with peritoneal carcinomatosis from colorectal cancer, the morbidity rate for CSR plus HIPEC was 33% (±13.4). Meta-analysis of 15 studies reported that the mean morbidity rate for the CSR plus HIPEC groups was 20% (±9.2) compared with 21% (±12.3) for the traditional treatment group (not statistically significant)[8].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: retained surgical drain, chemotoxicity, and cerebrovascular accident. They considered that the following were theoretical adverse events: device related and thermal injuries.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. The following databases were searched, covering the period from their start to 28.08.2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with peritoneal carcinomatosis.
Intervention/test	Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 19,109 patients from 5 meta-analyses, 4 systematic reviews and 1 randomised controlled trial. There is an overlap of primary studies in some systematic reviews and meta-analyses. Primary studies (other than randomised controlled trials not included in the systematic reviews) were excluded from this overview.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Peritoneal carcinomatosis from gynaecological cancers (ovarian cancer and endometrial cancers)

Study 1 Hotouras A 2016

Details

Study type	**Systematic review**
Country	UK
Study period	Search period: between 1980 to February 2015; databases searched: PubMed, Medline. In addition, bibliographies of selected articles were checked by hand.
Study population and number	n=**16 studies (1,168 patients) with recurrent ovarian cancer** who had cytoreductive surgery(CRS), of whom 81% (n=953) had HIPEC. (1 randomised controlled trial, 4 case-control studies, and 11 case series)
Age and sex	Age not reported; all female
Patient selection criteria	English articles assessing the impact of CRS with HIPEC in patients with recurrent ovarian cancer were included. Multiple or duplicate articles with shorter follow-up periods, studies on primary ovarian cancer, mixed cohort with primary or recurrent disease without any subgroup analysis, studies not assessing the effect of HIPEC were excluded.
Technique	Cytoreductive surgery plus HIPEC HIPEC is done either using open (580 procedures) or closed technique (324 procedures). Cisplatin was the main chemotherapeutic agent used (in 11 studies) but wide variations were noted in the choice of HIPEC drug regimen (temperature of perfusate, dose used, duration of infusion, either used as a single drug or in combination with other drugs). Other drugs used included oxaliplatin, carboplatin, paclitaxel. Some patients who are resistant to platinum-based agents were given a combination of doxorubicin, paclitaxel and mitomycin (Spiliotis 2015). 2 studies (Spiliotis 2015 and Bakrin) used both techniques (open and closed) at a ratio of 2:1. After CRS and HIPEC most patients had systemic chemotherapy.
Follow-up	**Varied across studies**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up times varied in individual studies.

Study design issues: majority of the studies included are retrospective; quality assessment was done by 2 reviewers using the Oxford Centre for evidence-based medicine 2011 levels of evidence. 11 studies were level IV, 4 were level III and 1 level II. Any disagreements were resolved by consensus. Primary outcome was overall survival and secondary outcomes were disease free survival and HIPEC related morbidity.

Study population issues: studies had heterogeneous cohorts that were treated at different time points and had different pre-treatment regimens; techniques and treatment protocols were not standardised and varied across studies (different drugs, doses, temperatures and infusion times).

Other issues: there is some overlap of primary studies in 2 or more included systematic reviews.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **16 studies (1,168 patients)**

Mean overall survival

	CRS+HIPEC group +chemo	CRS and non HIPEC group (chemo)	P value
Spiliotis 2014	26.7	13.4	0.006
In platinum sensitive cases	26.8	15.2	0.035
In platinum resistant cases			NS
Piso 2004	30±6 months		

Median overall survival (6 studies)

Study	Months
Ceelen 2012	37
Cotte 2007	28.4
Deraco 2012	25.7
Delotte 2015	35
Konigsrainer 2014	35 (in patients with CC score 0/1) 14 (in patients with CC score 2/3)
Bakrin 2013	45.7

5-year survival rates

	CRS+HIPEC group +chemo	CRS and non HIPEC group (chemo)	P value
Fagotti 2012	68.4%	42.7%	0.017
Munoz Casares 2009	57%	17%	0.046
CC score 0	67%	29%	
Safra 2014	79%	45%	0.016
Ceelen 2012	41.3%		
Deraco 2012	23%		
Roviello 2010	44%		

Disease free survival (DFS) (11 studies)

5-year DFS rate

Safety

Morbidity (CTCAE grades I-V) n=6 studies

Deraco *	26.3% grade III-V
Procedure related mortality rate (caused by anastomotic leak, severe pneumonia, and sepsis)	5.3% (n=3)
Argenta 2013	30% grade III-V (1 acute kidney injury, thrombocytopenia, and neutropenia)
Delotte 2015	20% grade III-IV
Roviello 2010	12% grade III-IV
Bakrin 2013	30% grade III -IV
Cascales campos 2015	Grade III-IV 14% in non HIPEC group 21% in HIPEC group

*The most frequent events were bone marrow depression (n=7), gastrointestinal fistulation (n=5), anaemia (n=5), and renal failure (n=3). Other adverse events included pleural effusion, postoperative bleeding, abdominal abscess, urinary tract infection, and leukopenia.

Morbidity (using Clavien Dindo scale) 3 studies

Konigsrainer 2014	42% (grade I-V)
Guoy 2013	Grade III- Lymphocyst needing drainage Grade II-infected catheter, UTI, transient haematological toxicity, transient confusional syndrome
Munoz casares 2009	Grade I=II HIPEC 29% Non HIPEC 25%

Ceelen 2012	Major morbidity 21% (3 needed operation for ureteric necrosis, staple line bleeding, thoracic empyema)

Ceelen 2012	12.5%
Deraco 2012	7%

3-year DFS rate

	CRS+HIPEC group +chemo	CRS and non HIPEC group (chemo)
Casales Campos 2015	45%	23%
Munoz Casares 2009	Mean 48±42 months	Mean 24±18 months
Safra 2014	Median 15 months	Median 6 months
Fagotti 2012	33.3% (at median follow-up of 45 months)	0% (at median follow-up of 36 months)
Zivianovic 2014	13.6 months	
Cotte 2007	8.5 months	
Delotte 2015	15.6 months	
Argenta 2013	70% (at median follow-up 16 months)	
Gouy 2013	28.6% (at median follow-up 32 months)	

Median time between treatment and recurrence

	CRS+HIPEC group +chemo	CRS and non HIPEC group (chemo)	P value
Fagotti 2012	26 months	15 months	0.004
Time between treatment and recurrence relative to initial recurrence from primary disease			
Fagotti 2012	53.4%	32.4%	0.07

	Minor morbidity 43% (most frequent prolonged ileus, UTI, wound infection)
Cotte 2007	Major morbidity 13.6% Most common anastomatic leak (n=3), pleural effusion (n=3), and grade 3 leukopenia (n=2).
Zivanovic 2014	25%, a grade III intraabdominal collection and pancreatic leak, uretic injury and sepsis.
Safra 2014	All had mild electrolyte imbalances, mild nausea.

Abbreviations used: CC, complete cytoreduction; CRS, cytoreduction surgery; CTCAE, common terminology criteria for adverse events; DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; NS, not significant; UTI, urinary tract infection.

Study 2 Dellinger TH (2018)

Details

Study type	**Systematic review and meta-analysis**
Country	USA
Study period	1990 to 2015; databases searched –, PubMed; reference lists were manually searched.
Study population and number	n= **26 studies (n=1,608) patients with advanced or recurrent ovarian cancer.** **Advanced cancer: 13 studies (n=534); recurrent cancer: 14 studies (n=1,074)** 15 prospective case series (193 advanced cancer patients and 322 recurrent cancer patients) 11 retrospective studies (356 advanced cancer patients and 729 recurrent cancer patients)
Age and sex	Median age ranged from 46 to 65 years; all female
Patient selection criteria	Inclusion criteria: studies on both advanced and recurrent epithelial ovarian cancer, with more than 10 patients that reported overall survival curves or point estimates. Exclusion criteria: studies where results for advanced and recurrent cancer reported only as pooled statistics, studies on other cancers and multiple publications.
Technique	CRS and HIPEC Optimal cytoreductive surgical resection- 71% of recurrent cancer studies used <0.5cm as cut off compared with 43% of advanced cancer studies. The majority of studies used a 90-minute administration of HIPEC. Other durations included 120 minutes and 30-60 minutes. The most commonly used chemotherapy drug in both advanced and recurrent cancers was cisplatin (dose range from 15 to 100mg/m^2). Other drugs used were carboplatin in advanced cancer patients and doxorubicin in recurrent cancer patients. Temperature ranged from 37 to 44 degrees.
Follow-up	**Median 41 months for advanced cancer (range 14-70)** **Median 23 months for recurrent cancer (range 16-47)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: median follow-up for advanced and recurrent cancer studies varied.

Study design issues: studies included in the systematic review were mainly case series. One study that included separate statistics for advanced and ovarian cancer was counted twice. Details on the use of HIPEC, timing of neoadjuvant therapies, number of cycles administered were not reported properly in the studies. Studies used different definitions for optimal cytoreduction (ranging from no residual disease to less than 2cm) and widely varied in HIPEC protocols used. Authors extracted data from point estimates and modelled these with a weighted linear model. The weighting was based on the number of patients and not on inverse weighting. Multivariate analysis was done for overall survival and progression free survival based on modelling the point estimates with weighted fixed effects models.

Morbidity was not analysed due to the non-uniform reporting of complications in studies.

Study population issues: over half of the patients in recurrent cancer studies were chemo-resistant patients.

Other issues: there is some overlap of primary studies in 2 or more included systematic reviews.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1608**

Outcomes of CRS and HIPEC

	Advanced cancer (n=534)	**Recurrent cancer (n=1,074)**
Duration of CRS; hours	Mean 7.5 (range 5 -10)	Mean 7.4 (range 4 -10)
Length of stay; days	15.7±6.8	15.0±5.5
Optimal cytoreduction (residual disease <1 cm)	Mean 79% (range 57-100%)	Mean 77% (range 50-92%)
3-year overall survival	61.7% (95%CI 60.7-62.6%)	47.7% (95% CI 46.8-48.8%)
5-year overall survival	39.7% (95% CI 37.8-41.7%)	32% (95%CI 30.3-33.7%)
Median overall survival	63 months	39 months

Safety

Safety outcomes

	Advanced cancer	**Recurrent cancer**
Peri-operative mortality	Mean 1.5% (range 0-4%)	3.4% (range 0-10%)

Abbreviations used: CRS, cytoreduction surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

Study 3 Chua TC (2009)

Details

Study type	**Systematic review** (including 4 non-randomised controlled studies and 15 case series)
Country	International
Study period	Up to May 2009; databases searched – Medline, Embase, PubMed; reference lists were manually searched.
Study population and number	n= **19 studies (n=895) patients with advanced** (International Federation of Gynaecology and Obstetrics stage III and IV) **or recurrent ovarian cancer.** (All observational case series)
Age and sex	Not reported; all female
Patient selection criteria	Inclusion criteria: English language studies with more than 10 patients having CRS and HIPEC treatment with a diagnosis of advanced (Stage III/IV) or recurrent ovarian cancer, studies with sub-group analyses of ovarian cancer patients. Exclusion criteria: phase 1 studies (pharmacokinetic data) and multiple studies.
Technique	CRS and HIPEC Following maximal surgical cytoreduction, HIPEC was given intraoperatively (in 11 studies) and/or as consolidation therapy after complete pathological response following initial therapy conformed by second look laparotomy or at time or first recurrence or as salvage therapy (11 studies). The chemotherapy agent used was heated to different temperatures (37–64 degrees C) and different chemotherapy drugs (e.g. paclitaxel, mitomycin C, cisplatin, doxorubicin and carboplatin) were used at different doses in the studies.
Follow-up	**14-64 months (median/mean, 14 studies)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up times varied in individual studies.

Study design issues: All studies assessed for quality independently (method and results of this are unclear). Authors stated that “meta-analysis was inappropriate because of the heterogeneous nature of the included studies and the lack of a comparative arm in most studies”. Narrative review of results done.

Study population issues: a significant proportion of patients were chemo-resistant and had had multiple treatments.

Other issues: there is some overlap of primary studies in 2 or more included systematic reviews.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **895** **Survival** **Overall:** Median: 25–64 months (13 studies) **For optimal cytoreduction only** Median: 26–66 months (10 studies) **Median/mean disease-free survival:** 10–57 months (16 studies) **3-year survival:** 35–63% (7 studies) **5-year survival:** 12–66% (9 studies) **Included studies:** Bereder 2009 Pavlov 2009 Fagotti 2009 Guardiola 2009 Di Giorgio 2008 Bae 2007 Cottee 2007 Helm 2007 Rufian 2006 Raspagliesi 2006 Reichman 2005 Gori 2005 Look 2004 Ryu 2004 Piso 2004 Zanon 2004 Chatzigeorgiou 2003 De Bree 2003 Cavaliere 2000	**Mortality** (time period not defined): 0–10% (16 studies) **Morbidity:** **Grade 1** (diagnosis established but no intervention necessary): 0–70% (12 studies) **Grade 2** (medical treatments required for resolution): 1–50% (12 studies) **Grade 3** (postoperative complication requiring intensive intervention such as radiological intervention for resolution):0–40% (13 studies) **Grade 4** (postoperative complication requiring urgent intervention such as return to operating theatre or ICU for resolution): 0–15% (14 studies) **Common postoperative complications include** ileus, anastomotic leakage, bleeding, wound infection, toxicity, pleural effusion, infections, fistula, transient hepatitis and thrombocytopenia.
Abbreviations used: CRS, cytoreduction surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.	

Study 4 van Driel WJ 2018

Details

Study type	**Randomised controlled trial**
Country	The Netherlands and Belgium (8 centres)
Recruitment period	2007 to 2016
Study population and number	n=**245 patients with advanced (stage III) ovarian, fallopian tube, or peritoneal cancer (123 CRS plus HIPEC compared with 122 CRS only)**
Age and sex	Median age: CRS plus HIPEC group (63 years); CRS only group (61 years)
Patient selection criteria	Patients with stage III ovarian, fallopian tube or peritoneal cancer (had 3 cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel because their abdominal disease was too extensive for primary reductive surgery or surgery has been done but was incomplete, had 1 or more residual tumours measuring more than 1 cm in diameter), with WHO performance status score 0 to 2, normal blood counts and adequate renal function were included.
Technique	Cytoreductive surgery with or without HIPEC HIPEC was administered at the end of cytoreductive surgical procedure with the use of open technique. Abdominal temperature was maintained at 40 degrees C. Perfusion was done with cisplatin at a dose of 100 mg per square meter and at a flow rate of 1 litre per minute. The HIPEC procedure took 120 minutes including the 90 minutes perfusion period. Patients had an additional 3 cycles of carboplatin and paclitaxel immediately after the procedures in both groups. Follow up examinations and measurements were done every 3 months for 2 years and every 6 months until 5 years. CT was done every 6 months until 2 years.
Follow-up	**Median 4.7 years**
Conflict of interest/source of funding	Supported by the Dutch Cancer Society.

Analysis

Follow-up issues: In the CRS plus HIPEC group, 1 patient was lost to follow-up after disease recurrence at 7 months. In the CRS only group, 1 patient was lost to follow-up at 1 month and 1 after recurrence at 20 months. 4 patients were excluded from the safety analysis as they did not have the assigned treatment.

Study design issues: randomisation was done at the time of surgery in a 1:1 ratio in cases in which complete (no visible) or optimal (less than 2.5mm) cytoreduction was anticipated. It was done with the use of a minimisation procedure with stratification according to previous surgery, the hospital where it was done and the number of involved regions in the abdominal cavity. The primary end point was recurrence free survival. Secondary end points include overall survival, side effects and quality of life. HRQOL was measured using the European Organisation for research and treatment of cancer (ERTOC), Quality of life questionnaire-core 30 (QLQ-C30), Quality of life questionnaire-ovarian cancer module (QLQ-OV28), and quality of life questionnaire -colorectal cancer module (QLQ-CR38) before and after the procedure at different time points. Analysis was based on intention to treat population.

Study population issues: there was no significant differences between the two groups in baseline disease and treatment characteristics. The percentage of patients who had ileostomy or colostomy were higher in CRS plus HIPEC group (p=0.04). All patients had neoadjuvant chemotherapy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **245** (**123 in CRS plus HIPEC group compared with 122 in CRS only group)**

	CRS plus HIPEC (n=123)	**CRS only (n=122)**	
Median recurrence-free survival*	14.2 months	10.7 months	
Probability of recurrence free survival at 3 years^	17% (95% CI 11 to 26)	8% (95% CI 4 to 16)	
Disease recurrence or death	81% (99/122)	89% (110/123)	HR 0.66; 95% CI 0.50 to 0.87; p=0.003
Median overall survival	45.7 months	33.9 months	
Probability of overall survival at 3 years^	62% (95% CI 54 to 72)	48% (95% CI 39 to 58)	
Death	50% (61/123)	62% (76/122)	HR 0.67; 95% CI 0.48 to 0.94; p=0.02)

*defined as the time from randomisation to disease recurrence or progression (elevation of CA-125 level) nor death from any cause, whichever occurred first.

^assessed using Kaplan-Meier estimates.

Health-related quality of life

No significant differences were noted between the two groups in health-related quality of life outcomes.

Safety

Adverse events

More than 95% of patients in each group had at least one adverse event of any grade. No significant differences were noted in the incidence of adverse events of any grade between the two groups.

	CRS plus HIPEC (n=118)		**CRS only (n=122)**		
Death within 30 days	0		1		
Bowel resection	29 (colostomy/ileostomy in 21)		30 (colostomy/ileostomy in 13)		0.04
	Any grade % (n)	**Grade 3 or 4 % (n)**	**Any grade % (n)**	**Grade 3 or 4 % (n)**	**P value**
Total adverse events		**27 (32)**		**25 (30)**	**0.76**
Infection	18 (21)	6 (7)	11 (14)	2 (3)	
Abdominal pain	60 (71)	5 (6)	57 (70)	6 (7)	
Ileus	8 (9)	4(5)	3 (4)	2(2)	
Pain	33 (39)	3 (4)	23 (28)	2 (2)	
Thromboembolic event	6 (7)	3(4)	2(2)	2(2)	
Pulmonary event	9 (11)	3(3)	7 (8)	1(1)	
Dyspnoea	7(8)	3(3)	11(13)	0	
Electrolyte disturbance	6 (7)	3 (3)	5 (6)	1(1)	
Gastrointestinal anastomotic leak	3(3)	3(3)	2(2)	2(3)	
Nausea	63 (74)	2(2)	57 (70)	2(3)	
Fatigue	37 (44)	2(2)	30 (37)	0	
Cardiac, not otherwise specified	7(8)	2(2)	5(6)	2(2)	
Neuropathy	31 (37)	1(1)	27(33)	1(1)	
Vomiting	27 (32)	1(1)	39 (47)	1(1)	
Anaemia	4 (5)	1(1)	6 (7)	5(6)	
Pneumonia	2(2)	1(1)	1(1)	1(1)	
Postoperative haemorrhage	1(1)	1(1)	9(11)	1(1)	
Hypotension	1(1)	1(1)	9 (11)	1(1)	
Sepsis	1(1)	1(1)	2(2)	2(2)	
Constipation	19 (23)	0	26 (32)	1(1)	

	Alopecia	19 (22)	0	16 (19)	0	
	Diarrhoea	9 (11)	0	14 (16)	0	
	Fever	12 (14)	0	8 (10)	0	
	Dizziness	8 (9)	0	12 (15)	0	
	Gastroparesis	1(1)	0	2(2)	2(2)	
	Intestinal perforation	0	0	2(2)	2(2)	
Abbreviations used: CI, confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; HRQOL, health related quality of life; HR, hazard ratio.						

Study 5 Tempfer CB 2019

Details

Study type	**Systematic review**
Country	Germany
Study period	Search period: up to February 2019; databases searched: PubMed, Cochrane Central Register of Controlled Trials. Cross reference searching was also done to identify additional studies.
Study population and number	n=8 **studies (68 patients) with endometrial cancer derived peritoneal carcinomatosis** who had CRS and HIPEC. (1 prospective cohort study, 1 retrospective cohort study, 5 case series and 1 case report). Mean PCI was 16.7; mean time from initial treatment to CRS and HIPEC was 22.3 months.
Age and sex	Mean age 57.1 years; all female
Patient selection criteria	Studies (clinical trials and case reports) assessing the safety and efficacy of CRS and HIPEC in patients with endometrial cancer derived peritoneal carcinomatosis were included. Studies not reporting individual patient data, studies with no clinical outcomes were excluded.
Technique	Cytoreductive surgery and HIPEC. HIPEC is done either using open/coliseum (13/68 patients) or closed technique (55/68 patients). Chemotherapy drugs used in HIPEC were variable. Cisplatin was the main chemotherapeutic agent used (in all) either alone (39/68 patients) or combined with doxorubicin or paclitaxel or mitomycin (29/68 patients). Duration of HIPEC also varied; 60 minutes in 51/68 patients and 90 minutes in 17/68 patients. Temperature was 41-43 degrees C. The procedures were variable with different numbers of inflow and outflow tubes, intraabdominal or intravesical temperature probes. Anastomoses was done before HIPEC in all except 1 study where it was done after HIPEC and reopening the abdomen.
Follow-up	**Varied across studies**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up times varied in individual studies.

Study design issues: systematic literature search was done. Most of the studies included were small and heterogenous in study designs; they were mainly retrospective studies prone to bias. Most patients in studies had systemic chemotherapy after CRS and HIPEC. quality assessment of studies was not done.

Study population issues: studies had heterogeneous cohorts; 64% (41/64) patients had adenocarcinoma, and type II cancers were present in 36% (23/64) patients.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **8 studies (68 patients)**

Studies included

Study	N	Time since initial treatment (months, range)	DFS (months; median range)	OS (months, median)
Cornali 2018	33	Median 17.5; 6-36	18	33.1
Abu-Zaid 2014	6	Mean 9, 1-18	13 (3-35)	-
Delotte 2014	13	Median 18.5, 0-53	11(2-124)	19.4
Santeufemia 2013	1	120	12	12
Bakrin 2010	5	Mean 47.5, 10-120	7 (0-32)	28
Helm 2007	5	Mean 47, 29-66	7 (0-32)	28
Pooled analysis	63	Mean 22.3, 0-120	Range 7 to 18	range 12-33

Surgical completeness

CC-0	70 (44/63)
CC-1	17 (11/63)
CC-2	11 (7/63)
CC-3	2 (1/63)

Postoperative chemotherapy

After CRS and HIPEC 68% (46/63) patients had systemic chemotherapy.

Safety

Adverse events

	% (n=63)
Morbidity*	
Grade1/2	33 (22/63)
Grade 3	19 (12/63)
Grade 4	10 (6/63)
Mortality (patient died intraoperatively of a massive pulmonary embolism before HIPEC)	1 (1/63)

No specific morbidity related to HIPEC reported.

Abbreviations used: CRS, cytoreduction surgery; CC, complete cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy;

Peritoneal carcinomatosis from gastric cancer

Study 6 Desiderio J 2017

Details

Study type	**Systematic review and meta-analysis**
Country	USA
Study period	Search period: 1985 to June 2016; databases searched: Medline, Embase. Manual reference searching was also done to identify additional studies.
Study population and number	n=14 **studies (620 patients) with gastric cancer peritoneal carcinomatosis** who had CRS and HIPEC. (2 randomised controlled trials (RCTs), 12 non-randomised controlled trials (NRCTs). **289 CRS+HIPEC compared with 331 controls [244 CRS and 87 systemic chemotherapy])**
Age and sex	not reported
Patient selection criteria	Studies (randomised controlled trials and high quality comparative non-randomised controlled trials) assessing the using of HIPEC following standard gastrectomy or CRS were included. Control procedures included standard gastrectomy for advanced gastric cancer without carcinomatosis and CRS or systemic chemotherapy for gastric cancer peritoneal carcinomatosis. Studies on intraperitoneal chemotherapy, without a specific description or other treatments such as normothermic intraperitoneal chemotherapy (NIC) or early postoperative intraperitoneal chemotherapy (EPIC); those with data on primary malignancies other than gastric cancer, with no separate subgroup analyses, duplicate studies, those with overlapping data were excluded.
Technique	Cytoreductive surgery and HIPEC. HIPEC is done either using open or closed techniques. Chemotherapy drugs used in HIPEC were variable (mitomycin C in 4 studies, a combination of MMC with cisplatin in 3 studies, cisplatin with etoposide in 3 studies and MMC with etoposide in 1 study; cisplatin or oxaliplatin alone in 2 studies and cisplatin with doxorubicin in 1 study).
Follow-up	**Varied across studies**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up times varied in individual studies.

Study design issues: systematic literature search was done according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. 2 reviewers extracted data, quality assessment of studies was done using Cochrane risk of bias tool for RCTs and the modified methodological index for non-randomised studies (MINORS) for NRCTs. Scoring was assigned and studies with 12 or more points were considered as high quality and the remaining were excluded. RCTs and NRCTs were analysed separately using a random effects model and then combined using a stratified analysis. Review manager was used to do the statistical analysis.

Study population issues: studies had similar patient selection criteria, and method of HIPEC administration but the use of chemotherapy drugs varied.

Other issues: studies assessing HIPEC and standard surgical management for the prevention of peritoneal carcinomatosis in patients with advanced gastric cancer (without PC but at high risk of developing PC) were excluded from this overview as it is out of the remit of this guidance. Only studies on CRS and HIPEC in treatment of gastric cancer peritoneal carcinomatosis were included.

IP overview: Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Studies were mainly done in Asia and the findings might not be generalisable.

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **14 studies (n=620 patients; 289 CRS+HIPEC compared with 331 controls [244 CRS and 87 systemic chemotherapy])**

For patients without the presence of peritoneal carcinomatosis (PC), the overall survival rates between the HIPEC and control groups at 3 or 5 years resulted in favor of the HIPEC group (RR=0.82, P=0.01). No difference in the 3-year overall survival (RR=0.99, P=0.85) in but a prolonged median survival of 4 months in favor of the HIPEC group (WMD=4.04, P<0.001) was seen in patients with PC.

Overall survival	CRS+HIPEC Total events (n)	Control Total events (n)	Risk ratio (95% CI)	P value
1-year follow-up	80/163	153/222	0.67 (0.52, 0.86)	0.002
2-year follow-up	62/83	95/114	0.87 (0.73, 1.04)	0.12
3-year follow-up	67/74	131/147	0.99 (0.93, 1.06)	0.85

Median survival for gastric cancer peritoneal carcinomatosis

Data analysis showed a benefit in favour of the HIPEC group with a median survival of 11.1 months compared with 7.06 months in the control group (WMD=4.04, 95% CI 2.40–5.67, P<0.001). This result is consistent in RCTs and NRCTs analysed separately. However, when comparing HIPEC compared with systemic chemotherapy alone, this analysis did not show a statistically significant difference between groups (WMD=2.95, 95% CI 0.92–6.83, P=0.14).

Extent of carcinomatosis

Data on limited peritoneal dissemination did not show any statistically significant differences in the survival rates at the 1-year (RR=0.62, 95% CI 0.35–1.12, P=0.11), 2-year (RR=0.75, 95% CI 0.50–1.14, P=0.18), and 3-year follow-up (RR=0.78, 95%CI 0.57–1.06, P=0.11). Data on the extensive peritoneal dissemination, also did not show differences in survival rates at 1-year (RR=0.84, 95% CI 0.64–1.11, P=0.22) and 2 years (RR=0.94, 95% CI 0.77–1.13, P=0.51) between groups.

Impact of the PCI index on survival (2 studies: Yang 2011, Yarema 2014)

In the “low PCI” group (< 20 points), the median survival was not significantly different between the two arms (11.57 months in the HIPEC group compared with 8.6 months in the control group, WMD=2.97, 95% CI 0.62–6.57, P=0.11), while the effect in the “high PCI” group (> 20 points) was shown only in one study (Yang 2011) (13.5 months in the HIPEC group compared with 3 months in the control group, P=0.012).

Safety

Significant high risk of developing postoperative complications was reported in the HIPEC group (RR=2.15, 95%CI 1.29–3.58, P<0.01), and was consistent among RCTs (RR=2.88, 95%CI 1.04–7.97, P=0.04) and NRCTs (RR=1.86, 95%CI 1.04–3.33, P=0.04). HIPEC is also related to a high risk of developing respiratory failure (RR=3.67, 95% CI 2.02–6.67, P<0.001) and renal dysfunction (RR=4.46, 95% CI 1.42–13.99, P=0.01). The anastomotic leakage analysis did not reach a statistical significance gastric cancer peritoneal carcinomatosis group (P=0.42).

Abbreviations used: CI, confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinomatosis index; RCTs, randomised controlled trials, NRCTs, non-randomised controlled trials; RR, risk ratio; WMD, weighted mean difference.

Study 7 Chia CS 2016

Details

Study type	**Systematic review**
Country	International
Study period	Search period: 1970 to 2016; databases searched: PubMed, Medline, Embase, Cochrane database and Ovid search.
Study population and number	n=**17 studies (1,578 patients) with gastric cancer peritoneal carcinomatosis** who had CRS and HIPEC. 1 systematic review, 1 RCT, 11 prospective studies and 4 retrospective studies.
Age and sex	not reported
Patient selection criteria	All retrospective and prospective studies in English, assessing the use of CRS and HIPEC for peritoneal carcinomatosis from gastric cancer, with at least 10 patients, reporting survival outcomes and separate data analysis for gastric cancer PC (if heterogenous group of tumour types) were included. Studies in prophylactic setting reporting separate outcomes for peritoneal carcinomatosis patients were also included. All other studies including case reports were excluded.
Technique	Cytoreductive surgery and HIPEC 8 studies used closed technique, 5 studies used open technique and 2 studies used both techniques. The common chemotherapy drugs used were mitomycin and cisplatin. Other drugs used were etoposide, oxaliplatin, docetaxel. Dosage varied between studies from 5 µg/ml to 460 mg/m2. Temperatures ranged between 41-48 degrees C. The duration of infusion ranged from 40 to 120 minutes.
Follow-up	**Varied across studies**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up times varied in individual studies.

Study design issues: systematic literature search was done and 2 reviewers independently selected studies and extracted data, quality assessment of studies was not done. Studies were mainly heterogenous. Variations were in terms of technique of HIPEC, chemotherapy used, dose of drugs, duration of HIPEC and temperature used.

Other issues: there is some overlap of primary studies between the systematic review included in this study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **17 studies (n=1578 patients)**

Survival

For all patients (n=17 studies)	
Median survival	Range 6.6 to 15.8 months
1-year survival rate	44%
2-year survival rate	43 to 45%
3-year survival rate	5.9 to 28.5%
4-year survival rate	76%
5-year overall survival	Range 6 to 31%
For patients with complete cytoreduction (n=11 studies)	
Median survival	11.2 to 43.4 months
5-year overall survival	13 to 23%

Survival in comparative studies

RCT (Yang 2011)	**HIPEC**	**Surgery**
Median survival	11.5 months	6.5 months
3-year survival rate	5.9%	0
Case control studies		
Hirose 1999		
Median survival	11 months	6 months
1-year survival	44.4%	15.8% (p=0.04)
Fujimoto 1999		
4 year-survival	76%	48% (p=0.04)
8-year survival	62%	49%

Disease free survival

Disease free survival was 10.7% at 3 years in 1 study and 11% at 5 years in another study.

Factors affecting survival

The two important prognostic factors that affect survival were the extent of disease (in 5 studies) and the completeness of cytoreduction (in 11 studies).

Safety

Adverse events after CRS and HIPEC (n=14 studies)

	N	**Mortality % (n)**	**Morbidity % (n)**
Yonemura 1991	41	0	12
Fujimoto 1999	71	NR	2.8
Hirose 1999	17	5.8	35.2
Glehen 2004	49	4	27
Hall 2004	34	0	35
Yonemura 2005	42	7	43
Scaringi 2008	37	5.4	27
Glehen 2010	159	6.5	27.8
Yang 2010	28	0	14.3
Yang 2011	34	NR	14.7
Gill 2011(systematic review)	441	4.8	21.5
Canbay 2013	152	3.9	23.6
Magge 2014	23	4.3	52.2
Chia 2016	81	2.5	44
Overall		**Range 0 to 7**	**Range 2.8 to 52.2**

Abbreviations used: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; RCT, randomised controlled trial.

Peritoneal carcinomatosis from colorectal cancers

Study 8 Huang CQ 2017

Details

Study type	**Systematic review and meta-analysis**
Country	China (individual studies from 19 countries)
Recruitment period	Searched up to 2016
Study population and number	**n=76 studies (n=10,036 patients with peritoneal carcinomatosis from colorectal cancer who had CRS plus HIPEC** (1 randomised controlled trial, 14 non-randomised controlled trials, and 61 non-controlled studies) **15 controlled studies (n=3,179) were included in meta-analysis**
Age and sex	Not reported
Patient selection criteria	**Inclusion criteria**: All patients diagnosed with peritoneal carcinomatosis from colorectal cancer; studies with key outcome measures (overall survival, disease-free survival, recurrence-free survival, progression-free survival, morbidity and mortality), multivariate analysis, and follow-up times; English language studies; both fully published articles and abstracts. Also, according to the North-England evidence-based guidelines, excluded from IV levels evidence of literatures were included. **Exclusion criteria**: animal studies; pathological research; imageology research; pharmacokinetics research; quality of life assessment; literature review, commentary, letters, books etc; duplicate publications or overlapping data; sample size <10; multiple cancers; unresectable liver metastases or other distant metastasis; missing rate of follow-up >5%.
Technique	HIPEC techniques varied by institutions: 22 institutions used open technique, 10 institutions used closed technique, and 41 institutions used both open and closed techniques. The commonly used chemotherapy agents were mitomycin C(MMC) alone (n = 63, dosage of 30-50 mg/m2 in 88% of institutions, median temperature 41.5°C, ranging from 40-43°C, and median duration 90 min, ranging from 60 – 90 min), oxaliplatin (L-OHP) alone (n = 43, dosage of 460 mg/m2 in 60% of institutions, median temperature 43°C, ranging from 40 - 43°C; and median duration 60 min), and a combination of MMC and cisplatin (CDDP) (n = 24, dosage of 30-50 mg/m2 + 50-100 mg/m2 in 33% of institutions).
Follow-up	**Mean 33.1 (SD ± 22.5) months**
Conflict of interest/source of funding	The authors of this study declared no conflicts of interest.

Analysis

Follow-up issues: Follow-up times varied in the individual studies with mean follow-ups ranging from 10.5 months to 113 months. 17 out of 76 studies did not report follow-up times.

Study design issues: Comprehensive search strategy was used. Data extraction for outcome measures, such as overall survival, disease free survival, morbidity and mortality, was done by three authors. The study conducted meta-analysis of 15 controlled studies (1 RCT and 14 non-randomised controlled studies) and a summary of 76 HIPEC-related studies (including 15 controlled studies and 61 non-controlled studies). 63 out of 76 studies were retrospective studies. In the meta-analysis, the CRS plus HIPEC therapy was compared with the traditional treatment of palliative surgery alone or systemic chemotherapy. Hazard ratios with 95% CI were calculated for the 15 controlled studies. The heterogeneity in the meta-analysis was evaluated by I^2 statistics and if I^2 was <50%, fixed effect model was used to get pooled HR, otherwise random effect model was used. Sensitivity analysis was done for sample size difference, geographic difference and published-time difference. Sub-group analysis by chemotherapy regimen was also done in the meta-analysis.

Study population issues: The complete cytoreduction rate ranged from 32.4% to 100% in 15 studies in the meta-analysis. Out of the 15 studies, 8 were from Europe, 3 from North America, 3 from Australia and 1 from Asia. 9 out of the 15 studies had sample size of <100. 58 out of 76 studies were single centre studies.

Other issues:

Key efficacy and safety findings

Efficacy

Number of patients analysed: **10,036 patients in 76 studies**

Meta-analysis (15 controlled studies, n=3179)

Mean overall survival (OS)(SD)

- HIPEC group – 34.3±14.8 months
- Traditional group – 18.8 ± 8.8 months

The summarised hazard ratio for overall survival in 15 controlled studies was 2.67 (95% CI, 2.21-3.23, p<0.00001, I^2=0%), suggesting that CRS+HIPEC was better than traditional therapy for colorectal cancer patients with peritoneal carcinomatosis.

Subgroup analysis

Chemotherapy regimens	**Hazard ratio (95% CI)**	***p* value**
Mitomycin C based chemotherapy	2.88(2.26-3.68)	<0.00001
Oxaliplatin based chemotherapy	2.18(1.57-3.04)	<0.00001
Other regimens	3.90(1.73-8.81)	0.001

I^2=0% for all chemo regimens

Mean survival rate (SR) of 15 controlled studies

	HIPEC(SD)	**Traditional (SD)**
1-year SR	84.5% (±12.6%)	58.1% (±20.6%)
2-year SR	61.7% (±20.3%)	38.8% (±18.7%)
3-year SR	46.8% (±16.2%)	23.6% (±15.2%)
4-year SR	48.8% (±6.4%)	20.4% (±10.1%)
5-year SR	40.0% (±11.5%)	18.1% (±14.1%)

Summary of 76 studies (including 15 controlled studies), n=10036

Overall survival (OS)(SD)

- Mean OS - 29.2±11.3 months

Disease-free survival (DFS)/recurrence free survival (RFS)

- Mean DFS/RFS - 15.9±7.7 months

Safety

In 15 controlled studies:

Mean mortality rate (SD)

HIPEC Group	4.3% (±3.7%)	p=0.423
Traditional Group	6.2% (±4.2%)	

Mean morbidity rate (SD)

HIPEC Group	19.8% (±9.2%)	p=0.815
Traditional Group	20.5% (±12.3%)	

In all 76 studies:

Mean mortality rate (SD): 2.8% (±2.9%)

Mean morbidity rate (SD): 33.0% (±13.4%)

Mean Survival rate (SR)(SD) • 1-year SR – 79.7% (±14.5%) • 2-year SR – 56.5% (±17.3%) • 3-year SR – 42.3% (±17.1%) • 4-year SR – 33.8% (±15.4%) • 5-year SR – 27.5% (±14.1%)	
Abbreviations used: CI, confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy DFS, disease free survival; OS, overall survival; RFS, recurrence free survival; RCT, randomised controlled trial; SD, standard deviation; SR, survival rate	

Study 9 Tonello M 2019

Details

Study type	**Systematic review and meta-analysis**
Country	Italy (not reported for individual studies)
Recruitment period	Searched on August 2018
Study population and number	**n=9 studies (n=1,308 patients) (1,153 colonic peritoneal metastasis, 155 rectal peritoneal metastasis) who had CRS and HIPEC** 3 prospective studies, 4 retrospective studies and 2 case-control studies included in the meta-analysis.
Age and sex	Not reported
Patient selection criteria	Inclusion criteria:(1) patients with colorectal peritoneal metastases with pathological confirmation, who had CRS plus HIPEC or CRS and early post-operative intraperitoneal chemotherapy(EPIC), or CRS and HIPEC followed by EPIC; (2) complete cytoreduction (CC0 or CC1 score); (3) reported completed survival data such as OS, DFS or hazard ratio with confidence intervals; data reported dividing primary tumour origin(colon vs rectum). Exclusion criteria: incomplete reduction; review and duplicated articles; editorial; non-English papers; radiologic or pharmacokinetics research, quality of life assessment, commentary, letters, books etc; studies that did not separate results according to primary tumour site; incomplete data on survival.
Technique	CRS and HIPEC Treatment strategy varied in the studies. Various chemo regimens were used including Mitomycin C± Cisplatin or Oxaliplatin ± irinotecan. Some studies reported systemic treatment with chemotherapy or radio-chemotherapy after CRS+HIPEC, and others did not report.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Follow-up times varied in individual studies.

Study design issues: The study evaluated the relation between survival and primary tumour site in colorectal peritoneal metastases who had CRS and HIPEC. The study was conducted according to the Cochrane Collaboration and PRISMA statements. Comprehensive search strategy was used. References from selected relevant studies were manually searched. Main authors were contacted for minor missing or incomplete data. Main outcome measures were overall survival and disease-free survival. Overall survival has been further divided and analysed as two groups because 6

IP overview: Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

studies reported mean overall survival and 3 reported hazard ratios. If the data were incomplete, hazard ratio was estimated using Tierney's method and mean difference was estimated using Hozo's method. The I^2 statistics was used for heterogeneity. Fixed effect model or random effects model has been used, depending on the I^2 value.

Study population issues: 88.15% (n=1153) of total sample had peritoneal metastases from colonic origin and 11.85%(n=155) had rectal origin.

Other issues: This meta-analysis compared the outcome of CRS plus HIPEC therapy on patients with peritoneal metastasis from colonic or rectal cancer and it only reported the mean difference or hazard ratio for overall survival and disease survival. Disease survival was only available in 4 studies. **T**here is some overlap of primary studies in 2 or more included systematic reviews.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1,308 (1,153 colon origin peritoneal carcinomatosis and 155 rectal origin)**

Overall survival, Mean

Individual studies	Colonic origin		Rectal origin		Mean Difference IV, Random, 95%CI
	n	Mean months (SD)	n	Mean months (SD)	
Chua 2011- Morris 2018	244	55.00(3.90)	24	42.69(5.05)	12.31(10.23,14.39)
DaSilva 2005	64	78.50(50.92)	6	18.75(6.63)	59.75(46.19,73.31)
Huang 2014	21	13.00(1.11)	12	14.85(4.65)	-1.85(-4.52,0.82)
Simkens 2016	58	35.08(5.33)	29	26.03(1.90)	9.05(7.51,10.59)
Tonello 2018	31	47.40(21.22)	5	30.93(15.64)	16.47(0.85,32.08)
Yonemura 2013-2018	203	86.33(58.44)	37	23.21(14.15)	63.12(53.88,72.36)
Overall	**621**		**113**		**24.49(14.70,34.28)***

I^2= 98%, * Weighted mean difference, Test for overall effect: p<0.00001

When treating with CRS plus HIPEC, overall survival is longer in patients with peritoneal metastases arising from colonic primary tumour, compared with rectal one, with OS mean difference of 24.49 months (95% CI: 14.70,34.28; p<0.00001).

Overall survival, Hazard ratio

Individual studies	Colonic origin, n	Rectal origin, n	Hazzard ratio IV, Fixed (95% CI)
Elias 2010	341	27	1.15(0.59,2.22)
Froynes 2016	109	10	1.84(0.77,4.40)
Verwaal 2004	82	5	3.14(1.11, 8.88)
Overall	**532**	**42**	**1.62(1.01,2.59) ***

*I^2=25%, * Weighted Hazard ratio, test for overall effect: p=0.05*

When treating with CRS plus HIPEC, overall survival is longer in patients with peritoneal metastases from colonic tumour, compared with rectal one, with pooled hazard ratio of 1.62(95%CI: 1.01,2.59; p=0.05) for rectal origin vs colonic origin.

Disease free survival

Individual studies	Colonic origin		Rectal origin		Mean Difference IV, Random, 95%CI
	n	Mean months (SD)	n	Mean months (SD)	
Chua 2011 – Morris 2018	171	21.52(2.80)	15	17.91(5.30)	3.61(0.90,6.32)
Simkens 2016	58	13.60(1.40)	29	13.48(1.51)	0.13(-0.53,0.78)
Tonello 2018	31	21.42(17.73)	5	9.47(4.41)	11.95(6.03,17.87)
Yonemura 2013 - 2018	203	37.33(22.98)	37	19.68(14.22)	17.65(12.08,23.22)
Overall	**463**		**86**		**7.75(1.37,14.13) ***

*I^2=95%, *Weighted mean difference, test for overall effect: p=0.02*

When treating with CRS plus HIPEC, disease free survival is greater for colonic origin peritoneal metastases compared with rectal origin, with mean difference of 7.75 months (95%CI:1.37,14.13; p=0.02).

Abbreviations used: CI, confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; SD, standard deviation.

IP overview: Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Peritoneal carcinomatosis from various primary origins

Study 10 Shan 2014

Details

Study type	**Systematic review and meta-analysis**
Country	Australia
Study period	Search period: 2000 to 2013; databases searched: PubMed, Medline, Embase, and Ovid search. additional manual search of reference lists of each included study was done.
Study population and number	n= **15 prospective studies (1,583 patients) with peritoneal carcinomatosis from various origins** who had CRS and HIPEC.
Age and sex	Age range 48-56 years; male 24% to 65%
Patient selection criteria	English studies on CRS and HIPEC for primary or secondary peritoneal carcinomatosis, disease-specific and/or generic health related quality of life (HRQOL) data recorded, and HRQOL comparisons to pre-operative status and reference populations were included.
Technique	Cytoreductive surgery and HIPEC
Follow-up	**Varied across studies; range 2 months to 5.8 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up times varied in individual studies. Only 5 studies had a response rate of more than 85%.

Study design issues: systematic review was done according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist and recommended guidelines were followed. 2 reviewers independently selected studies and any disagreements were resolved by consensus, quality assessment and data extraction were done using pre-determined forms. Data were synthesised by narrative review and random-effects meta-analysis (if more than 5 studies included) using review manager. Clinical and statistical heterogeneity and risk of bias were analysed. Key outcomes were postoperative HRQOL compared with pre-operative levels and reference populations using a time-dependent approach. All studies utilised disease-specific HRQOL instruments, but only 8 had both disease-specific and generic HRQOL data.

Study population issues: patients have a variety of primary tumour origins, histopathological differences and extent of disease and prognosis. 11 studies had less than 100 patients. Comparison reference populations are also heterogenous.

Other issues: type of HRQOL instruments used varied across studies and there is no validated standardised tool.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **15 prospective studies (1583 patients)**

Pre-operative disease specific HRQOL scores (combined FACT-C & EORTC scores) compared with post-operative scores at 1-year follow-up (8 studies)

Overall health
The pooled-effects of combined post-operative FACT-C and EORTC scores were significantly improved from baseline on overall health status (MD 0.28, 95% CI -0.52 to 0.29, p =0.0010).
HRQOL after 1 year is less clear, but benefits may persist up to 5 years especially on overall and physical health domains.
Evidence is conflicted and inconclusive on HRQOL compared with reference populations.

Qualitative analysis
Overall post-operative HRQOL is similar or better compared with baseline/before surgery (on FACT-C and FACT-G total scores) at 1 year (in 4 studies) and EORTC global health status at 1 and 2 years (in 2 studies). General health is similar at 2 years after surgery on SF-36 (in 1 study). Overall FACT-C and general health domains on SF-36 remain improved/may be maintained for up to 5 years [I study].
General health on SF-36 is worse compared with the reference population at 2 years (in 2 studies). global health status on EORTC QLQ-C30 is better than reference populations at 2 and 3 years [2 studies], but not at 4 years [in 1 study].

Emotional health
Subgroup analysis showed significant improvements in emotional health from baseline (MD 0.38 ,95% CI 0.15 to 0.60; p = 0.001).

Qualitative analysis: Post-operative emotional well-being on FACT-C is similar or better at approximately 3, 6 and 12 months [10,29,33e35,38], but is not significantly different at 5 years [3]. SF-36 role emotional and mental health domains appear to improve as a result of surgery after an initial decline [3,10,29,32,35]. Similarly, emotional function on EORTC improved at 1 or 2 years [8,30,37]. Many patients avoid becoming clinically depressed as measured by CES-D [3,10,35] even though there may be an initial worsening of depressive symptoms at 3 months [29]. Compared with the reference population, the mental health domain on SF-36 is better at 1 year post-operatively [11]. Role emotional, mental health and emotional functioning is worse on SF-36 and EORTC QLQ-C30 at 2 and 4 years respectively [30,36]. The level of depression and anxiety are not significantly different to reference population [26].

Physical health
Subgroup analysis showed no significant difference in pooled effect for physical health from baseline (MD 0.03, 95% CI -0.24 to 0.30, p = 0.83).

Qualitative analysis:
Physical well-being (subscale on FACT-C and FACT-G) declines after surgery and is worse at around 3 months, but increases to be similar or better by 6 or 12 months [10,29,33e35,38]. This is also supported by EORTC physical function scores [8] and SF-36 bodily pain scores [3,10,29,32,35]. These benefits for physical well-being appear to be sustained up to 5 years post-operatively [3] even though it may be 3 years before returning to baseline [37] Patient's vitality on SF-36 declined after an initial improvement at 3 months [10,35]. Other studies show that patients' vitality on SF-36 improved slowly, but steadily after an initial decline [29,30]. Specific symptomatology varies between studies.

Social health
Subgroup analysis showed no significant difference in pooled effect for social health from baseline (MD -0.06, 95% CI -0.23 to 0.11, p = 0.48), they remained similar.

Qualitative analysis: Social well-being on FACT-C, FACT-G and EORTC remains largely unchanged after surgery compared with baseline [3,10,29,33e35,37,38]. Fewer difficulties on EORTC social functioning are reported in 88% of patients [26]. Social function on SF- 36 may be worse at 1 year [29,35], but reaches baseline level at 2 years [30] and may become superior to post-operative

status at 5 years [3]. Compared with the reference population, social functioning is worse or similar on SF-36 at 1 and 2 years [10,11,30] and EORTC QLQ-C30 at 1 and 4 years [8,36].

Functional health
Subgroup analysis showed no significant difference in pooled effect for functional health from baseline (MD 0.21, 95% CI -0.14 to 0.55, p = 0.24), they remained similar.

Qualitative analysis: Most patients reach a post-operative functional state at least as good as pre-operatively by 6 months or 12 months in functional well-being on FACT-C [10,29,34,35,38] Role function on EORTC declines at 1 month, but improves by 12 months and remains similar or better at 2 years [8,30,37]. After an initial decline in the early post-operative period, physical function [10,34,35] and role physical on SF-36 improves to be at least as good as pre-operatively [3,10,29,32,35]. This benefit may persist to 5 years [3]. However, functional well-being on Fact-G is reported to be worse at 6 months [33] and both SF-36 physical function and role physical domains may be worse at 2 years [30].
Post-operative ECOG performance status was 0 in 58e88% patients [3,10,34,35]. At 1 year, less patients were able to participate in vigorous activities and walk long distances [10,34,35]. However, more were able to climb a flight of stairs, walk short distances and bathe independently [10,34,35]. Sixty-three percent of patients report no pain with walking around at 1 year [29] and 73e85% were able to return to most of their normal activities [3,10,29,35].
Compared with the reference population, role function is persistently worse on EORTC QLQ-C30 and SF-36 for up to 4 years of follow-up [30,36,37].

Abbreviations used: CRS, cytoreductive surgery; CES-D, centre for epidemiologic studies-depression scale; EORTC score, European Organisation for research and treatment of cancer; EORTC QLQ-C30, European organisation for research and treatment quality of life questionnaire-cancer specific; ECOG, eastern cooperative oncology group performance status rating; HIPEC, hyperthermic intraperitoneal chemotherapy; FACT-C, functional assessment of cancer therapy; FACT-G, functional assessment of cancer therapy-general score; HRQOL, health related quality of life; MD, mean difference; SF-36, medical outcomes survey short form 36 questions.

Validity and generalisability of the studies

- Evidence on cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy is presented for peritoneal carcinomatosis derived from gynaecological, gastric and colorectal cancers only. Evidence on prophylactic studies for people without peritoneal carcinomatosis is excluded in this overview because it is out of the remit of this guidance.

- Systematic reviews included different types of studies but were predominantly based on non-randomised studies.

- The extent of cytoreductive surgery varied across studies.

- There is no standardised method or protocol for HIPEC treatment. HIPEC was done using open or closed techniques. Variations were noted in the choice of HIPEC drug regimen (different temperatures, drug doses, duration of infusion times, and used either on its own or in combination with other drugs). These variations might have influenced treatment outcomes.

- Most patients had systemic chemotherapy during or after CRS and HIPEC. So, the value of HIPEC to CRS is not clear.

- There is limited evidence assessing the effect of CRS and HIPEC on quality of life. There are no subgroup analyses of patients who are most likely to improve their quality of life.

Existing assessments of this procedure

A systematic review of national and international guidelines on recommendations and a consensus on the treatment of peritoneal metastases from colorectal cancer origin reported that in 21 currently available guidelines, the consensus on treatment was lacking. 15 guidelines recommended CRS with HIPEC in selected patients based on level 1 evidence, but eligibility and surgical procedure vary. Consensus was reached on the benefit of MDT and achieving a near complete

cytoreduction (CC 0-1) without supporting evidence. There was no evidence or consensus on optimal patient selection, preoperative CT, second look surgery in high risk patients, procedural aspects of HIPEC and perioperative systemic chemotherapy.[11]

NHS England published a Clinical Commissioning Policy in April 2013. The policy covered cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis secondary to colorectal carcinoma, gastric carcinoma, pancreatic carcinoma and ovarian carcinoma. NHS England will commission this procedure for patients with peritoneal carcinomatosis secondary to colorectal cancer. It will not be commissioned when metastatic disease is more extensive than the peritoneum alone. This policy states 'for colorectal cancer there is a clear long term survival benefit for selected patients. For ovarian, gastric and pancreatic cancers the scientific evidence is equivocal or lacking.'[12]

Summary of findings from the evidence review for this policy

Clinical effectiveness

- When delivered by surgeon and units with the experience and expertise in achieving high rates of complete cytoreduction provides a significant survival benefit in peritoneal carcinomatosis secondary to colorectal and ovarian carcinoma.

- Cytoreduction surgery plus hyperthermic intraperitoneal chemotherapy is more effective than cytoreduction surgery alone in gastric carcinoma, but the literature has not yet explored its specific benefit over systemic chemotherapy.

- The evidence suggests that the completeness of cytoreduction is an important determinant of effectiveness, and therefore this parameter should be monitored where the procedure is done.

Safety

- Cytoreduction surgery and hyperthermic intraperitoneal chemotherapy is of equivalent safety to other major abdominal procedures. But it is important to consider the evidence for cytoreduction surgery and hyperthermic intraperitoneal chemotherapy separately for peritoneal carcinomatosis from each of colorectal, gastric, pancreatic and ovarian carcinoma.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique). NICE interventional procedures guidance 056 (2004). Available from httpS://www.nice.org.uk/guidance/IPG56
- Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis, NICE interventional procedure guidance 331 (2010). Available from http://www.nice.org.uk/guidance/IPG331 [current guidance]

Technology appraisals

- Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy. NICE technology appraisal 381 (2016). Available from http://www.nice.org.uk/guidance/TA353

NICE guidelines

- Ovarian Cancer-recognition and initial management NICE guideline CG122 (2011). Available from http://www.nice.org.uk/guidance/CG122
- Metastatic malignant disease of unknown primary origin in adults: diagnosis and management. NICE guideline CG104 (2010). Available from http://www.nice.org.uk/guidance/CG104
- Colorectal cancer. NICE clinical guideline CG151 (2020). Available from http://www.nice.org.uk/guidance/CG151
- Improving outcomes in colorectal cancer, cancer service guideline. NICE guideline CSG5 (2004). Available from http://www.nice.org.uk/guidance/CSG5

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Five professional expert questionnaires for cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 2 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- The procedure is already in use in 3 NHS centres following Clinical Commissioning Policy by NHS England for the treatment of peritoneal carcinomatosis from colorectal cancer.
- NICE Colorectal cancer guideline published in January 2020 supports the use of CRS and HIPEC for people with metastatic colorectal cancer in the

peritoneum (see section 1.5.9). 'Although the evidence on the effectiveness was mixed, the committee decided that it was important to recommend referral to a nationally commissioned specialist centre after discussion within a multidisciplinary team for consideration of CRS and HIPEC so that more patients can have potentially curative treatment. This advice is in line with the NICE IPG 331'.

- All patients who had this procedure in the UK (Basingstoke, Manchester, Birmingham, Dublin and Dundee) are entered onto the UK and Ireland Colorectal Peritoneal metastases Registry.
- Evidence for CRS and HIPEC on pseudomyxoma peritonei, peritoneal mesothelioma induced peritoneal carcinomatosis and peritoneal carcinomatosis from other primary origins was not included in this overview.
- **Ongoing studies**
  - A systematic review and meta-analyses of clinical and cost effectiveness on CRS with HIPEC compared with standard of care in people with peritoneal metastases from colorectal, ovarian or gastric origin is currently ongoing and is expected to publish results for different cancer types between 2021 and 2022. This work is conducted by the evidence review of peritoneal tumours working group (at The Christie NHS Foundation trust and University College London) and supported by NIHR HTA programme (HTA project 17/135/02).
  - **Ovarian cancer:**
  - NCT01376752 A phase III randomized study evaluating hyperthermic intra-peritoneal chemotherapy (HIPEC) in the treatment of relapse ovarian cancer (CHIPOR); n=444 patients; intervention- CRS with HIPEC compared with CRS without HIPEC; primary outcome-overall survival; location: Europe-Belgium, France and Spain; start date April 2011, completion date April 2025.

- NCT01539785 Surgery plus hyperthermic intra-peritoneal chemotherapy (HIPEC-cisplatin) compared with surgery alone in patients with platinum-sensitive first recurrence of ovarian cancer: a prospective randomized multicenter trial (HORSE); n=158; primary outcome-progression free survival; completion date September 2018; location: Italy; status: unknown.
- NCT01767675 A phase II randomized study: outcomes after secondary cytoreductive surgery with or without carboplatin hyperthermic intraperitoneal chemotherapy (HIPEC-carboplatin) followed by platinum based systemic combination chemotherapy for recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer; n=98; primary outcome: proportion of patients without evidence of disease progression at 24 months; location USA, status: recruiting.
- **Gastric cancer:**
- NCT02158988 The GASTRIPEC trial is recruiting patients with gastric cancer and synchronous peritoneal carcinomatosis. CRS+HIPEC (drugs MMC and cisplatin) is compared with CRS alone; n=180 patients; primary outcome- overall survival through a 2.5 years maximum follow-up per patient; secondary outcomes -complication rate, time to disease progression, and quality of life. Completion date September 2020.
- **Colorectal cancer:**
- NCT00769405 **PRODIGE 7** randomised phase III multicenter trial evaluating the use of systemic chemotherapy and chemo-hyperthermia intraperitoneal preoperatively (CHIP) and after maximum resection of peritoneal carcinomatosis originating with colorectal cancer, randomised controlled trial, n=265 patients, patients were who had CRS plus HIPEC with oxaliplatin or CRS alone, 132 in arm without HIPEC and 133 in arm with HIPEC. in association with systemic chemotherapy. primary outcome-

overall survival, location France, completion date 2015; status completed **(abstract published; full article not available)**

- NCT01628211 Randomized phase 2 study comparing second look laparoscopy to standard follow up in patients with no radiologic evidence of disease at 6 months after complete resection of colorectal mucinous carcinoma. Randomised controlled trial, n=140, primary outcome-overall survival, completion date 2018, location Italy, status unknown'.,
- NCT01815359 ICARuS (Intraperitoneal chemotherapy after cytoreductive surgery): A multi-center, randomized phase II trial of early post-operative intraperitoneal chemotherapy (EPIC) and hyperthermic intraperitoneal chemotherapy (HIPEC) after optimal cytoreductive surgery (CRS) for neoplasms of the appendix, colon or rectum with isolated peritoneal metastasis. Randomised controlled trial, n=282, primary outcome-disease free survival; location USA, completion date 2020; status recruiting.

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12. Clinical Commissioning Policy for cytoreduction surgery for patients with peritoneal carcinomatosis. NHS commissioning board. April 2013 Reference : NHSCB/A08/P/a https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/09/a08-p-a.pdf

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	28/08/2019	Issue 8 of 12, August 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	28/08/2019	Issue 8 of 12, August 2019
HTA database (CRD website)	28/08/2019	n/a
MEDLINE (Ovid) & MEDLINE In-Process (Ovid)	28/08/2019	1946 to August 27, 2019
Medline ePub ahead (Ovid)	28/08/2019	August 27, 2019
EMBASE (Ovid)	28/08/2019	1974 to 2019 August 27

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Peritoneal Neoplasms/ (14508)
2 Carcinoma/ (88715)
3 ((periton* or (intra-periton* or intra?periton* or "intra periton*")) adj4 (carcinomato* or carcino* or disseminat* or metast* or neoplasm* or cancer or malign* or tumo?r* or lump*)).tw. (17287)
4 ((intra-abdom* or intra?abdom* or "intra abdom*") adj4 (carcinomato* or carcino* or disseminat* or metast* or neoplasm* or cancer or malign* or tumo?r* or lump*)).tw. (2032)
5 or/1-4 (112839)
6 CYTOREDUCTION SURGICAL PROCEDURES/ (1607)
7 (cytoreduc* or debulk*).tw. (12664)
8 CRS.tw. (8150)
9 (plasma adj4 surg*).tw. (2527)
10 plasmajet.tw. (21)
11 or/6-10 (22714)
12 combined modality therapy/ or drug therapy/ (199149)
13 injections, Intraperitoneal/ (31085)
14 Antineoplastic Combined Chemotherapy Protocols/ or Chemotherapy, Adjuvant/ (159998)
15 (chemo?therap* or chemo* or pharmacotherap*).tw. (570124)

16 (drug* adj4 (therap* or treat*)).tw. (200268)
17 'combined modality therap*'.tw. (1855)
18 (multimod* adj4 (therap* or treat*)).tw. (11063)
19 or/12-18 (980034)
20 Hyperthermia, Induced/ (16050)
21 (heat* or hypertherm* or therm* or warm* or thermotherap* or 'fever therap*).tw. (499691)
22 or/20-21 (503135)
23 (Thermochem* or sugarbaker* or HIPEC or IPHC or IPH).tw. (3794)
24 5 and 11 and 19 and 22 (1539)
25 5 and (11 or 23) (3454)
26 24 or 25 (3454)
27 Animals/ not Humans/ (4579433)
28 26 not 27 (3380)
29 limit 28 to ed=20090513-20190228
29 limit 28 to ed=20190201-20190831 (212)
30 limit 29 to english language (191)

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Baratti D, Kusamura S, Pietrantonio F et al. (2016) Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review. Critical Reviews in Oncology-Hematology (100) 209-22.	Systematic review 19 cohort studies and 13 comparative studies included.	The weighted median overall survival was 31.6 months (range 16-51). Major morbidity was 17.6-52.4% (weighted average 32.6%). Mortality was 0-8.1% (weighted average 2.9%). Additional relevant topics, such as CRC-PM prevalence, results by systemic therapies, preoperative work-up, and technical aspects were summarized through a narrative review. The recent literature suggests that CRS/HIPEC is gaining acceptance as standard of care for selected CRC-PM patients. Refinement of selection criteria, and rationalization of comprehensive systemic and local-regional management is ongoing.	More comprehensive reviews added to table 2.
Barrios P, Roque M, Lozano JM et al (2009) Systematic review of the multidisciplinary combined treatment in peritoneal neoplasms. Radical surgical citoreduction + intraperitoneal chemotherapy +/- hyperthermia (Sugarbaker's technique). Barcelona: Catalan Agency for Health Technology Assessment and Research (CAHTA).	Systematic review	Intraperitoneal hyperthermic chemotherapy (IPHC) is used as an adjunct to surgery for the treatment of gastrointestinal, appendiceal, ovarian, or mesothelial cancers that have metastasized or may metastasize into the peritoneal cavity. Chemotherapeutic drugs are introduced directly into the peritoneal space to eliminate microscopic tumor on the peritoneal lining and the outer surfaces of affected organs and to kill tumor cells that have disseminated throughout the cavity. Heating enhances the cytotoxic effect of the drugs.	More comprehensive and recent reviews added to table 2.

Bakrin N, Cotte E, Golfier F et al. (2012) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. Annals of Surgical Oncology (19) 13 4052-8.	Retrospective case series N=246 patients with recurrent or persistent ovarian cancer, treated by cytoreductive surgery and HIPEC	An optimal cytoreductive surgery was possible in 92.2 % of patients. Mortality and morbidity rates were 0.37 % and 11.6 %, respectively. The overall median survival was 48.9 months. There was no significant difference in overall survival in patients with persistent or recurrent disease.	More comprehensive and recent reviews added to table 2
Bakrin N, Bereder JM, Decullier E et al (2013) Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. European Journal of Surgical Oncology (39) 12 1435-43.	Retrospective cohort study N=566 patients with epithelial ovarian carcinoma (EOC) 92 patients with advanced EOC (first-line treatment), and 474 patients with recurrent EOC	A complete cytoreductive surgery was performed in 74.9% of patients. Mortality and grades 3 to 4 morbidity rates were 0.8% and 31.3%, respectively. The median overall survivals were 35.4 months and 45.7 months for advanced and recurrent EOC, respectively. There was no significant difference in overall survival between patients with chemosensitive and with chemoresistant recurrence. Peritoneal Cancer Index (PCI) that evaluated disease extent was the strongest independent prognostic factor for overall and disease-free survival in all groups.	More comprehensive and recent reviews added to table 2.
Ben -Yacov A, Nizri E, Lahat G et al (2019). Treatment of Peritoneal Surface Malignancies with Cytoreductive Surgery and Hyperthermic Intra-peritoneal Chemotherapy (HIPEC): Experience in Israel. Indian Journal of Surgical Oncology (February 2019) 10 (Suppl 1):S19–S23	Systematic review Cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) for the treatment of peritoneal surface malignancies.	Between 1990 and 2018, there were 1462 patients treated by CRS/HIPEC in Israel by eight different surgical groups in six medical centers. Currently, there are seven surgical groups in six medical centers routinely performing CRS/HIPEC. The annual rate of CRS/HIPEC was 171 cases in 2017 with a range of (4–69 cases/center).	More comprehensive and recent reviews added to table 2.
Bonnot PE, Piessen G, Kepenekian V et al (2019) Cytoreductive Surgery with or Without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer with	Propensity score analysis 7 patients with peritoneal metastases from gastric cancer who were who had complete CRS with curative inten-t180	Compared with CRS alone, CRS-HIPEC improved OS and recurrence-free survival, without additional morbidity or mortality. When complete CRS is possible, CRS-HIPEC may be considered a valuable therapy for strictly selected	Larger studies included in table 2.

Peritoneal Metastases (CYTO-CHIP study): A Propensity Score Analysis. J Clin Oncol. 2019 Aug 10;37(23):2028-2040. doi: 10.1200/JCO.18.01688. Epub 2019 May 14.	underwent HIPEC and 97 CRS alone.	patients with limited PMs from GC.	
Cai, Z., Cai, Z., He, T et al. (2018) Comparative effectiveness of hyperthermic intraperitoneal chemotherapy for gastric cancer: A systematic review and network meta-analysis protocol. Medicine (97) 33 e11949.	systematic review and network meta-analysis of RCTs	The results will provide useful information about the effectiveness and safety of HIPEC regimens in patients with resected gastric cancer.	Protocol only
Cao C, Yan TD, Black D et al. (2009) A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Annals of Surgical Oncology (16) 8 2152-65.	systematic review n=47 studies (4 comparative studies and 43 observational studies of CRS with PIC).	Meta-analysis shows that a significant improvement in survival was associated with treatment by CRS and hyperthermic intraperitoneal chemotherapy compared with palliative approach (P < 0.0001). The pooled data did not show a significant improvement in overall survival for patients treated by CRS and early postoperative intraperitoneal chemotherapy compared with surgery and systemic chemotherapy (P = 0.35). The overall effect of PIC is significantly better than the control group (P = 0.0002). The current literature suggests that patients with liver metastasis amendable to resection should not be excluded from CRS and PIC.	More comprehensive and recent reviews added to table 2.
Chua TC, Yan TD, Saxena A. and Morris DL (2009). Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of	Systematic review	The morbidity and mortality outcomes of CRS and HIPEC are similar to a major gastrointestinal surgery, such as a Whipple's procedure. To derive the maximal benefit of this treatment, careful patient selection with an optimal level of postoperative care must be advocated to avoid undesirable complications of this treatment.	More comprehensive and recent reviews added to table 2.

morbidity and mortality. Annals of Surgery (249) 6 900-7.			
Chua TC, Esquivel J, Pelz JO et al (2013) Summary of current therapeutic options for peritoneal metastases from colorectal cancer. Journal of Surgical Oncology (107) 6 566-73.	Systematic review 2,492 patients from 19 studies were reviewed. 1084 who had complete cytoreductive surgery (CCS) and hyperthermic intraperitoneal chemotherapy (HIPEC) and 1,408 patients were who had palliative surgery and/or systemic chemotherapy.	For CCS HIPEC, the overall survival ranged between 20 and 63 (median 33) months, and 5-year survival ranged between 17% and 51% (median 40%). For palliative surgery and/or systemic chemotherapy, the overall survival ranged between 5 and 24 (median 12.5) months, and 5-year survival ranged between 13% and 22% (median 13%).	More comprehensive and recent reviews added to table 2.
Cornali T, Sammartino P, Kopanakis N et al. (2018) Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy for Patients with Peritoneal Metastases from Endometrial Cancer. Annals of Surgical Oncology (25) 3 679-687.	Case series N=33 patients with peritoneal metastases from EC who underwent CRS plus HIPEC	During a median follow-up period of 73 months, Kaplan-Meier analysis indicated a 5-year OS of 30% (median 33.1 months) and a PFS of 15.5% (median 18 months). Multivariate analysis identified the completeness of cytoreduction (CC) score as the only significant factor independently influencing OS.	More comprehensive and recent reviews added to table 2.
Di Vita M, Cappellani A, Piccolo G et al (2015) The role of HIPEC in the treatment of peritoneal carcinomatosis from gastric cancer: between lights and shadows. Anti-Cancer Drugs (26) 2 123-38.	Systematic review	On reviewing the literature, despite the lack of trials comparing the different methods, we found that HIPEC has been shown to be an effective tool whenever a complete or an almost complete resection of the peritoneal implants can be performed. Therefore, it is advisable to refer all at-risk patients to specialized centers to be enrolled in randomized trials to achieve truly reliable results.	More comprehensive and recent reviews added to table 2
Dube P, Sideris L, Law C et al (2015) Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal	Guideline	Patients with resectable peritoneal surface malignancies (psm) arising from colorectal or appendiceal neoplasms should be reviewed by a multidisciplinary team including surgeons and medical oncologists with	Recent comprehensive systematic review on international guidelines added to the overview.

surface malignancy arising from colorectal or appendiceal neoplasms. *Curr Oncol*, Vol. 22, pp. e100-112		experience in treating patients with psm. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy should be offered to appropriately selected patients and performed at experienced centres.	
Elias D, Gilly F, Boutitie F et al (2010) 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) 1 63-8.	Retrospective case series N=523 Median follow-up 45 months	Mortality and grades 3 to 4 morbidity at 30 days were 3% and 31%, overall median survival was 30.1 months. Five-year overall survival was 27%- and five-year disease free survival was 10%. Complete CRS was done in 84% patients and median survival was 33 months.	More comprehensive and recent reviews added to table 2.
Eveno C and Pocard M. (2016) 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) 4 169-182.	Systematic review	Review published, recruiting or planned randomized controlled trials (RCTs) evaluating CRS and HIPEC compared with standard of care. Comparator was systemic chemotherapy and/or CRS alone.	information was mainly on recruiting or planned RCTs.
Gill RS, Al-Adra DP, Nagendran J et al. (2011) Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. Journal of Surgical Oncology (104) 6 692-8.	Systematic review CRS + HIPEC	Following CRS + HIPEC, overall median survival was 7.9 months and improved to 15 months for patients with completeness of cytoreduction scores of 0/1, however with a 30-day mortality rate of 4.8%.	More comprehensive and recent reviews added to table 2.
He T, Chen Z and Xing C. Cytoreductive surgery combined with intraperitoneal	A meta-analysis 8 trials were involved in the first group,	Compared with control group, the overall survival of the CRS+IPC group was much higher, with a total HR of 0.46	More comprehensive and

chemotherapy in the treatment of colorectal peritoneal metastasis: A meta-analysis. International Journal of Clinical and Experimental Medicine 2016 (9) 11 20562-20570	n=684 patients who were divided into CRS+IPC group (n=413) and control group (n=272) 4 case-control studies were involved in the second group, n=780 patients who were divided into oxaliplatin group (n=253) and mytomycin C group (n=527).	(95% CI, 0.37-0.56; P<0.00001). The outcome was the same when comparing CRS+IPC group with CRS+SC group (HR, 0.41; 95% CI, 0.28-0.60; P<0.0001). In CRS+SC group, the incidence of related complications such as haemorrhage, intestinal leakage, and intestinal obstruction was higher than that in CRS+IPC group, whereas chemotherapy-related side effects in CRS+SC group were less than CRS+IPC group (OR, 0.9; 95% CI, 0.56-1.45; P=0.67), suggesting that the difference between the two groups was not statistically significant. Compared with mytomycin C group, the overall survival of oxaliplatin group was lower (HR, 1.39; 95% CI, 1.04-1.87; P=0.03). The difference of the incidence of complications between the two groups was not statistically significant (OR, 1.04; 95% CI, 0.50-2.20; P=0.91).	recent reviews added to table 2.
Hyperthermic intraperitoneal chemotherapy. Health technology assessment report. DGHR, HTA department, Ministry of health Ankara. 2018.01/00.	HTA report on CRS and HIPEC	There are no treatment guidelines on which a full consensus has been reached and standardization in the treatment has not yet been established for HIPEC. limited number of randomized clinical trials performed for evaluating clinical effectiveness of the HIPEC treatment with CRS in the treatment of peritoneal carcinomatosis demonstrate that this intervention improves the overall survival rates, survival rates in the first, second, third, fourth and fifth years, disease-free survival, and recurrence rates with correct patient selection. There are limited studies in ovarian cancer treatment. It is understood that a well-designed, multicenter, prospective, randomized clinical trials focusing on ovarian cancers are necessary, especially it	More comprehensive reviews added to table 2.

		possible the results of in the treatment of gastric and colon cancers for the interpretation of the outcome of HIPEC in the treatment of ovarian cancers.	
Huang CQ, Yang XJ, Yu Y et al (2014) 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 [Electronic Resource] (9) 9 e108509.	Case series N=60 colorectal cancer PC patients underwent 63 procedures consisting of CRS+HIPEC and postoperative chemotherapy median follow-up was 29.9 (range 3.5-108.9) months	Complete cytoreductive surgery (CC0-1) was performed in 53.0% of patients. The median OS was 16.0 (95% confidence interval [CI] 12.2-19.8) months, and the 1-, 2-, 3-, and 5-year survival rates were 70.5%, 34.2%, 22.0% and 22.0%, respectively. Mortality and grades 3 to 5 morbidity rates in postoperative 30 days were 0.0% and 30.2%, respectively.	More comprehensive and recent reviews added to table 2.
Kopanakis N, Argyriou EO, Vassiliadou D et al (2018) Quality of life after cytoreductive surgery and HIPEC: A single centre prospective study. Journal of B.U.On. (23) 2 488-493.	Case series N=80 patients with peritoneal metastasis underwent CRS plus HIPEC. They completed the colorectal version of the Functional Assessment of Cancer Therapy questionnaire (FACTC, version 4) at different time points. All subscales were assessed	In all subscales, fluctuations in the scores indicated a worsening of QoL in the first 3 post-operative months, followed by improvement back to pre-operative levels and even better scores later on. Statistical improvement was proven for the physical and emotional well-being subscales.	More comprehensive and recent reviews added to table 2.
Kwakman R, Schrama AM, van Olmen JP et al (2016). Clinicopathological parameters in patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer. A meta-analysis. Annals of surgery 263 (6), 1102-1111.	Meta-analysis 25 studies used to perform a meta-analysis on 10 prognostic factors	Current clinical practice which selects patients based on extraperitoneal metastasis, lymph node stage, performance status and tumour histology is validated by pooled analysis. Our data merit further research into neoadjuvant chemotherapy in the setting of CRS and HIPEC for PMs.	More comprehensive and recent reviews added to table 2.
Leo Swenne C, Cederholm, K, Gustafsson, M and Arakelian E. (2015) Postoperative health	Case series N=16 patients who had CRS and HIPEC	Despite bodily complications, mental fatigue and worries about the return of the disease, the patient's everyday life was focused on	More relevant studies added to table 2.

and patients' experiences of efficiency and quality of care after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, two to six months after surgery. European Journal of Oncology Nursing (19) 2 191-7.	for peritoneal carcinomatosis	finding his/her new self and adapting to the new circumstances. Difficulties in contacting care facilities and the lack of an ongoing medical and nursing rehabilitation plan called for a need for network support for patients and their families.	
Lopez-Lopez V, Cascales-Campos PA, Schneider MA et al. (2016) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in elderly patients. A systematic literature review. Surgical Oncology 25 378-384	Systematic review 9 studies included.	Severe morbidity of all elderly patients ranges from 17% to 56% in centres with high experience. In-hospital and 30-day mortality ranges from 0% to 8%. In only two studies were the differences in morbidity and mortality statistically significant related to the control group. However, older adults undergoing cytoreductive surgery and HIPEC consistently had lower survival rates across all study settings and procedure types than younger individuals. In studies that stratified for elderly patients, PCI, completeness of cytoreduction, tumor histology and albumin levels were predictive factors of survival.	More comprehensive and recent reviews added to table 2.
Ludwigs, K., Breimer, ME, Brorson, F et al (2014). Cytoreductive surgery and intraperitoneal chemotherapy (HIPEC or EPIC) in patients with colorectal adenocarcinoma and peritoneal carcinomatosis. Gothenburg: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland.	HTA Colorectal PC Included 1 RCT	There is moderate quality evidence for prolonged survival (22.4 compared with 12.6 months) by CRS+HIPEC compared with systemic chemotherapy in patients with colorectal cancer and isolated peritoneal carcinosis. The effects on health-related quality of life are unknown. The prolonged survival by CRS+HIPEC is observed mainly in those patients where complete cytoreduction is obtained. CRS+HIPEC is associated with high morbidity, significant mortality and high costs.	More comprehensive and recent reviews added to table 2.
Mirnezami R, Moran BJ, Harvey K et al. (2014) Cytoreductive surgery and	Systematic review included 27 studies (n=2838)	In the majority of included studies (20/27) CRS was combined with hyperthermic intraperitoneal chemotherapy	More comprehensive and recent reviews added to table 2.

intraperitoneal chemotherapy for colorectal peritoneal metastases. World Journal of Gastroenterology (20) 38 14018-32	21 case series, 5 case-control studies and 1 randomised controlled trial. 4 studies provided comparative (CRS in combination with IPC vs systemic chemotherapy alone) Primary CPM in 96% of cases (2714/2838) and recurrent CPM (rCPM) in the remaining 4% (124/2838)	(HIPEC). In 3 studies HIPEC was used in combination with early post-operative intraperitoneal chemotherapy (EPIC), and 2 studies used EPIC only, following CRS. Two studies evaluated comparative outcomes with CRS + HIPEC vs CRS + EPIC for treatment of CPM. The delivery of IPC was performed using an "open" or "closed" abdomen approach in the included studies. The evidence indicates that enhanced survival times can be achieved for CPM after combined treatment with CRS and IPC.	
Morano WF, Khalili M, Chi DS et al (2018) Clinical studies in CRS and HIPEC: Trials, tribulations, and future directions-A systematic review. Journal of Surgical Oncology (117) 2 245-259.	Systematic review on CRS/HIPEC trials investigating adult patient populations	13 published trials and 57 active clinical trials were included. These are defining important parameters that include improving patient selection, strategic sequences of treatment, cytoreductive strategies, chemotherapeutics, optimal hyperthermic temperature and timing, and toxicity profiles. Main barriers or limitations to trial development remain patient enrollment, trial design, and oncologic community collaboration.	More comprehensive and recent reviews added to table 2.
Nadler A, McCart JA. and Govindarajan A (2015). Peritoneal Carcinomatosis from Colon Cancer: A Systematic Review of the Data for Cytoreduction and Intraperitoneal Chemotherapy. Clinics in Colon & Rectal Surgery (28) 4 234-46.	Systematic Review 46 studies included.	Mean weighted overall morbidity following CRS and IPC was 49% (range 22-76%) and mortality was 3.6% (range 0-19%). Median overall survival ranged from 15 to 63 months, and 5-year overall survival ranged from 7 to 100%. This represents an improvement over historical treatment with systemic chemotherapy alone, even in the era of modern chemotherapeutic agents. Quality of life following surgery is initially decreased but improves with time and approaches baseline. Available data appear to support the treatment of PC from colon cancer with CRS and IPC. There is a large	More comprehensive and recent reviews added to table 2.

		amount of variability among studies and few high-quality studies exist. Further studies are needed to standardize techniques.	
Pinto A and Pocard M (2019). Hyperthermic intraperitoneal chemotherapy with cisplatin and mitomycin C for colorectal cancer peritoneal metastases: A systematic review of the literature. Pleura and Peritoneum 2019; 20190006	Systematic review focuses on the association of cisplatin (CDDP) with mitomycin C (MMC) in HIPEC in CR PM.	Recent studies with highly selected patients reported unusual prolonged survival with a median overall survival (OS) of approximately 60 months, with a HIPEC combination of CDDP (25 mg/m2/L) plus MMC (3.3 mg/m2/L) at a temperature of 41.5–42.5 °C for 60–90 min. Major complications occurred in less than 30% of patients with limited haematological toxicity (less than 15%). In addition, in a phase 2 trial, an adjuvant HIPEC benefit was demonstrated in colorectal cancer patients with high risk for peritoneal failure (5-year OS: 81.3% vs. 70% for the HIPEC group vs. the control group, respectively, p=0.047). After a recurrence, an iterative procedure permitted similar recurrence-free disease (13 vs. 13.7 months) with an acceptable morbidity (18.7% of severe complications).	More comprehensive and recent reviews added to table 2.
Simkens GA, Rovers KP, Nienhuijs SW et al (2017) Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. Cancer management and research (9) 259-266.	Review	The aim of this review is to provide a comprehensive overview of clinically relevant factors associated with overall survival. Extent of peritoneal disease, completeness of cytoreduction, and signet ring cell histology have great influence on the outcome after CRS and HIPEC. Other factors that seem to have a negative prognostic value are the presence of liver metastases and the absence of treatment with neo-adjuvant systemic therapy.	Review
Simkens GA, van Oudheusden TR, Braam HJ et al (2016) Cytoreductive surgery and HIPEC offers similar outcomes in patients with rectal	Case control study cytoreduction and HIPEC in 29 patients with rectal PM compared with 58 colon PM patients.	Major morbidity was 27.6% and 34.5% in the rectal and colon group, respectively (P = 0.516). Median disease-free survival was 13.5 months in the rectal group and 13.6 months in the colon group (P =	More comprehensive and recent reviews added to table 2.

peritoneal metastases compared to colon cancer patients: a matched case control study. Journal of Surgical Oncology (113) 5 548-53.		0.621). Two- and five-year overall survival rates were 54%/32% in rectal cancer patients, and 61%/24% in colon cancer patients (P = 0.987). Cytoreduction and HIPEC in selected patients with rectal PM is feasible and provides similar outcomes as in colon cancer patients.	
Spiliotis J, Halkia E, Lianos, E et al. (2015) Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Annals of Surgical Oncology (22) 5 1570-5.	Randomised controlled trial N=120 women with advanced ovarian cancer, disease recurrence after initial treatment with conservative or debulking surgery and systemic chemotherapy were randomized into 2 groups. Group A -60 patients who had CRS followed by HIPEC and then systemic chemotherapy. Group B - 60 patients who had CRS only and systemic chemotherapy.	The mean survival for group A was 26.7 compared with 13.4 months in group B ($p < 0.006$). Three-year survival was 75 % for group A compared with 18 % for group B ($p < 0.01$). In the HIPEC group, the mean survival was not different between patients with platinum-resistant disease compared with platinum-sensitive disease (26.6 vs. 26.8 months). On the other hand, in the non-HIPEC group, there was a statistically significant difference between platinum-sensitive compared with platinum-resistant disease (15.2 vs. 10.2 months, $p < 0.002$). Complete cytoreduction was associated with longer survival. Patients with a peritoneal cancer index score of <15 appeared also to have longer survival.	Included in systematic review added to table 2.
Seretis, C. and Youssef, H (2014). Quality of life after cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies: a systematic review. European Journal of Surgical Oncology (40) 12 1605-13.	Systematic review on QoL after performing CRS + HIPEC for tumours of varying primary origin N=20 studies	The results of these studies, although of significant heterogeneity, clearly demonstrate that although overall QoL scores drop in the immediate postoperative period, at an average of 3 months post procedure they recover to 80%-100% or even exceed baseline values. Furthermore, between 6 and 12 months postoperatively, overall QoL is improved in survivors compared with pre-operative status. CRS and HIPEC can preserve or even improve patients' overall quality of life.	More comprehensive and recent reviews added to table 2.
Solomon D, DeNicola N, Feingold D et al	Case series	The 3-year survival rate after CRS/HIPEC was 5.7% for the	More comprehensive and

(2019) Signet ring cell features with peritoneal carcinomatosis in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are associated with poor overall survival. Journal of Surgical Oncology (16) 16.	N=204 patients with PC due to appendiceal (AC101 (49.5%)), colorectal (CRC 85 (41.7%)), and gastric cancer (GC18 (8.8%) undergoing CRS/HIPEC Patients with GC had higher rates of SRC pathology than AC and CRC: 12 (66.7%) vs 16 (15.8%) and 10 (11.7%).	SRC group and 66.1% for the non-SRC group (P < 0.001). This was true for both AC and CRC subgroups (P < 0.001 for both). Overall, patients with SRC were more likely to have a peritoneal carcinomatosis index (PCI) score > 15 (P = 0.046). Upon multivariate analysis of the SRC population, PCI > 20 (P = 0.007) and GC (P = 0.008) were found to be independent predictors of poor overall survival.	recent reviews added to table 2
Tonello M, Ortega-Perez G, Alonso-Casado O et al. (2018) Peritoneal carcinomatosis arising from rectal or colonic adenocarcinoma treated with cytoreductive surgery (CRS) hyperthermic intraperitoneal chemotherapy (HIPEC): two different diseases. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico (20) 10 1268-1273.	Case series N=36 patients with colorectal PC (31 patients in colonic and 5 in rectal group) had CRS and HIPEC	Median survival (OS) is significantly higher in colonic compared with rectal group (47.83 vs. 22.0 months, p 0.008). 3- and 5-year survival rate is 74 and 50% in colonic group vs. 20 and 0% in rectal group.	More comprehensive and recent reviews added to table 2.
Ubago-Pérez, R., Matas-Hoces, A., Beltrán-Calvo, C. and Romero-Tabares, A. Hyperthermic intraperitoneal chemotherapy. Efficacy and safety in the treatment of ovarian cancer peritoneal carcinomatosis. Seville: Andalusian Agency for Health Technology Assessment (AETSA) 2013.	HTA cytoreductive surgery + HIPEC for the treatment of ovarian cancer-derived peritoneal carcinomatosis no RCT included.	The review revealed that there is more evidence on the potential benefit of HIPEC + Cytoreductive surgery in the treatment of recurrent cancer (mainly in chemosensitive patients receiving HIPEC after achieving optimal cytoreduction). Comparative studies assessing surgery + HIPEC vs. surgery alone obtained similar results. there are no randomized trials Currently, definite conclusions cannot be drawn on the efficacy and safety.	More comprehensive reviews added to table 2.
Vallicelli C, Cavaliere D, Catena F et al (2014). Management of peritoneal	Review	Combined treatment of CRS and HIPEC for CRC PC, suggests a survival benefit in highly selected patients. Only	Review

carcinomatosis from colorectal cancer: review of the literature. International Journal of Colorectal Disease (29) 8 895-8		one trial is randomized and presents some biases. The two main prognostic factors are Peritoneal Cancer Index (PCI) and completeness of cytoreduction score (CC score). There is no universal agreement on how to approach the synchronous presence of PC and liver metastasis with a curative intent during the same procedure.	
Vasquez Jimenez, W., Gonzalez Bayon, L., Garcia-Sabrido, J. L. and Gonzalez Moreno, S. (2010) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignant disease. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico (12) 12 794-804.	Review	CRS plus HIPEC combined treatment may change the natural history of Peritoneal Malignant Disease, it is translated into a higher overall survival and cancer-free survival and it offers the option of cure in selected cases. The high-complexity procedure is also associated with complications and mortality, but in similar rates as other major oncologic procedures.	Review
Verzijden, JCM, Klaver, YLB, de Hingh, Ihjt and Bleichrodt, RP. (2010) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis in patients with colorectal cancer. Cochrane Database of Systematic Reviews 4.	Systematic review	To determine whether the performance of cytoreductive surgery and HIPEC results in a survival advantage in patients with PC from colorectal origin when compared with standard palliative treatment. to assess morbidity and mortality associated with this treatment.	Protocol
Waite K. and Youssef H. (2017) The Role of Neoadjuvant and Adjuvant Systemic Chemotherapy with Cytoreductive Surgery and Heated Intraperitoneal Chemotherapy for	Systematic Review. N=16 studies Neoadjuvant and adjuvant systemic chemotherapy in patients with CPM undergoing CRS and HIPEC compared with	7 studies on neoadjuvant chemotherapy, reported there was no strong evidence for the efficacy of neoadjuvant chemotherapy. 1 study observed worse survival outcomes when neoadjuvant therapy was used. 14 studies on adjuvant chemotherapy	More comprehensive reviews included in table 2.

Colorectal Peritoneal Metastases: A Systematic Review. Annals of Surgical Oncology (24) 3 705-720.	those who receive CRS and HIPEC alone	reported there was limited evidence that adjuvant systemic chemotherapy improves survival following CRS and HIPEC. Systemic adjuvant chemotherapy may be associated with improved overall survival, but the role of systemic neoadjuvant chemotherapy cannot be determined by the currently available evidence.	
Wisselink DD, Braakhuis LF, Gallo G et al. (2019). Systematic review of published literature on oxaliplatin and mitomycin C as chemotherapeutic agents for hyperthermic intraperitoneal chemotherapy in patients with peritoneal metastases from colorectal cancer. Critical Reviews in Oncology / Hematology 142 (2019) 119–129	Systematic review 46 studies on CRS/HIPEC using either oxaliplatin of mitomycin C	Oxaliplatin and mitomycin C studies were comparable regarding extent of disease, but differed substantially regarding synchronous compared with metachronous presentation, application of neo-adjuvant systemic chemotherapy, duration of HIPEC, and completeness of cytoreduction for at least one of the oncological endpoints. Severe postoperative complication rate seemed significantly higher after oxaliplatin-based CRS/HIPEC. No meaningful comparison could be made regarding DFS and OS.	More comprehensive reviews included in table 2.
Wu X, Li Z, Li Z et al. (2015) Hyperthermic intraperitoneal chemotherapy plus simultaneous versus staged cytoreductive surgery for gastric cancer with occult peritoneal metastasis. Journal of Surgical Oncology (111) 7 840-7	Retrospective case series N=26gastric cancer patients with occult peritoneal metastasis Patients were treated by HIPEC plus either simultaneous CRS (CRS+HIPEC group, n = 11) or staged CRS after systematic chemotherapy (HIPEC+Chemo+CRS group, n = 15).	There is no mortality observed in both groups. The treatment complications in two group is comparable (P = 0.683), with 26.7% (4/15) in HIPEC+Chemo+CRS group, and 36.4% (4/11) in CRS+HIPEC group, respectively. The compliance of patients undergoing subsequent chemotherapy is higher in HIPEC+Chemo+CRS group (93.3%, 14/15) than that of CRS+HIPEC group (45.5%, 5/11) (P = 0.021). The mean interval time between CRS and first post-CRS systematic chemotherapy were 42.0 +/- 12.0 days in HIPEC+Chemo+CRS group compared with 69.8 +/- 36.3 in CRS+HIPEC group (P = 0.163), respectively. The median OS in the HIPEC+Chemo+CRS group	More comprehensive reviews/studies included in table 2.

		was 25.0 months, while 28.2 months in the CRS+HIPEC group (P = 0.738). HIPEC plus staged CRS is with better tolerance and compliance than simultaneous CRS.	
Yan TD, Black D, Savady R et al (2006). Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. Journal of Clinical Oncology 24 (24), 4011-4019.	Systematic review	2 randomised controlled trials, one comparative study and one registry study and 10 case series included. Level of evidence was low, median survival varied from 13 to 29 months and 5-year survival ranged from 11% to 19%. Patients who had complete cytoreduction benefited most, median survival ranging from 28 to 60 months and 5-year survival from 22 to 49%. Overall morbidity rate varied from 23 to 44% and mortality ranged from 0 to 12%.	More comprehensive reviews included in table 2.
Yang XJ, Huang CQ, Suo T et al. (2011) Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final results of a Phase III Randomized Clinical Trial. Ann Surg Oncol (2011) 18:1575–1581	Randomised controlled trial. N=68 PC patients were randomized into CRS alone (n = 34) or CRS ? HIPEC (n = 34) receiving cisplatin 120 mg and mitomycin C 30 mg each in 6000 ml of normal saline at 43 ± 0.5° C for 60–90 min.	The completeness of CRS score (CC 0–1) was 58.8% (20 of 34) in the CRS and 58.8% (20 of 34) in the CRS plus HIPEC groups (P = 1.000). At a median follow-up of 32 months (7.5–83.5 months), death occurred in 33 of 34 (97.1%) cases in the CRS group and 29 of 34 (85.3%) cases of the CRS plus HIPEC group. The median survival was 6.5 months (95% confidence interval 4.8–8.2 months) in CRS and 11.0 months (95% confidence interval 10.0– 11.9 months) in the CRS plus HIPEC groups (P = 0.046). Four patients (11.7%) in the CRS group and 5 (14.7%) patients in the CRS plus HIPEC group developed serious adverse events (P = 0.839).	Included in systematic reviews added to table 2.
Yurttas C, Hoffmann G, Tolios A et al (2018) Systematic Review of Variations in Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal	Systematic Review	171 reports on HIPEC conduct foremost with mitomycin C and oxaliplatin, but also other drugs and drug combinations, comprising at least 60 different procedures. HIPEC conduct and practices need to be reassessed. Unfortunately,	More comprehensive reviews included in table 2.

Metastasis from Colorectal Cancer. Journal of Clinical Medicine (7) 12 19.		imprecise and lacking reporting is frequent, which is why minimal information requirements should be established for HIPEC.	