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Guideline 17-12

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Indications for Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery

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An assessment conducted in February 2024 deferred the review of Guideline 17-12. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 17-12 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/61856

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Indications for Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To determine evidence-based indications for cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).

TARGET POPULATION

Adults (≥18 years old) with a diagnosis of mesothelioma, appendiceal (including appendiceal mucinous neoplasm), colorectal, gastric, ovarian, or primary peritoneal carcinoma.

INTENDED USERS

This guideline is intended for clinicians involved in the care of patients with mesothelioma, appendiceal (including appendiceal mucinous neoplasm), colorectal, gastric, ovarian, or primary peritoneal carcinoma.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

NOTE: This guideline addresses the role of HIPEC with CRS and not the role of CRS alone. Interventions and terms are reported as stated in the individual papers. While there is a lack of evidence to make recommendations for many of the target sites, it is noted that there are a large number of ongoing randomized controlled trials (RCTs). This guideline will be reviewed annually for any new evidence. When writing these recommendations, the Working Group considered overall survival (OS) to be a critical outcome, and progression-free survival (PFS), recurrence-free survival (RFS), adverse events, and quality of life (QoL) to be important outcomes. Some patient input was sought and patients identified that all of the outcomes mentioned would be important to them in making any treatment decisions.

Recommendation 1a
For patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, HIPEC should be considered for those with at least stable disease following neoadjuvant chemotherapy at the time of interval CRS if complete or optimal cytoreduction is achieved.
Qualifying Statements for Recommendation 1a
The Working Group members recommend prospectively collecting data on these patients to evaluate real-world outcomes and applicability.

Recommendation 1b
There is insufficient evidence to recommend the addition of HIPEC when primary CRS is performed for patients with newly diagnosed, primary advanced epithelial ovarian, fallopian tube, or primary peritoneal carcinoma outside of a clinical trial.

Recommendation 2
There is insufficient evidence to recommend HIPEC with CRS in patients with recurrent ovarian cancer outside of a clinical trial.

Recommendation 3
There is insufficient evidence to recommend HIPEC with CRS in patients with peritoneal colorectal carcinomatosis outside of a clinical trial.

Recommendation 4
There is insufficient evidence to recommend HIPEC with CRS for the prevention of peritoneal carcinomatosis in CRC outside of a clinical trial; however HIPEC using oxaliplatin is not recommended.

Recommendation 5
There is insufficient evidence to recommend HIPEC with CRS for the treatment of gastric peritoneal carcinomatosis outside of a clinical trial.

Recommendation 6
There is insufficient evidence to recommend HIPEC with CRS for the prevention of gastric peritoneal carcinomatosis outside of a clinical trial.

Recommendation 7
There is insufficient evidence to recommend HIPEC with CRS in patients with malignant peritoneal mesothelioma as a standard of care; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol.
Qualifying Statements for Recommendation 7
• The Working Group members recommend prospective research protocols with standardized treatment approaches at high-volume centres as this will provide survival benchmarks and feasibility data for future comparative studies.

Recommendation 8
There is insufficient evidence to recommend HIPEC with CRS in patients with disseminated mucinous neoplasm in the appendix as a standard of care; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol.
Qualifying Statements for Recommendation 8
• The Working Group members recommend prospective research protocols with standardized treatment approaches at high-volume centres as this will provide survival benchmarks and feasibility data for future comparative studies.

Indications for Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To determine evidence-based indications for hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery (CRS).

TARGET POPULATION

Adults (≥18 years old) with a diagnosis of mesothelioma, appendiceal (including appendiceal mucinous neoplasm), colorectal, gastric, ovarian, or primary peritoneal carcinoma.

INTENDED USERS

This guideline is intended for clinicians involved in the care of patients with mesothelioma, appendiceal (including appendiceal mucinous neoplasm), colorectal, gastric, ovarian, or primary peritoneal carcinoma.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

NOTE: This guideline addresses the role of HIPEC with CRS and not the role of CRS alone. Interventions and terms are reported as stated in the individual papers. While there is a lack of evidence to make recommendations for many of the target sites, it is noted that there are a large number of ongoing randomized controlled trials (RCTs). This guideline will be reviewed annually for any new evidence. When writing these recommendations, the Working Group considered overall survival (OS) to be a critical outcome, and progression-free survival (PFS), recurrence-free survival (RFS), adverse events, and quality of life (QoL) to be important outcomes. Some patient input was sought and patients identified that all of the outcomes mentioned would be important to them in making any treatment decisions.

Recommendation 1a
For patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, HIPEC should be considered for those with at least stable disease following neoadjuvant chemotherapy at the time of interval CRS if complete or optimal cytoreduction is achieved.
Qualifying Statements for Recommendation 1a
The Working Group members recommend prospectively collecting data on these patients to evaluate real-world outcomes and applicability.
Key Evidence for Recommendation 1a
The evidence comes from one RCT [1,2], where the overall certainty of the evidence for all outcomes is moderate. • The multicentre trial by van Driel et al. [1] compared patients with newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer who received interval CRS plus HIPEC using cisplatin (n=122) with interval CRS alone (n=123). There was no upper age limit to enroll in the trial, but the oldest patient was 66 years. All women had at least stable disease after neoadjuvant chemotherapy and achieved complete or optimal cytoreduction at the time of surgery. Patients received an additional three cycles of carboplatin and paclitaxel after interval surgery. Significant differences in median OS between the CRS plus HIPEC arm (45.7 months) and the CRS-only arm (33.9

months; hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.48 to 0.94; p=0.02) were reported after a median follow-up of 4.7 years. Similar results were obtained for median RFS between the CRS plus HIPEC arm (14.2 months) and the CRS-only arm (10.7 months; HR, 0.66; 95% CI, 0.50 to 0.87; p=0.003) were reported. Exploratory subgroup analysis of OS or RFS did not reveal any specific subgroup (i.e., age, histologic type, previous surgery, number of involved regions, or laparoscopy before surgery) that experienced better or worse outcomes with CRS and HIPEC or standard treatment.

- The probability of OS at three years was 62% (95% CI, 54% to 72%) and 48% (95% CI, 39% to 58%) in the treatment and standard arms, respectively. A p-value was not reported. The probability of RFS at three years was 17% (95% CI, 11% to 26%) and 8% (95% CI, 4% to 16%) in the treatment and standard arms, respectively. A p-value was not reported.
- No significant differences between the groups were noted in the incidence of adverse events of any grade [1] and no significant differences in health-related QoL outcomes were reported over time [2].

Interpretation of Evidence for Recommendation 1a

- In patients receiving neoadjuvant chemotherapy followed by interval CRS with HIPEC, the Working Group members determined the benefits (i.e., increased OS) outweigh the harms (i.e., adverse events). Given its large survival benefit and no significant difference in adverse events and QoL, patients with newly diagnosed, advanced epithelial ovarian cancer would consider this as an acceptable treatment option.
- This recommendation is generalizable to all patients with primary stage III epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who had complete or optimal cytoreduction and cannot be generalized to patients with suboptimal cytoreduction.

Recommendation 1b

There is insufficient evidence to recommend the addition of HIPEC when primary CRS is performed for patients with newly diagnosed, primary advanced epithelial ovarian, fallopian tube, or primary peritoneal carcinoma outside of a clinical trial.

Key Evidence for Recommendation 1b

The evidence comes from one RCT [3] available in abstract form, where the overall certainty of the evidence for all outcomes is low.

- The multicentre trial by Lim et al. [3], currently published in abstract form, compared patients with stage III or IV primary epithelial ovarian cancer who received primary CRS plus HIPEC using cisplatin (n=92) with CRS alone (n=92). Only patients who achieved optimal cytoreduction were included. This RCT showed no difference in five-year OS (HIPEC/cisplatin, 51%; non-HIPEC arm, 49.4%; p=0.574) or five-year PFS (HIPEC/cisplatin arm, 20.9%; non-HIPEC arm, 16.0%; p=0.569). Median follow-up was not reported. In a subgroup analysis of women who had received neoadjuvant chemotherapy, there was no difference in median OS (p=0.407) or median PFS (p=0.137) between the two arms.
- The most common adverse event was anemia, with significantly more participants in the HIPEC/cisplatin arm (67.4%) experiencing it than in the non-HIPEC arm (50%, p=0.025). Elevation of creatinine was also significantly higher in the HIPEC/cisplatin arm (p=0.026). There were no differences between the two arms for transfusion (p=0.432), neutropenia (p=0.151), and thrombocytopenia (p=0.136).

Interpretation of Evidence for Recommendation 1b

- The Working Group members determined the evidence from an abstract of an RCT is insufficient to make definitive recommendations about the use of HIPEC following primary CRS in this patient population.

Recommendation 2

There is insufficient evidence to recommend HIPEC with CRS in patients with recurrent ovarian cancer outside of a clinical trial.

Key Evidence for Recommendation 2

The evidence comes from one RCT [4] comparing patients who received surgery plus HIPEC with surgery alone, where the overall certainty of this evidence for all outcomes is considered to be low. Although this trial reported itself as a phase III RCT, it presents unclear methods and statistical analyses questioning its validity; results should be interpreted with caution. Further, it was not found in any clinical trial registry.

- A mean OS of 26.7 months was reported in patients who received surgery plus HIPEC (n=60) and a mean OS of 13.4 months in patients who received surgery only (n=60; p=0.006). In exploratory subgroup analyses, survival was significantly higher in patients with a complete cytoreduction (no residual tumour, CC-0) who received HIPEC (30.9 months) compared with patients who received surgery only (16.9 months, p=0.038); in patients who received surgery only, survival was longer in those who received CC-0 cytoreduction (16.1 months) compared with those who received CC-2 (residual tumour 2.5 mm to 2.5 cm) cytoreduction (6.7 months, p=0.002). In a subgroup analysis by the peritoneal carcinomatosis index (PCI) score, survival was significantly higher in patients who received surgery plus HIPEC than those who received surgery only for those patients with PCI ≤15 (30.4 months vs. 15.4 months, p=0.031) and with PCI >15 (21.5 months vs. 9.2 months, p=0.049).
- No mortality, morbidity, or QoL data were presented.

Interpretation of Evidence for Recommendation 2

- There was agreement among the members of the Working Group that evidence with such unclear methods and statistical analyses was insufficient to make definitive recommendations and to be generalizable to all patients with recurrent ovarian cancer.

Recommendation 3

There is insufficient evidence to recommend HIPEC with CRS in patients with peritoneal colorectal carcinomatosis outside of a clinical trial.

Key Evidence for Recommendation 3

The evidence comes from two RCTs [5-7], one fully published and the other available in abstract form, where the overall certainty of the evidence for all outcomes is low.

- The trial by Verwaal et al. [6,7] compared patients who received CRS plus HIPEC using mitomycin C (MMC) and systemic chemotherapy (n=54) with patients who received standard therapy (n=51), which consisted of single agent systemic chemotherapy and surgery in cases of symptoms of intestinal obstruction. This trial reported significant differences in disease-specific survival (DSS) (CRS + HIPEC/MMC arm, 22.2 months; systemic chemotherapy arm, 12.6 months; p=0.028) and PFS (CRS + HIPEC/MMC arm, 12.6 months; systemic chemotherapy arm, 7.7 months; p=0.020), after a median follow-up of 94 months. However, the systemic chemotherapy regimen administered in the control arm consisted of fluorouracil and leucovorin, which is not representative of current systemic chemotherapy regimens. Exploratory subgroup analysis did not reveal that any specific subgroup (i.e., sex, age, site or origin of tumour) experienced better or worse outcomes with CRS and HIPEC or standard treatment.
- Four patients (8%) died as a result of treatment and two stopped adjuvant chemotherapy as a result of toxicity in the HIPEC/MMC arm, while two stopped treatment in the non-HIPEC arm due to toxicity.
- The PRODIGE 7 trial [5], currently published in abstract form, compared patients who received CRS plus HIPEC using oxaliplatin and systemic chemotherapy (n=133) with patients who received CRS and systemic chemotherapy (n=132). This trial showed no difference in median OS (CRS + HIPEC arm, 41.7 months; CRS-only arm, 41.2 months; HR,1.00; 95% CI, 0.73 to 1.37; p=0.995) or median RFS (CRS + HIPEC/oxaliplatin arm, 13.1 months; CRS-only arm, 11.1 months; HR, 0.90; 95% CI, 0.69 to 1.90; p=0.486) after a median follow-up of 63.8 months. However, the systemic chemotherapy regimen administered in the control arm consisted of fluorouracil and leucovorin, which is not representative of current systemic chemotherapy regimens.
- In a subgroup analysis of patients with medium-range PCI (>11 to ≤15), the median OS was 32.7 months (95% CI, 23.5 to 38.9) for the non-HIPEC arm and 41.6 months (95% CI, 36.1 to not reached) in the HIPEC/oxaliplatin arm (HR,0.437; 95% CI, 0.21 to 0.90; p=0.0209).
- There was no difference reported in postoperative mortality rate between the experimental and standard arms. The morbidity rates did not differ at 30 days but at 60 days, there were significant differences in the grade 3 to 5 morbidity rate (HIPEC/oxaliplatin arm, 24.1%; non-HIPEC arm, 13.6%; p=0.030).
- None of the studies reported QoL data.

Interpretation of Evidence for Recommendation 3

- The Working Group members noted that although two RCTs exist, one currently available in abstract form, recommendations could not be made since the control arms of both trials are not representative of current oncological practices resulting in outcomes that are not generalizable to current practice.
- The Working Group members determined the evidence from an abstract of an RCT is insufficient to make definitive recommendations about the use of HIPEC following CRS in this patient population.
- There was one dissenting opinion from the Working Group: One member suggested that the recommendation state, “There is insufficient evidence for or against the use of HIPEC

with CRS in patients with peritoneal colorectal carcinomatosis." The rationale for this dissenting opinion was that the Verwaal et al. study showed a large difference in DSS when using HIPEC with MMC and CRS compared with the control arm which used systemic chemotherapy consisting of fluorouracil and leucovorin. While best systemic chemotherapy was not used, it is uncertain whether use of best systemic chemotherapy would completely negate this survival benefit with HIPEC and CRS.

Recommendation 4

There is insufficient evidence to recommend HIPEC with CRS for the prevention of peritoneal carcinomatosis in CRC outside of a clinical trial; however HIPEC using oxaliplatin is not recommended.

Key Evidence for Recommendation 4

The evidence comes from two RCTs [8,9] with one available in abstract form, where the overall certainty of the evidence for all outcomes is moderate.

- The multicentre COLOPEC trial by Klaver et al. [8], compared patients with T4 or perforated colon cancer who received adjuvant HIPEC plus CRS and adjuvant systemic chemotherapy (n=100) with adjuvant systemic chemotherapy alone (n=102). Adjuvant HIPEC was performed simultaneously (9%) or within five to eight weeks (91%) after the primary tumour resection. Within the experimental arm, 87% of patients received adjuvant HIPEC and 19% of patients were diagnosed with peritoneal metastases (9% preceding adjuvant HIPEC). This RCT showed no difference in 18-month DFS (69.0% [60.0-78.0] versus 69.3% [60.3%-78.3%]; p=0.99), 18-month OS (93.0% [87.9-98.1] versus 94.1% [89.6-98.6]; p=0.82) or 18-month peritoneal metastases-free survival (80.9%; 95% CI, 73.3-88.5 versus 76.2%; 95% CI, 68.0-84.4; p=0.28) between the experimental and control arms, respectively.
- The COLOPEC trial [8] reported postoperative complications occurred in 14% of patients who received adjuvant HIPEC (n=87).
- The ProphyloCHIP trial by Goere et al. [9] currently published in abstract form, included patients with a high-risk of developing colorectal peritoneal metastases after six months of adjuvant chemotherapy and randomized them to a surveillance arm (n=79) or a systemic second-look surgery plus HIPEC using oxaliplatin arm (n=71). The RCT showed no difference in three-year DFS (p=0.75) or three-year OS (p=not reported).

Interpretation of Evidence for Recommendation 4

- In patients with T4 or perforated colon cancer receiving adjuvant HIPEC plus CRS and adjuvant systemic chemotherapy, the Working Group members determined the desirable effect of increased survival did not occur. Given the absence of a survival benefit, patients would not consider this to be an acceptable treatment option.
- The Working Group members determined the evidence from an abstract of an RCT is insufficient to make definitive recommendations about the use of HIPEC following primary CRS in this patient population.

Recommendation 5

There is insufficient evidence to recommend HIPEC with CRS for the treatment of gastric peritoneal carcinomatosis outside of a clinical trial.

Key Evidence for Recommendation 5

The evidence comes from one RCT [10] where the overall certainty of the evidence for all outcomes is low.

- This RCT by Yang et al. [10] showed a significant difference in median OS between the CRS plus HIPEC/cisplatin and MMC arm (11.0 months; 95% CI, 10.0 to 11.9) and the CRS-alone arm (6.5 months; 95% CI, 4.8 to 8.2; p=0.046). There were 34 patients in each arm. In subgroup analyses, patients who had CC scores of 0 to 1 had a significantly higher median OS than patients who had CC scores of 2 to 3 within both the HIPEC/cisplatin and MMC arm (p=0.000) and the non-HIPEC arm (p=0.000). In patients with incomplete cytoreduction, the HIPEC/MMC arm resulted in longer OS than the non-HIPEC arm (HIPEC/cisplatin and MMC arm, 8.2 months; non-HIPEC arm, 4.0 months; p=0.024). Similarly in subgroup analyses by PCI score, patients who had a high PCI score had a significantly higher median OS in the HIPEC/ cisplatin and MMC arm (13.5 months, 95% CI, 8.7 to 18.3) when compared with the non-HIPEC arm (3.0 months; 95% CI, 2.4 to 3.6; p=0.012), while patients with a low PCI score showed no difference between the two arms (p=0.464).
- In a multivariate analysis, CRS plus HIPEC (HR, 2.617; 95% CI, 1.436 to 4.769; p=0.002), synchronous peritoneal carcinomatosis (p=0.02), a CC score of 0 to 1 (p=0.003), chemotherapy ≥6 cycles (p=0) and no serious adverse effects (p=0) were identified as major independent prognostic factors for survival.
- No significant differences in serious adverse events between patients receiving CRS plus HIPEC (14.7%) and CRS alone (11.7%, p=0.839) were demonstrated.
- No QoL data were presented.

Interpretation of Evidence for Recommendation 5

- Although the benefits (i.e., increased OS) outweighed the harms (i.e., adverse events), the Working Group members concluded that a single small study conducted in an Asian population was insufficient to form a recommendation. Further, the control arm of this trial was CRS alone, which is currently not the standard of care in these patients in North America.
- Differences in the biology of gastric cancers between Asian and non-Asian patients limit the generalizability of these results.

Recommendation 6

There is insufficient evidence to recommend HIPEC with CRS for the prevention of gastric peritoneal carcinomatosis outside of a clinical trial.

Key Evidence for Recommendation 6

The evidence comes from four Asian RCTs [11-14] (three from Japan and one from China) where the certainty of the evidence for all outcomes is low. These trials present unclear methods and statistical analyses, which include not providing any randomization details or specifying the primary outcome, assumed to be OS, or the outcomes of interest.

- The trial by Cui et al. [11] reported that the differences in median survival among those who received surgery only (27 months), neoadjuvant chemotherapy with surgery (33 months), surgery with HIPEC/cisplatin (32 months) and neoadjuvant chemotherapy with surgery plus HIPEC/cisplatin (36 months) were statistically significant (p=0.001). The differences in median PFS were also statistically significant among the four groups (p<0.001). There were 48 patients in each arm.
- The trial by Yonemura et al. [12] showed survival was significantly better in patients who received continuous hyperthermic peritoneal perfusion (CHPP)/MMC and cisplatin (5-year, 61%) when compared with patients who received continuous normothermic peritoneal perfusion (CNPP) (5-year, 44%; p=0.017) or surgery alone (5-year, 42%; p=0.019). There were 48, 44, and 47 patients in each arm, respectively.
- Similarly, Fujimoto et al. [13] reported survival rates were significantly higher in the HIPEC/MMC arm (2-year, 88%; 4-year, 76%; 8-year, 62%) compared with the control arm (2-year, 77%; 4-year, 58%; 8-year, 49%; p=0.0362). There were 71 and 70 patients in each arm, respectively. Peritoneal recurrence occurred more frequently in the control arm (p<0.001).
- The final results of the RCT reported by Hamazoe et al. [14] found no significant differences in 5-year survival between the CHPP/MMC arm (64.3%) and the surgery-alone arm (52.5%, p=0.2427) with 42 and 40 patients in each arm, respectively. Median survival was reported as 77 months in the CHPP plus surgery arm and 66 months in the control arm.
- All four RCTs [11-14] found no significant differences in adverse events between the experimental and control arms.
- None of the studies reported QoL data.

Interpretation of Evidence for Recommendation 6

- Although the benefits (i.e., increased OS) outweighed the harms (i.e., adverse events), the Working Group members concluded that studies conducted in Asian populations, the lack of methodological details provided, and a low certainty of the evidence were insufficient to form recommendations.
- Differences in the biology of gastric cancers between Asian and non-Asian patients limit the generalizability of these results.

Recommendation 7

There is insufficient evidence to recommend HIPEC with CRS in patients with malignant peritoneal mesothelioma as a standard of care; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol.

Qualifying Statements for Recommendation 7

- The Working Group members recommend prospective research protocols with standardized treatment approaches at high-volume centres as this will provide survival benchmarks and feasibility data for future comparative studies.

Key Evidence for Recommendation 7

To date, there have been no randomized or comparative studies conducted to compare the use of CRS plus HIPEC with other methods of oncological management in patients with peritoneal mesothelioma. The evidence comes from one retrospective cohort study [15] (n=1547), which conducted a multivariable analysis, including the use of CRS/HIPEC as a variable. The certainty of this evidence is very low.

- When compared with the CRS plus HIPEC cohort, receipt of chemotherapy alone, CRS alone, and observation were independently associated with poorer OS ($p<0.001$) while controlling for age, sex, Charlson/Deyo score, insurance, and histology [15]. However, there was no statistically significant difference in OS when comparing CRS plus HIPEC with CRS plus chemotherapy ($p=0.397$).
- Adverse events were not reported.
- No QoL data were presented.

Interpretation of Evidence for Recommendation 7

- The balance between the benefits (i.e., increased OS) and harms (i.e., adverse events) cannot be evaluated due to the absence of adverse events data.
- The Working Group members recognize the rarity of peritoneal mesothelioma and the complexity of conducting RCTs in this patient population; however, no compelling comparative data were found in the published literature.

Recommendation 8

There is insufficient evidence to recommend HIPEC with CRS in patients with disseminated mucinous neoplasm in the appendix as a standard of care; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol.

Qualifying Statements for Recommendation 8

- The Working Group members recommend prospective research protocols with standardized treatment approaches at high-volume centres as this will provide survival benchmarks and feasibility data for future comparative studies.

Key Evidence for Recommendation 8

To date, there have been no randomized studies conducted to compare the use of CRS plus HIPEC with other methods of oncological management in patients with disseminated mucinous neoplasms. The evidence comes from one comparative study [16], which studied the differences between patients treated during the debulking era (n=33) and the CRS/HIPEC era (n=87), and four retrospective cohort studies [17-20], which conducted multivariable analyses, including the use of CRS plus HIPEC as a variable. The certainty of this evidence is very low. All four cohort studies included a combination of patients with disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and hybrid histologies.

- The comparative study by Jarvinen et al. [16] showed no significant difference in five-year OS rates between the CRS plus HIPEC era (69%) and the debulking era (67%, p=0.92). The treatment received in the CRS plus HIPEC era was heterogeneous and only 64% of patients received CRS plus HIPEC.
- The first retrospective study by Sinukumar et al. [17] showed that the use of HIPEC was not associated with OS but independently associated with increased PFS (HR, not reported; 95% CI, 1.26-9.8; p=0.016).
- In both studies by Chua et al. [18,19], the use of HIPEC was not independently associated with OS (p>0.05). However, the use of HIPEC was independently associated with PFS (HR, 0.645; 95% CI, 0.44 to 0.96; p=0.030) [18]. In an exploratory subgroup analysis by histologic subtype, the use of HIPEC remained non-significant.
- The study by Glehen et al. [20] showed that the use of HIPEC was independently associated with increased survival (p<0.001) in patients who had received an incomplete cytoreduction. The HRs and CIs were not provided.
- There was no significant difference in 30-day mortality between both groups in the study by Jarvinen et al. [16]. The four cohort studies [17-20] reported aggregate morbidity and mortality data and not by treatment group.
- None of the studies reported QoL data.

Interpretation of Evidence for Recommendation 8

- The balance between the benefits (i.e., increased OS) and harms (i.e., adverse events) cannot be evaluated due to insufficient adverse event data.

IMPLEMENTATION CONSIDERATIONS

The Working Group members considered these recommendations to be the best possible recommendations given the currently available data. It is important to note that HIPEC is currently only performed at one centre in Ontario (i.e., Mount Sinai in Toronto). Currently, HIPEC is performed for primary ovarian cancer in Ontario as part of a study protocol. Most often HIPEC is performed in Ontario for patients with peritoneal colorectal carcinomatosis and other high- and low-grade gastrointestinal cancers as well as for a small number of peritoneal mesothelioma cases each year. HIPEC should be offered by a dedicated team and patients should be presented at a multidisciplinary cancer conference to ensure they meet the appropriate criteria.

Indications for Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR GUIDELINE

This guideline was developed to provide evidence-based guidance regarding the provision of HIPEC with CRS in the treatment of peritoneal cancers.

GUIDELINE DEVELOPERS

This guideline was developed by the Indications for HIPEC GDG (Appendix 1), which was convened at the request of the Surgical Oncology Program.

The project was led by a small Working Group of the Indications for HIPEC GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in surgical oncology, pathology, gynecological oncology, medical oncology, and health research methodology. Other members of the Indications for HIPEC GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [21,22]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [23] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: National Institute for Health and Care Excellence (NICE) Evidence Search; Canadian Partnership Against Cancer Database, Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: NICE, Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), National Health and Medical Research Council Australia, and Cancer Council Australia.

The following criteria were used to search for and select potentially relevant guidelines:

- Guideline databases and websites were searched using the search terms “HIPEC” or “intraperitoneal chemotherapy”.
- Only guidelines published after 2015 (i.e., less than 3 years old) were considered to ensure currency.

This search for existing guidelines yielded three guidelines [24-26]. None of these guidelines were considered suitable for endorsement or adaptation and were excluded.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline

recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Five patients/survivors/caregivers participated as Consultation Group members for the HIPEC GDG. They reviewed copies of draft recommendations and provided feedback on its comprehensibility, appropriateness and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

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- Jillian Sing for conducting a data audit.
- Sara Miller for copy editing.

Indications for Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery

Section 4: Systematic Review

INTRODUCTION

Peritoneal malignancies include cancers that arise from the lining of the peritoneal cavity (primary peritoneal malignancy, including mesothelioma and serous carcinoma of the peritoneum) and those that have spread to the peritoneum from a primary cancer site within the abdominal cavity (secondary peritoneal malignancy). Coupled with the rarity of primary peritoneal malignancies and the time it takes to collect and report cancer data, Canadian and Ontario-specific incidence data are currently not available. An incidence rate of 0.2 to 3 per million has been reported for peritoneal mesothelioma in industrialized countries [27]; secondary isolated peritoneal spread is relatively common with ovarian and gastrointestinal malignancies, including colorectal, appendiceal, and gastric. The natural history of peritoneal malignancies is similar in all cases and includes debilitating ascites, intestinal obstruction, and malnutrition and cachexia [28]. Survival rates vary depending on the histology and burden of disease and the median ranges from months (gastric cancer) [29] to almost five years (ovarian cancer) [30].

In an effort to improve both the survival and QoL for patients with this devastating manifestation of intra-abdominal malignancies, aggressive peritoneal therapies have been introduced over the last century, including CRS and HIPEC. These therapies are based on the premise that when the cancer is isolated to the peritoneal cavity, this represents a form of locoregional disease. CRS is a complex surgical procedure that comprises a peritonectomy and resection of involved viscera as indicated, with the goal of leaving the patient with only microscopic residual disease [31]. A systematic approach toward comprehensive CRS was described in 1995 by Dr. Paul Sugarbaker [32], an approach that has generally been adopted. The extent of disease preoperatively is reported using the PCI [33], which divides the abdomen into 13 sections and each section is assigned a score from 0 (no tumour) to 3 (>5 cm tumour). The addition of HIPEC to CRS was first evaluated in the 1980s. The biological rationale for intraperitoneal delivery was based on studies demonstrating a pharmacokinetic advantage because the peritoneal-plasma barrier allows a high concentration gradient of chemotherapeutic drugs between the peritoneal cavity and the systemic circulation [34] and that blood drainage from the peritoneal cavity is through the portal system, providing a "first-pass" effect through the liver, which reduces systemic toxicity while simultaneously increasing intrahepatic concentrations [35]. The addition of hyperthermia is based on experimental evidence that malignant cells are more sensitive to the effects of hyperthermia in the range of 41°C to 43°C, resulting in accelerated cell death [36]. Moreover, synergism between heat and enhanced cytotoxicity of certain chemotherapeutics used during HIPEC has been well documented [37].

The surgical expertise required for the CRS procedure, the experience, technical requirements and infrastructure required to deliver intraoperative HIPEC, and the multidisciplinary team required to care for these patients have dictated that specialized centres be created for care delivery [25,38,39]. While the use of HIPEC is an emerging field, the current standard of care in Ontario for these various disease sites is systemic chemotherapy or best supportive care.

The lack of an evidence-based guideline on this topic coupled with a need to develop indications to ensure appropriate patients are deriving benefit and that patients are being treated equitably across the province resulted in the development of this guideline to evaluate the impact of HIPEC with CRS on survival, adverse events and QoL in primary peritoneal mesothelioma and in secondary peritoneal cancers, including colorectal, appendiceal (defined as disseminated peritoneal adenomucinosis or clinical pseudomyxoma peritonei [PMP]), gastric and ovarian. The current review is focused on the use of HIPEC, when used with formal CRS or in the prophylactic setting following resection of the primary tumour. It does not evaluate either early postoperative intraperitoneal chemotherapy (EPIC) or sequential postoperative intraperitoneal chemotherapy (SPIC), both of which have been explored in ovarian cancer.

The Working Group of the Indications for HIPEC Guideline Development Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with ovarian cancer? If so, which patients derive greater benefit?

2. Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with peritoneal colorectal carcinomatosis? If so, which patients derive greater benefit?

3. Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with gastric peritoneal carcinomatosis? If so, which patients derive greater benefit?

4. Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with peritoneal mesothelioma? If so, which patients derive greater benefit?

5. Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with disseminated mucinous neoplasm of the appendix? If so, which patients derive greater benefit?

Current oncological management can include any of the following treatments or combinations: systemic chemotherapy, EPIC, SPIC, or surgery.

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. This included original systematic reviews and systematic reviews published as a component of practice guidelines. The MEDLINE (2008 to July 19, 2019) and EMBASE (1946 to July 19, 2019) databases, as well as

the Cochrane Database of Systematic Reviews (2008 to July 19, 2019) were searched. A comprehensive systematic search was conducted beginning 2008; however, only reviews published since 2013 (≤5 years old) were considered for inclusion. The full search strategy is available in Appendix 2.

Search for Primary Literature

A search for primary literature was conducted to locate literature where no existing systematic reviews were found.

Literature Search Strategy

The MEDLINE (1985 to July 19, 2019) and EMBASE (1985 to July 19, 2019) databases were searched for RCTs. If no RCTs were found then the databases were searched for comparative studies. The full search strategy is available in Appendix 2. Reference lists of included primary literature were scanned for additional citations. The following conference proceedings were also searched from 2015 to 2019: ASCO, ESMO, Society of Surgical Oncology, Peritoneal Surface Oncology Group International, Society of Gynecologic Oncology, and International Gynecologic Cancer Society.

Study Selection Criteria and Process

Inclusion Criteria

- RCTs (if no RCTs then prospective and retrospective comparative studies, where confounders are controlled for) with ≥30 participants; and
- Studies assessing adult patients with a diagnosis of mesothelioma, appendiceal (including appendiceal mucinous neoplasm), colorectal, gastric, ovarian, or primary peritoneal carcinoma; and
- Studies comparing CRS plus HIPEC with systemic chemotherapy, EPIC, or SPIC, CRS alone or any combination of the listed and reporting the following clinical outcomes: OS, PFS, RFS, adverse events, and QoL.

Exclusion Criteria

- Abstracts of non-randomized studies (single-arm clinical trials, case series, etc.); or
- Abstracts of interim analyses; or
- Papers or abstracts not available in English; or
- Letters and editorials that reported clinical trial outcomes; or
- Papers and abstracts published before 1985.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (DS). For items that warranted full-text review, one reviewer (DS) reviewed each item.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one reviewer (DS) and audited by a second independent auditor (JS).

Ratios, including HRs, were expressed with a ratio <1.0 indicating benefit for the experimental group for a given outcome.

Important quality features, such as generation of allocation sequence, allocation concealment, blinding, intention-to-treat (ITT) analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, differences in baseline patient characteristics, and early termination, were extracted for each RCT. Risk of bias was assessed for each included RCT using Cochrane's Risk of Bias tool, http://handbook.cochrane.org/ (Part

2, Section 8.5). Criteria from the Cochrane Risk of Bias for Non-randomized Studies of Interventions (ROBINS-I) tool were used to assess the risk of bias for all non-randomized studies.

The overall certainty of the evidence for each site was assessed using criteria from the GRADE method [40]: risk of bias, inconsistency, indirectness, and imprecision.

Synthesizing the Evidence

A meta-analysis was not feasible given the heterogeneity across trials.

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews yielded 119 documents. Seven systematic reviews examining the use of HIPEC with CRS for peritoneal colorectal carcinomatosis, two for gastric peritoneal carcinomatosis, one for mesothelioma, and three for ovarian cancer underwent full-text review. All reviews were excluded for various methodological and quality reasons.

Search for Primary Literature

Literature Search Results

A PRISMA flow diagram of the complete search is available in Appendix 3. Tables A5-1 to A5-5 in Appendix 5 summarize the characteristics of the included studies. Where multiple reports and abstracts were published for a single trial, only the most recent full publication was included, unless other reports contained data that were not available in the most recent publication.

Ovarian Cancer

Three RCTs [1-4] were found with one currently published in abstract form only.

Colorectal Peritoneal Carcinomatosis

Four RCTs were found [5-9]; two [8,9] (one in abstract form) addressed the prevention of colorectal peritoneal carcinomatosis and two [5-7] (one in abstract form) addressed the treatment of colorectal peritoneal carcinomatosis.

Gastric Peritoneal Carcinomatosis

Five RCTs [10-14] were found; four addressed the prevention of peritoneal carcinomatosis [11-14] and one [10] addressed the treatment of peritoneal carcinomatosis.

Mesothelioma

Two studies [15,41] met the inclusion criteria for the use of HIPEC compared with other oncological management of patients. However, data were not extracted from one [41] due to incorrect reporting of results from multivariable analysis.

Disseminated Mucinous Neoplasm of the Appendix

Five studies [16-20] met the inclusion criteria for the use of HIPEC compared with other oncological management of patients.

Study Design and Quality

Risk of bias assessments for RCTs and non-RCTs are reported in Tables A4-1 and A4-2, respectively, and the quality characteristics of the RCTs are reported in Table A4-3 (Appendix 4).

Ovarian Cancer

Risk of Bias

RCTs

Three RCTs [1-4] were included and assessed. The trial by Lim et al. [3] is currently published in abstract form and could not be assessed on three domains of the risk-of-bias tool, relating to selection and attrition bias, given the information needed was not discussed. These items were rated as 'unclear'. The RCT by Spiliotis et al. [4] rated 'unclear' on most domains as a result of poor methodology or poor reporting of methods used. The third RCT by van Driel et al. [1] scored 'low' on most domains of the risk-of-bias tool although allocation concealment was not described clearly in the publication. Overall, it was considered to have a low risk of bias. All RCTs scored 'high' for performance bias and detection bias; however, it is not feasible to blind participants, personnel, and outcome assessors to intensive surgical and chemotherapy treatments.

Certainty of the Evidence

The evidence for primary ovarian cancer comes from two RCTs [1-3], one published in full [1,2] and the other currently available in abstract form [3]. The overall certainty for all outcomes from this evidence is moderate due to the potential risk of bias and imprecision (i.e., the effect estimate comes from two RCTs with 184 and 245 patients, respectively).

For patients with recurrent ovarian cancer, the best evidence comes from one RCT [4]. The certainty of the evidence for all outcomes is low due to the potential risk of bias and imprecision (i.e., the effect estimate comes from one RCT with 120 patients).

Peritoneal Colorectal Carcinomatosis

Risk of Bias

RCTs

Four RCTs [5-9] were included and assessed. The PRODIGE 7 trial by Quenet et al. [5] and the ProphyloCHIP trial by Goere et al. [9] are currently published in abstract form and could not be assessed on three domains of the risk-of-bias tool, relating to selection and attrition bias, given the information needed was not discussed. These items were rated as 'unclear'. The remaining two RCTs by Klaver et al. [8] (COLOPEC trial) and Verwaal et al. [6,7] scored 'low' on most domains of the risk-of-bias tool. Both RCTs scored 'high' for performance bias and detection bias; however, it is not feasible to blind participants, personnel and outcome assessors to intensive surgical and chemotherapy treatments.

Certainty of the Evidence

Treatment of Peritoneal Colorectal Carcinomatosis

The certainty of the evidence for all outcomes is low due to the potential risk of bias, indirectness (i.e., the control arms of both trials vary and are not representative of current oncological practices), and inconsistency (i.e., variation in point estimates and confidence estimates do not overlap).

Prevention of Peritoneal Colorectal Carcinomatosis

The evidence for the prevention of peritoneal colorectal carcinmatosis comes from two RCTs [8,9], one published in full [8] and the other currently available in abstract form [9]. The overall certainty for all outcomes from this evidence is moderate due to the potential risk of bias and imprecision (i.e., the effect estimate comes from two RCTs with 202 and 150 patients, respectively).

Gastric Peritoneal Carcinomatosis

Risk of Bias

RCTs

The RCT by Yang et al. [10] scored 'low' on most domains of the risk-of-bias tool. Overall, it would be considered to have a low risk of bias. The remaining four RCTs [11-14] did not provide any randomization details. Three of these RCTs did not specify their primary outcome or the outcomes of interest resulting in a score of 'unclear' for selective outcome reporting, while the other RCT scored a 'low'. Overall, three RCTs would be considered to have an unclear risk of bias while the one would be considered to have a low risk of bias.

All RCTs scored 'high' for performance bias and detection bias; however, it is not feasible to blind participants, personnel, and outcome assessors to intensive surgical and chemotherapy treatments.

Certainty of the Evidence

Treatment of Peritoneal Carcinomatosis

The certainty of the evidence for all outcomes [10] is moderate due to the potential risk of bias and imprecision (i.e., the effect estimate comes from one RCT with 68 patients).

Prevention of Peritoneal Carcinomatosis

The certainty of the evidence for all outcomes [11-14] is low due to the potential risk of bias, indirectness (i.e., all trials come from Japan where patient population may differ biologically when compared with other populations) and inconsistency (i.e., difference in point estimates and confidence estimates do not overlap).

Mesothelioma

Risk of Bias

Non-randomized Studies

The one retrospective study [15] was assessed as having a serious risk of bias.

Certainty of the Evidence

According to GRADE [40], observational studies without special strengths or important limitations provide evidence with a low level of certainty.

Disseminated Mucinous Neoplasm of the Appendix

Risk of Bias

Non-randomized Studies

Overall, the four retrospective studies [17-20] were assessed as having a moderate risk of bias, while the comparative study [16] has a serious risk of bias.

Certainty of the Evidence

According to GRADE [40], observational studies without special strengths or important limitations provide evidence with a low level of certainty.

Outcomes

Question 1: Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with ovarian cancer? If so, which patients derive greater benefit?

To date, there have been three published RCTs [1-4] that have compared the use of CRS plus HIPEC with other methods of oncological management in patients with ovarian cancer. Two of these trials included women with primary epithelial ovarian cancer while one only included those with recurrent ovarian cancer. Table 4-1 presents a summary of the outcomes, while Table A5-1 in Appendix 5 provides details regarding treatment regimens.

HIPEC following Neoadjuvant Chemotherapy and Interval CRS for Newly Diagnosed Epithelial Ovarian Cancer

The multicentre trial by van Driel et al. [1] compared patients with newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer who received CRS plus HIPEC using cisplatin with CRS alone. All women had at least stable disease after neoadjuvant chemotherapy and achieved optimal or complete surgical cytoreduction at the time of surgery. Patients received an additional three cycles of carboplatin and paclitaxel after interval surgery. Patients were randomized with the use of a minimization procedure and power and sample size calculations were provided. Patients were stratified according to previous surgery, hospital in which surgery was being performed, and the number of involved regions in the abdomen. ITT analysis was performed. Patient and tumour characteristics were balanced within both arms. The majority of the patients had high-grade serous cancer, 92% in the experimental arm and 87% in the control arm. The remaining patients had histologies including high-grade endometrioid, carcinosarcoma, mucinous, clear-cell carcinoma, low-grade serous, low-grade endometrioid, and gastrointestinal tumour metastasis. The median age of patients was 61 years (range, 55 to 66 years) in the experimental arm and 63 years (range, 56 to 66 years) in the control arm.

Survival

The RCT by van Driel et al. [1] reported significant differences in median OS (HR, 0.67; 95% CI, 0.48 to 0.94; p=0.02) and median RFS (HR, 0.66; 95% CI, 0.50 to 0.87; p=0.003), after a median follow-up of 4.7 years. Exploratory subgroup analysis of OS or RFS did not reveal any specific subgroup (i.e., age, histologic type, previous surgery, number of involved regions, or laparoscopy before surgery) that experienced better or worse outcomes with CRS and HIPEC or standard treatment. The probability of OS at three years was 62% (95% CI, 54% to 72%) and 48% (95% CI, 39% to 58%) in the treatment and standard arms, respectively. The probability of RFS at three years was 17% (95% CI, 11% to 26%) and 8% (95% CI, 4% to 16%) in the treatment and standard arms, respectively.

Adverse Events

van Driel et al. [1] reported no significant differences between the groups in the incidence of adverse events of any grade.

Quality of Life

Health-related QoL was assessed with the EORTC QLQ-C30 version 3.0 and the associated ovarian and colorectal cancer questionnaire modules (QLQ-OV28 and QLQ-CR38) in the RCT by van Driel et al. [1,2]. The QLQ-CR38 was used for patients in whom CRS for ovarian cancer involved major abdominal surgery, including colonic surgery. Questionnaires were administered within four weeks prior to randomization (baseline), before start of adjuvant chemotherapy, at the end of treatment, and every three years of follow-up, for two years. Eighty percent of

patients completed at least one health-related QoL questionnaire. No significant differences in health-related QoL outcomes were reported over time.

HIPEC following Primary CRS for Newly Diagnosed Epithelial Ovarian Cancer

The trial by Lim et al. [3], currently published in abstract form, compared patients with stage III or IV primary epithelial ovarian cancer who received primary CRS plus HIPEC using cisplatin with CRS alone. Patient and tumour characteristics were balanced within both arms (i.e., age, body mass index, performance status, stage, histology, serum CA125 level, and the use of neoadjuvant chemotherapy at study entry). Many methodological details were not provided in this abstract.

Survival

The abstract reporting the trial by Lim et al. [3] showed no difference in five-year OS (HIPEC/cisplatin, 51%; non-HIPEC arm, 49.4%; p=0.574) or five-year PFS (HIPEC/cisplatin arm, 20.9%; non-HIPEC arm, 16.0%; p=0.569). Median follow-up was not reported. In a subgroup analysis of women who had received neoadjuvant chemotherapy, there was no difference in median OS (p=0.407) or median PFS (p=0.137) between the two arms.

Adverse Events

Lim et al. [3] reported the most common adverse event was anemia with significantly more participants in the HIPEC/cisplatin arm (67.4%) experiencing it than in the non-HIPEC arm (50%, p=0.025). Elevation of creatinine was also significantly higher in the HIPEC/cisplatin arm (15.2%) than in the non-HIPEC arm (4.3%, p=0.026). There were no differences between the two arms for transfusion (p=0.432), neutropenia (p=0.151), and thrombocytopenia (p=0.136).

HIPEC after Cytoreduction for Recurrent Epithelial Ovarian Cancer

The third RCT, Spilliotis et al. [4], compared women with stage III or IV recurrent epithelial ovarian cancer who received CRS plus HIPEC using cisplatin and paclitaxel for platinum-sensitive disease and CRS plus HIPEC using doxorubicin and paclitaxel or MMC for platinum-resistant disease with patients who received CRS only and systemic chemotherapy. Patients were randomized through the use of Graphpad software; however, power and sample size calculations were not provided. It was unclear whether all randomized patients received treatment because stratification of patients during randomization and ITT analysis were not mentioned. Further, details regarding statistical tests used and details about the systemic chemotherapy provided are absent. The majority of the patients had stage III_c ovarian cancer (68.3% in the experimental arm and 58.3% in the control arm) with the remaining patients having stage IV. The mean age of patients was approximately 58 years in both groups.

Survival

Spilliotis et al. [4] studied patients with recurrent ovarian cancer and reported a mean OS of 26.7 months in patients who received surgery plus HIPEC and a mean OS of 13.4 months in patients who received surgery only (p=0.006). In a subgroup analysis of patients who received CC-0 cytoreduction, survival was significantly higher in patients who received surgery plus HIPEC (30.9 months) compared with patients who received surgery only (16.9 months, p=0.038). In a subgroup analysis by PCI score, survival was significantly higher in patients who received surgery plus HIPEC than those who received surgery only for those with PCI ≤15 (30.4 months vs. 15.4 months, p=0.031) and PCI >15 (21.5 months vs. 9.2 months, p=0.049).

Adverse Events

Spiliotis et al. [4] did not report on any adverse events.

Table 4-1: Outcomes for the use of HIPEC with CRS in patients with ovarian cancer

Trial, year	Treatment allocation	N	Median follow-up	Median Age	Completeness of surgery (%)			PCI (%)			Survival		Adverse Events and/or Quality of Life
					R-1 CC-0	R-2a CC-1	R-2b CC-2	PCI <5	5< PCI <10	PCI >10			
Primary ovarian cancer													
van Driel et al. (2018) [1] Koole et al. (2019) [2]	CRS + HIPEC	122	4.7yrs	61 (55-66)	69	18	11	NR			Median OS, 45.7 mths	Median RFS, 14.2 mths	No significant differences between the groups in the incidence of adverse events of any grade. No significant differences in health-related QoL outcomes over time.
	CRS	123		63 (56-66)	67	20	11				33.9 mths HR, 0.67; 95% CI (0.48-0.94); p=0.02	10.7 mths HR, 0.66; 95% CI (0.50-0.87); p=0.003	
Lim et al. (2017) [3] Abstract	Surgery + HIPEC	92	NR	NR	-	-	-	NR			5-year OS, 51.0%	5-year PFS, 20.9%	Adverse events included anemia (p=0.025), elevation of creatinine (0.026)
	Surgery	92			-	-	-				49.4% p=0.574	16.0% p=0.569	
Recurrent ovarian cancer													
Spiliotis et al. (2015) [4]	CRS + HIPEC + systemic chemotherapy	60	NR	mean, 58.3	65	20	15	11.7	40	48.3	Mean OS, 26.7 mths	NR	NR
	CRS + systemic chemotherapy	60		mean, 58.1	55	33.3	11.7	13.3	36.7	50	13.4 mths p<0.006		

Abbreviations: CI: confidence interval; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; mths: months; NR: not reported; OS: overall survival; PFS: progression-free survival; QoL: quality of life; RFS: recurrence-free survival; yrs: years

Question 2: Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with peritoneal colorectal carcinomatosis? If so, which patients derive greater benefit?

RCTs

In total, four RCTs [5-9] have compared CRS plus HIPEC with other oncological management. Table 4-2 presents a summary of the outcomes, while Table A5-2 in Appendix 5 provides details regarding treatment regimens.

Prevention of Colorectal Peritoneal Carcinomatosis

The COLOPEC trial [8] determined the efficacy of adjuvant HIPEC using oxaliplatin and adjuvant systemic chemotherapy after a curative resection of T4 or perforated colon cancer in patients with locally advanced colon cancer. Adjuvant HIPEC was performed simultaneously (9%) or within five to eight weeks (91%) after the primary tumour resection. Within the experimental arm, 87% of patients received adjuvant HIPEC and 19% of patients were diagnosed with peritoneal metastases (9% preceding adjuvant HIPEC). 85% of patients in the experimental arm received adjuvant systemic chemotherapy compared with 88% in the control arm (p=0.50). Patients were block randomized centrally using a web-based randomization application and power and sample size calculations were provided. Patients were stratified according to tumour characteristics, surgical approach of the primary tumour resection and age. ITT analysis was performed. Patient and tumour characteristics were balanced within both arms. The primary outcome was peritoneal metastases-free survival. The majority of the patients had well differentiated adenocarcinoma, 75% in the experimental arm and 71% in the control arm. The remaining patients had histologies including poorly differentiated or undifferentiated adenocarcinoma, mucinous carcinoma, signet ring cell carcinoma, and medullar carcinoma. The median age of patients was 61 years (range, 56 to 68 years) in the experimental arm and 61 years (range, 54 to 68 years) in the control arm with a median follow-up of 23 months (interquartile range, 18 to 26 months).

The ProphyloCHIP trial [9], currently published in abstract form, compared patients with a high risk of developing colorectal peritoneal metastases after six months of adjuvant chemotherapy by randomizing them in to a surveillance arm or a systemic second-look surgery plus HIPEC using oxaliplatin arm. During the second-look laparotomy, colorectal peritoneal metastases were diagnosed in 52% of patients. Many methodological details, including power and sample size calculations, are not yet provided. The primary outcome was three-year DFS.

Treatment of Colorectal Peritoneal Carcinomatosis

The PRODIGE 7 trial [5], currently published in abstract form, compared patients who received CRS, HIPEC using oxaliplatin, and systemic chemotherapy with patients who received CRS and systemic chemotherapy. While power and sample size calculations were provided, many other methodological details were not. Patients were stratified by centre, complete macroscopic resections, and neoadjuvant systemic chemotherapy. The median age of patients was 60 years (range, 30 to 74 years).

The trial by Verwaal et al. [6,7] compared patients who received CRS plus HIPEC using MMC and systemic chemotherapy with patients who received standard therapy which consisted of systemic chemotherapy and surgery in cases of symptoms of intestinal obstruction, and consisted of either bypass or stoma surgery. Patients who received fluorouracil within 12 months before random assignment were initially excluded, but an amendment was later made to allow inclusion of these patients. Patients were randomized centrally by computer and stratified for presentation (primary or recurrence) and site (appendix, colon, or rectum). Power and sample size calculations were also provided and ITT analysis was performed. Patient and

tumour characteristics were balanced within both arms. Approximately 97.1% of the patients had large tumours (T3 or T4) and 3.1% had moderate or poor grade tumours. The median age of patients was 54 years (range, 28 to 70 years).

Survival

Prevention of Colorectal Peritoneal Carcinomatosis

The COLOPEC trial [8] showed no difference in 18-month DFS (69.0% [60.0-78.0] versus 69.3% [60.3%-78.3%]; p=0.99), 18-month OS (93.0% [87.9-98.1] versus 94.1% [89.6-98.6]; p=0.82) or 18-month peritoneal metastases-free survival (80.9%; 95% CI, 73.3-88.5 versus 76.2%; 95% CI, 68.0-84.4; p=0.28) between the experimental and control arms, respectively.

The ProphyloCHIP trial [9] showed no difference in three-year DFS (p=0.75) or three-year OS (p=not reported) between the surveillance arm and the HIPEC/oxaliplatin arm (p=0.75) after a median follow-up of 51 months.

Treatment of Colorectal Peritoneal Carcinomatosis

The PRODIGE 7 trial [5] showed no difference between the HIPEC/oxaliplatin arm and non-HIPEC arm in median OS (HR, 1.00; 95% CI, 0.73 to 1.37; p=0.995) or median RFS (HR, 0.90; 95% CI, 0.69 to 1.90; p=0.486) after a median follow-up of 63.8 months. In a subgroup analysis of patients with medium-range PCI (>11 to ≤15), the median OS was 32.7 months (95% CI, 23.5 to 38.9) for the non-HIPEC arm and 41.6 months (95% CI, 36.1 to not reached) in the HIPEC arm (HR,0.437; 95% CI, 0.21 to 0.90; p=0.0209).

The trial by Verwaal et al. [6] reported significant differences in DSS (HIPEC/MMC arm, 22.2 months; non-HIPEC arm, 12.6 months; p=0.028) and PFS (HIPEC/MMC arm, 12.6 months; non-HIPEC arm, 7.7 months; p=0.020), after a median follow-up of 94 months. Exploratory subgroup analysis did not reveal that any specific subgroup (i.e., sex, age, site or origin of tumour) experienced better or worse outcomes with CRS and HIPEC or standard treatment. In looking at the HIPEC/MMC arm grouped by completeness of cytoreduction, a median survival of 48 months and a 45% five-year survival were shown for patients who received complete cytoreduction (41%). Median DSS of 22.2 months and 12.6 months (p=0.028) for patients in the HIPEC/MMC and non-HIPEC arms, respectively, and five-year survivals of 45% and 7% for patients who received R-1 and R-2a cytoreductions, respectively, were extrapolated from the provided Kaplan-Meier survival estimates.

Adverse Events

Prevention of Colorectal Peritoneal Carcinomatosis

The abstract from the COLOPEC trial [8] reported postoperative complications occurred in 14% of patients who received adjuvant HIPEC (n=87). One patient developed encapsulating peritoneal sclerosis after receiving HIPEC resulting in long-term morbidity.

The ProphyloCHIP trial [9] reported that in patients receiving second-look surgery plus HIPEC, none died postoperatively and grade 3-4 complications occurred in 41%.

Treatment of Colorectal Peritoneal Carcinomatosis

The PRODIGE trial [5] reported a 1.5% postoperative mortality rate with no difference between the experimental and standard arms. The morbidity rates did not differ at 30 days but at 60 days, there were significant differences in the grade 3 to 5 morbidity rate (HIPEC/oxaliplatin arm, 24.1%; non-HIPEC arm, 13.6%; p=0.030).

In the trial by Verwaal et al. [6,7], four patients (8%) died as a result of treatment and two stopped adjuvant chemotherapy as a result of toxicity in the HIPEC/MMC arm, while two stopped treatment in the non-HIPEC arm due to toxicity.

Table 4-2: Outcomes for the use of HIPEC with CRS in patients with peritoneal colorectal carcinomatosis

Trial, year	Treatment allocation	N	Median age (years)	Median follow-up (months)	Primary Sites	Completeness of Surgery (%)			Survival		Adverse Events and/or Quality of Life
						R-1 CC-0	R-2a CC-1	R-2b CC-2			
Prevention of colorectal carcinomatosis											
Klaver et al. (2019) [8] COLOPEC	CRS + adjuvant HIPEC + systemic chemotherapy	100	61 (56-68)	23 (IQR, 18-26)	NR	NR	NR	NR	18-mth OS, 93.0% (87.9-98.1)	18-mth DFS, 69.0% (60.0-78.0)	Postoperative complications occurred in 14% of patients after adjuvant HIPEC. One patient presented with encapsulating peritoneal sclerosis 12 months after adjuvant HIPEC.
	Adjuvant systemic chemotherapy	102	61 (54-68)						94.1% (89.6-98.6) p=0.82	69.3% (60.3%-78.3%) p=0.99	
Goere et al. (2018) [9] Prophylo CHIP Abstract	Surveillance	79	NR	51 (47-55)	NR	NR	NR	NR	Three-year OS, 80% (95% CI, 69-88%)	Three-year DFS, 51% (95% CI, 40-62%)	In patients receiving second-look surgery + HIPEC, none died postoperatively and grade 3-4 complications occurred in 41%.
	Second-look surgery + HIPEC	71							79% (95% CI, 68-87) p=NR	44% (95% CI, 33-56) p=0.75	
Treatment of colorectal carcinomatosis											
Quenet et al. (2018) [5] PRODIGE 7 Abstract	CRS + HIPEC + systemic therapy	133	60 (30-74)	63.8 (95% CI, 58.9-69.8)	NR	NR	NR	NR	Median OS, 41.7 mths (95% CI, 36.2-52.8)	Median RFS, 13.1 mths (95% CI, 12.1-15.7)	Postoperative mortality rate was not different between the arms. At 60 days, grade 3-5 morbidity rate was significantly higher in the HIPEC arm (24.1% vs. 13.6%, p=0.030)
	CRS alone + systemic therapy	132				NR	NR	NR	41.2 mths (95% CI, 35.1-49.7) HR=1.00 (95% CI, 0.73-1.37), p=0.995	11.1 mths (95% CI, 9-12.7) HR=0.90 (95% CI, 0.69-1.90), p=0.486	
Verwaal et al. (2003) [7] (2008) [6]	CRS + HIPEC + systemic therapy	54	54 (28-70)	94 (72-115)	Appendix, 17.1% Colon, 71.4%	41	41	18	DSS, 22.2 mths	PFS, 12.6 mths	8% died as a result of treatment and 2 stopped adjuvant chemotherapy as a result of toxicity. Grade 3-4 toxicity – 17% leukopenia, 15% GI

					Rectum, 11.4%						fistula, 14% hemorrhage, and 12% heart failure.
	Surgery + systemic chemotherapy	51				NR	NR	NR	12.6 mths p=0.028	7.7 mths p=0.020	Two patients stopped systemic chemotherapy because of toxicity.

Abbreviations: CI: confidence interval; CRS: cytoreductive surgery; DSS: disease-specific survival; GI: gastrointestinal; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; IGR: interquartile range; mths: months; NR: not reported; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival

Question 3: Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with gastric peritoneal carcinomatosis? If so, which patients derive greater benefit?

RCTs

In total, five RCTs [10-14] have compared CRS plus HIPEC with other oncological management. Table 4-3 presents a summary of the outcomes, while Table A5-3 in Appendix 5 provides details regarding treatment regimens.

Prevention of Gastric Peritoneal Carcinomatosis

Four RCTs [11-14] were found that addressed the prevention of peritoneal carcinomatosis. Cui et al. [11] performed a trial in which patients with advanced gastric cancer that had undergone surgery were randomized to the following four arms: surgery alone, preoperative neoadjuvant chemotherapy plus surgery, surgery plus HIPEC using cisplatin, and preoperative neoadjuvant chemotherapy plus surgery plus HIPEC using cisplatin. Patient and tumour characteristics were balanced within all four arms (i.e., pathology [i.e., moderately/well differentiated adenocarcinoma, poorly/undifferentiated adenocarcinoma, and mucinous adenocarcinoma or mucinous cell carcinoma] and stage [i.e., stages IIIA and IIIB]). No other details were provided regarding patient characteristics. Four patients were lost to follow-up.

The publication by Yonemura et al. [12] presented the final results of an RCT where patients with advanced gastric cancer showing macroscopic serosal invasion (T3 or T4) but no established peritoneal metastasis where patients received either CHPP using MMC and cisplatin, CNPP using MMS and cisplatin, or surgery alone (i.e., extended gastrectomy). Patient and tumour characteristics were balanced within the three arms (i.e., sex, clinical stage [stage III or IV], histology [differentiated or undifferentiated], lymph node status, wall invasion, macroscopic type, or surgical procedure). The mean age of patients included in the trial was 59.5 years.

In the third trial, Fujimoto et al. [13] reported the results of patients with gastric carcinoma who received surgery plus HIPEC using MMC or surgery only. The baseline characteristics of patients were balanced between both arms (i.e., age, sex, TNM classification of lymph node metastasis, type of surgery, histology [well, moderately or poorly differentiated adenocarcinoma], and histologic curability), with the exception of those in the HIPEC arm having significantly more advanced serosal invasion than the surgery-only arm (p=0.0405). The mean age of patients was 58.5 years in the experimental arm and 59.2 years in the control arm.

Finally, the publication by Hamazoe et al. [14] presented the final results of an RCT where patients with macroscopic serosal invasion but no macroscopic peritoneal invasion were randomized into a CHPP arm using MMC and a control arm. The baseline characteristics of patients were balanced between both arms (i.e., age, sex, Borrmann classification, type of gastrectomy, histology [well, moderately or poorly differentiated adenocarcinoma], serosal invasion, lymph node metastasis, stage, and curability). The mean age of patients was 56.5 years in the experimental arm and 63.4 years in the control arm.

Randomization details, power and sample size calculations, source of funding and median follow-up were not provided for all four trials [11-14]. The primary outcome was unclear in the four trials but is assumed to be OS.

Treatment of Gastric Peritoneal Carcinomatosis

One RCT by Yang et al. [10] was found that compared CRS plus HIPEC, using cisplatin and MMC, with CRS alone in patients with gastric peritoneal carcinomatosis. Patients were randomized using a computer-generated number. Power and sample size calculations were also

provided and ITT analysis was performed. Patient and tumour characteristics were balanced within both arms (i.e., age, sex, PCI score, histological diagnosis, organ resections, and peritonectomy locations). The majority of patients had poorly differentiated/ undifferentiated adenocarcinoma (55.9% in the experimental arm and 70.4% in the control arm). The remaining patients had histologies including well-/intermediately differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma, and squamous cell carcinoma. The median PCI score was 15 in both arms and 58.8% of patients in both arms had a CC score ranging from 0 to 1.

Survival

Prevention of Gastric Peritoneal Carcinomatosis

The trial by Cui et al. [11] reported that the differences in median survival among those who received surgery only (27 months), neoadjuvant chemotherapy with surgery (33 months), surgery with HIPEC/cisplatin (32 months), and neoadjuvant chemotherapy with surgery plus HIPEC/cisplatin (36 months) were statistically significant (p=0.001). The differences in median PFS were also statistically significant among the four groups (26 months, 28 months, 31 months, and 33 months, respectively; p<0.001).

The trial by Yonemura et al. [12] showed survival was significantly better in patients who received CHPP/MMC and cisplatin (5-year, 61%) when compared with patients who received CNPP (5-year, 44%; p=0.017) or surgery alone (5-year, 42%; p=0.019). In a multivariate analysis, age, serosal invasion, nodal status, and CHPP were found to be prognostic factors.

Similarly, Fujimoto et al. [13] reported survival rates were significantly higher in the HIPEC/MMC arm (2-year, 88%; 4-year, 76%; 8-year, 62%) compared with the surgery arm (2-year, 77%; 4-year, 58%; 8-year, 49%; p=0.0362). Peritoneal recurrence also occurred more frequently in the control arm (p<0.001).

The final results of the RCT reported by Hamazoe et al. [14] found no significant differences in five-year survival between the HIPEC/MMC arm (64.3%) and control arm (52.5%, p=0.2427). Median survival was reported as 77 months in the HIPEC arm and 66 months in the control arm.

Treatment of Gastric Peritoneal Carcinomatosis

The RCT by Yang et al. [10] showed a significant difference in median OS between the CRS plus HIPEC/cisplatin and MMC arm (11.0 months; 95% CI, 10.0 to 11.9) and the non-HIPEC arm (6.5 months; 95% CI, 4.8 to 8.2; p=0.046). In subgroup analyses, patients who received a CC score ranging from 0 to 1 had a significantly higher median OS than patients who received a CC ranging from 2 to 3 within both the HIPEC/cisplatin and MMC arm (p=0.000) and the non-HIPEC arm (p=0.000). In patients with incomplete cytoreduction, the HIPEC/MMC arm brought longer OS than the non-HIPEC arm (HIPEC/cisplatin and MMC arm, 8.2 months; non-HIPEC arm, 4.0 months; p=0.024). Similarly, in subgroup analyses by PCI score, patients who had a high PCI score had a significantly higher median OS in the HIPEC/cisplatin and MMC arm (13.5 months, 95% CI, 8.7 to 18.3) when compared with the non-HIPEC arm (3.0 months; 95% CI, 2.4 to 3.6; p=0.012) while patients with a low PCI score showed no difference between the two arms (p=0.464).

In a multivariate analysis, CRS plus HIPEC (HR, 2.617; 95% CI, 1.436 to 4.769; p=0.002), synchronous peritoneal carcinomatosis (HR, 2.228; 95% CI, 1.136 to 4.367; p=0.02), a CC score of 0 to 1 (HR, 2.794; 95% CI, 1.405 to 5.556; p=0.003), chemotherapy ≥6 cycles (HR, 3.344; 95% CI, 1.838 to 6.061; p=0) and no serious adverse effects (HR, 4.295; 95% CI, 1.989 to 9.274; p=0) were identified as major independent predictors for survival.

Adverse Events

Prevention of Gastric Peritoneal Carcinomatosis

All four RCTs [11-14] found no significant differences in adverse events between the experimental and control arms.

Treatment of Gastric Peritoneal Carcinomatosis

The RCT by Yang et al. [10] showed no significant differences in serious adverse events between patients receiving CRS plus HIPEC (14.7%) and CRS alone (11.7%, p=0.839).

Table 4-3: Outcomes for the use of HIPEC with CRS in patients with gastric peritoneal carcinomatosis

Trial, year	Treatment allocation	N	Median follow-up	Median age (yrs)	Completeness of surgery (%)				Survival		Adverse Events and/or Quality of Life
					R-1 CC-0	R-2a CC-1	R-2b CC-2	CC-3			
Treatment of Gastric Peritoneal Carcinomatosis											
Yang et al. (2011) [10]	CRS + HIPEC	34	32mths (7.5-83.5)	50 (24-75)	58.8		41.2		Median OS, 11.0 mths (95% CI, 10.0-11.9)	NR	Serious adverse events[a], 14.7%
	CRS alone	34		51 (28-75)	58.8		41.2		6.5mths (95% CI, 4.8-8.2) p=0.046	NR	11.7% p=0.839
Prevention of Gastric Peritoneal Carcinomatosis											
Cui et al. (2014) [11]	Surgery alone	48	NR	mean, 56 (39-72)	NR	NR	NR	NR	Median survival, 27 mths	Median PFS, 26 mths	No significant differences between the rates of I-II degree myelosuppression (p=0.76), III-IV degree myelosuppression (p=0.84), I-II degree nausea (p=0.52) and III-IV degree nausea (p=0.9) among the 4 groups. No patients died during surgery.
	Preoperative neoadjuvant chemotherapy + surgery	48		55 (41-69)	NR	NR	NR	NR	33 mths	28 mths	
	Surgery + HIPEC	48		53 (39-70)	NR	NR	NR	NR	32 mths	31 mths	
	Preoperative neoadjuvant chemotherapy + surgery + HIPEC	48		55 (42-68)	NR	NR	NR	NR	36 mths p=0.001	33 mths p<0.001	
Yonemura et al. (2001) [12]	Surgery[b] + CHPP	48	NR	mean, 58.3	NR	NR	NR	NR	5yr, 61%	NR	No significant differences in major postoperative complications between the three groups. Two patients died in the CHPP arm and two in the surgery-alone arm but there were no significant differences among the 3 arms.
	Surgery[b] + CNPP	44		59.2	NR	NR	NR	NR	5yr, 44% CHPP vs CNPP, p=0.017	NR	
	Surgery[b] alone	47		61.1	NR	NR	NR	NR	5yr, 42% CHPP vs surgery	NR	

									alone, p=0.019		
Fujimoto et al. (1998) [13]	IHCP + surgery + postoperative adjuvant chemotherapy	71	NR	Mean, 58.5±8.1	NR	NR	NR	NR	Survival rates 2yr, 88% 4yr, 76% 8yr, 62%	Peritoneal recurrence occurred more frequently in the control group, p<0.001	2 patients in the IHCP group experienced minor leakage of the duodenal stump, of which one was cured without reoperation and the other required reoperation.
	Surgery + postoperative adjuvant chemotheray	70		59.2±9.1	NR	NR	NR	NR	2yr, 77% 4yr, 58% 8yr, 49% p=0.0362	NR	NR
Hamazoe R et al. (1993) [14]	CHPP + surgery	42	NR	Mean, 56.5±10.4	NR	NR	NR	NR	Median survival, 77 mths	Survival, 5yr, 64.3%	No significant difference in mortality rate from peritoneal recurrence between the two groups (0.0854). No significant differences in other adverse effects between the two groups.
	Surgery alone	40		63.4±9.6	NR	NR	NR	NR	66 mths	5yr, 52.5% p=0.2427	

Abbreviations: CHPP: continuous hyperthermic peritoneal perfusion; CI: confidence interval; CNPP: continuous normothermic peritoneal perfusion; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; IHCP: intraperitoneal hyperthermic chemoperfusion; mths: months; NR: not reported; OS: overall survival; PFS: progression-free survival; yr: years

[a] Serious adverse events included wound infection and sepsis, respiratory failure, gastrointestinal bleeding, severe bone marrow suppression, and intestinal obstruction

[b] Surgery defined as extended gastrectomy

Question 4: Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with peritoneal mesothelioma? If so, which patients derive greater benefit?

To date, there have been no randomized or comparative studies conducted to study the use of CRS plus HIPEC with other methods of oncological management in patients with peritoneal mesothelioma. One retrospective cohort study [15] conducted a multivariable analysis, including the use of CRS plus HIPEC as a variable. Table 4-4 presents a summary of the outcomes, while Table A5-4 in Appendix 5 provides details regarding treatment regimens. This retrospective study by Verma et al. [15] included 1514 patients with malignant peritoneal mesothelioma from the National Cancer Database User File from 2004 to 2013. Patients in this cohort received chemotherapy alone, CRS alone, CRS plus chemotherapy, CRS plus HIPEC, or neither chemotherapy nor surgery (i.e., observation). The CRS plus chemotherapy cohort was a heterogeneous cohort including EPIC, sequential chemotherapy, and adjuvant non-intraperitoneal chemotherapy. Information regarding chemotherapy and HIPEC regimens was not provided, in addition to information regarding CRS (i.e., completeness of cytoreduction).

Survival

The study by Verma et al. [15] showed that when compared with the CRS plus HIPEC cohort, receipt of chemotherapy alone, CRS alone and observation were independently associated with poorer OS ($p<0.001$). However, there was no statistically significant difference in OS when comparing CRS plus HIPEC with CRS plus chemotherapy ($p=0.397$). The potential confounders controlled for in the multivariable model are listed in Table 4-4.

Adverse Events

Adverse events were not reported in the Verma et al. [15] study for each of the treatment groups.

Table 4-4: Outcomes for the use of HIPEC with CRS in patients with mesothelioma

Trial, year	Treatment allocation	N (%)	Median follow-up	Median Age	Completeness of surgery (%)	PCI	Histology				Overall survival rates	MVA, Overall Survival Variables in analysis	Adverse Events and/or Quality of Life
							Epithelioid	Sarcomatoid	Biphasic	Not specified			
Verma et al. (2018) [15]	Observation	379 (25%)	50 mths (0-128)	NR	NR	NR	32%	4%	3%	62%	5yr, 9% (6-13%)	Treatment group[a] (CRS/chemo vs. CRS/HIPEC), p=0.397 (CRS alone vs. CRS/HIPEC) HR, 1.859; 95% CI, 1.378–2.509; p<0.001 (Chemo alone vs. CRS/HIPEC) HR, 1.843; 95% CI, 1.450–2.341; p<0.001 (Observation vs. CRS/HIPEC) HR, 2.903; 95% CI, 2.270–3.712; p<0.001	Not reported for the various treatment groups.
	Chemo only	370 (24%)					35%	4%	2%	58%	5yr, 22% (17-31)		
	CRS alone	197 (13%)					39%	4%	5%	53%	5yr, 22% (13-32)		
	CRS+chemo	352 (23%)					50%	3%	5%	42%	5yr, 43% (36-49)		
	CRS+HIPEC	216 (14%)					65%	1%	4%	31%	5yr, 52% (41-58)		
	CRS+EPIC	12 (3%)											
	CRS only HIPEC withheld/ EPIC	21 (5%)											

Abbreviations: Chemo: chemotherapy; CI: confidence interval; CRS: cytoreductive surgery; EPIC: early postoperative chemotherapy; HIPEC: hyperthermic intraperitoneal chemotherapy; MVA: multivariable analysis; NR: not reported; yr: year

[a] Variables included in MVA: Treatment group, age, sex, Charlson/Deyo score, insurance, histology

Question 5: Does the use of HIPEC with CRS provide better outcomes (i.e., improved survival and reduced adverse events) than current oncological management of patients with disseminated mucinous neoplasm of the appendix? If so, which patients derive greater benefit?

Disseminated Mucinous Neoplasms of the Appendix

To date, there have been no randomized trials conducted to study the use of CRS plus HIPEC with other methods of oncological management in patients with PMP. One comparative study [16] and four retrospective cohort studies [17-20], using CRS/HIPEC as a variable in the multivariate analysis were found. These studies all included a combination of DPAM, PMCA, and combined or different histologies. Table 4-5 presents a summary of the outcomes, while Table A5-5 in Appendix 5 provides details regarding treatment regimens.

The comparative study by Jarvinen et al. [16] compared the results of 33 consecutive patients of the debulking surgery era (1984 to 2008) with 87 consecutive patients from the HIPEC era (starting 2008) diagnosed with PMP. The median follow-up and median age of the debulking surgery era arm was 71 months (range, 7 to 257 months) and 50 years (range, 25 to 73 years), respectively, while it was 33 months (range, 0 to 66 months) and 54 years (range, 30 to 87 years), respectively, for the HIPEC era arm. The HIPEC era arm was heterogeneous in the treatment received in that 64% received HIPEC, 14% were treated non-radically in an attempt at HIPEC, 10% were debulked without an attempt at HIPEC, and 12% were referred back or transferred to palliative care without surgery.

Of the four retrospective, comparative studies, the study by Sinukumar et al. [17] reported on 91 patients from a retrospective registry with PMP of appendiceal origin between March 2013 and December 2017. Of these patients, 84% received CRS plus HIPEC and 16% received CRS alone or debulking. The median PCI was 27 (range, 3 to 39) and a CC-0/1 resection was achieved in 84% of patients.

The first study by Chua et al. [18] reported on 2298 patients with histologically confirmed PMP from an appendiceal mucinous neoplasm treated between 1993 and 2011 from the Peritoneal Surface Oncology Group International registry. Of these, 29% of patients received CRS plus HIPEC and EPIC, 60% received CRS plus HIPEC, 2% received CRS plus EPIC, and 9% received CRS alone. HIPEC was delivered intraoperatively in 89% of patients, of which MMC-based HIPEC was used in 77%. Sixteen percent of patients received systemic chemotherapy before cytoreduction. Optimal cytoreduction (CC-0 or -1) was achieved in 83% of patients.

Another study by Chua et al. [19] reported on 106 patients with PMP from a single institution from 1997 to 2008 who received CRS/HIPEC using MMC with the open technique, CRS plus HIPEC and EPIC and CRS plus EPIC using 5-fluorouracil. The number of patients in each treatment option is unclear. It is known that 78% of patients received HIPEC, 76% received EPIC postoperatively, and 63% had both HIPEC and EPIC. Optimal cytoreduction (CC-0 or -1) was achieved in 91% of patients.

The final included study by Glehen et al. [20] included 174 patients with PMP who had undergone incomplete cytoreductive surgery (i.e., residual tumour nodules >0.25 mm) between 1983 and 2003. These patients received CRS plus HIPEC using MMC (6.3%), CRS plus HIPEC and EPIC (28.7%), CRS plus EPIC using MMC and 5-fluorouracil (43.7%), and CRS alone (21.3%).

All four cohort studies [17-20] had a combination of patients with DPAM, PMCA, and hybrid histologies. The median age of patients ranged from 52 years (range, 26 to 79 years) to 54.0 years (range, 15 to 77 years) and the median follow-up ranged from 23 months (range, 0 to 140 months) to 86.3 months (range, 7 to 210 months).

Survival

The comparative study by Jarvinen et al. [16] showed no significant difference in five-year OS rates between the CRS/HIPEC era (69%) and the debulking era (67%, p=0.92).

The retrospective study by Sinukumar et al. [17] showed that the use of HIPEC was not associated with OS but was independently associated with increased PFS (HR, not reported; 95% CI, 1.26-9.8; p=0.016). The potential confounders controlled for in the multivariable model are listed in Table 4-5.

The study by Glehen et al. [20] showed that the use of HIPEC was independently associated with increased survival (p<0.001). The potential confounders controlled for in the multivariable model are listed in Table 4-5. The HRs and CIs were not provided.

In both studies by Chua et al. [18,19], the use of HIPEC was not independently associated with OS (p>0.05). However, the use of HIPEC was independently associated with PFS (HR, 0.645; 95% CI, 0.44 to 0.96; p=0.030) [18]. The potential confounders controlled for in the multivariable model are listed in Table 4-5. In an exploratory subgroup analysis by histologic subtype, the use of HIPEC remained non-significant [18].

Adverse Events

The comparative study by Jarvinen et al. [16] reported no significant difference in 30-day mortality between patients in debulking era (0%) and the CRS/HIPEC-era (2.6%, p=1.0). Morbidity and mortality data were not provided by individual treatment groups but as aggregate date in the retrospective cohort studies (Table 4-5).

Table 4-5: Outcomes for the use of HIPEC with CRS in patients with disseminated mucinous neoplasms of the appendix

Trial, year	Treatment allocation	N	Median follow-up	Median Age	Completeness of surgery (%)				PCI	Histological subtype	OS rates	PFS rates	MVA, Overall Survival Variables in analysis	Adverse Events and/or Quality of Life
					CC-0	CC-1	CC-2	CC-3						
Comparative														
Jarvinen et al. (2014) [16]	CRS + HIPEC era	87	33 mths (0-66)	54 yrs (30-87)	NR				NR	Low grade, 63% High grade, 37%	5yr, 69%	NR	NR	30-day mortality: HIPEC-era, 2.6%.
	Debulking era	33	71 mths (7-257)	50 yrs (25-73)	NR				NR		5yr, 67% (p=0.92) 10yr, 39%	NR		0% p=1.0
Retrospective														
Sinukumar et al. (2019) [17]	CRS + HIPEC[a]	76 (84%)	NR	53 yrs	44	40	9	8	< 20, 31% > 20, 69%	Low grade, 71% High grade, 19% Signet, 10%	NR	Median PFS, 53mths	PFS, CRS+HIPEC[b] 95% CI, 1.26-9.8; p=0.016	Grade 3-4 morbidity was 33%.
	CRS alone/debulking	15 (16%)										16mths		
Chua et al. (2012) [18]	CRS + HIPEC[c] + EPIC	668 (29%)	36 mths (1-220)	53 yrs (18-86)	51	32	17		0-10, 15% 11-20, 19% 21-30, 18% 31-39, 13% Unknown, 35%	DPAM, 62% Hybrid, 6% PMCA, 30% Unknown, 2%	5yr, 74% 10yr, 63%	NR	PFS, Use of HIPEC HR, 0.645; 95% CI, 0.44-0.96; p=0.030 OS, Use of HIPEC[d] non-signficant Subgroup analysis by histologic subtype, Use of HIPEC, non-significant	NR
	CRS + HIPEC	1382 (60%)												
	CRS + EPIC	44 (2%)												
	CRS alone	203 (9%)												
	Unknown	1 (0.04 %)												

Chua et al. (2009) [19]	CRS + HIPEC	83 (78%)	23 mths (0-140)	53 yrs (22-86)	69	22	8	1	Median, 21 (2-39)	DPAM, 69% Hybrid, 21% PMCA, 10%	5yr, 75% 10yr, 36%	5yr, 38%	OS,[e] non-significant	21% of pts died.
	CRS + HIPEC + EPIC	67 (63%)												
	CRS + EPIC	81 (76%)												
Glehen et al. (2004) [20]	CRS + IPCH	11 (6.3%)	55.9 mths (3-119)	mean, 53.3 (31-70)	0	0	21	79	NR	DPAM, 23.6% Hybrid, 36.8% Mucinous adenocarcinoma, 39.7%	5yr, 15.3%	NR	OS, Use of hyperthermia[f] p<0.001	Grade III/IV complications occurred in 33.33% of patients[g] No treatment-related mortality.
	CRS + IPCH + EPIC	50 (28.7%)	72.4 mths (7-120)	mean, 49.1 (28-78)										
	CRS + EPIC	76 (43.7%)	86.3 mths (7-210)	mean, 52.8 (19-88)										
	CRS alone	37 (21.3%)	55.6 mths (3-199)	mean, 57.2 (27-74)										

Abbreviations: CI: confidence interval; CRS: cytoreductive surgery; DPAM: disseminated peritoneal adenomucinosis; EPIC: early postoperative chemotherapy; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; IPCH: intraperitoneal chemohyperthermia; mths: months; MVA: multivariable analysis; NR: not reported; OS: overall survival; PCI: peritoneal carcinomatosis index; PFS: progression-free survival; PMCA: peritoneal mucinous carcinomatosis; yrs: years

[a] 41% of patients received mitomycin C, 26% received mitomycin C + adriamycin, 6% received cisplatin, 9% received oxaliplatin

[b] variables included in MVA: prior chemotherapy, use of HIPEC, PMP grade, CCR, PCI

[c] 77% of patients received mitomycin C, 11% received oxaliplatin

[d] variables included in MVA: sex, time from diagnosis to CRS, prior surgical score, number of prior operations, prior chemotherapy, tumour histopathology, lymph node metastasis, PCI, CCR, use of HIPEC, use of EPIC, major postoperative complications

[e] non-significant in univariate analysis

[f] variables that were close to significance (p<0.01) by univariate analysis were included in the model: presence of signet ring cells, lymph node involvement, number of procedures performed and use of hyperthermia

[g] morbidity and mortality was recorded after 1998 and so is available in 69 patients

Ongoing, Unpublished, or Incomplete Studies

A search for ongoing, unpublished, or incomplete phase III or IV trials was conducted on August 30, 2018 at clinicaltrials.gov using the terms "HIPEC" or "hyperthermic intraperitoneal chemotherapy".

Nine trials were found for ovarian cancer, five for colorectal, and nine for gastric peritoneal carcinomatosis . The trial details are provided in Appendix 6, Tables A6-1 to A6-3.

No phase III or IV trials were found for appendiceal cancer and mesothelioma and as a result, a search for phase II trials was undertaken. One ongoing trial was found for appendiceal cancer summarized in Appendix 6, Table A6-4.

DISCUSSION

Ovarian Cancer

While numerous studies have evaluated the survival benefit following addition of postoperative, non-heated intraperitoneal chemotherapy, either EPIC or SPIC, to CRS for the primary treatment of patients with epithelial ovarian cancer [42], studies evaluating the addition of HIPEC have only recently been reported. A fully published RCT [1] in primary epithelial ovarian cancer included patients who had partial or complete response following neoadjuvant chemotherapy and complete or optimal cytoreduction (≤1 cm residual disease) demonstrated a survival advantage with the addition of HIPEC with cisplatin. By contrast, the second study, published in abstract form [3], failed to demonstrate a significant improvement in survival with HIPEC in patients undergoing primary CRS followed by adjuvant chemotherapy for newly diagnosed epithelial ovarian cancer. Both studies confirm the overall similar rates of side effects with or without the addition of HIPEC to CRS. Based on these studies, the Working Group members currently recommend consideration be given to the addition of HIPEC only in patients with partial or complete response following neoadjuvant chemotherapy and optimal or complete interval CRS. This recommendation does not extend to patients undergoing primary CRS, without prior neoadjuvant chemotherapy, nor is it intended to suggest that neoadjuvant chemotherapy followed by HIPEC with CRS is superior to primary CRS without HIPEC, as these questions have not been addressed in the literature to date.

In the setting of recurrent epithelial ovarian cancer, following secondary CRS and systemic chemotherapy, a single RCT was identified; however, concerns raised about the quality of reporting of this trial [43] limit the strength of the conclusions that can be drawn from it. The study methodology reports on CC-0 (0 mm) resection and CC-2 resection (residual tumor 2.5 mm to 2.5 cm) and uses the PSI score to report their data. While these reporting systems are used in other solid malignancies, they are not used to describe surgical resection outcomes in ovarian carcinoma. There is evidence in ovarian carcinoma that complete resection to 0 mm harbours the best survival advantage. In addition, optimal cytoreduction with 1 to 9 mm residual disease has a survival advantage over suboptimal cytoreduction of greater than 1 cm of residual disease [44]. Therefore, the category of patients reported as CC-2 in this study is challenging to interpret since it mixes patients with optimal and suboptimal resection in the same category. In the absence of additional supportive level 1 data, the Working Group members concluded that there is insufficient evidence to recommend the addition of HIPEC to secondary CRS in patients with recurrent epithelial ovarian cancer.

There are nine randomized phase III trials that are currently ongoing with study completion dates ranging from December 2018 to April 2025 (Appendix 6, Table A6-1), that may provide evidence to enable refinement of the indications for HIPEC in ovarian cancer.

Peritoneal Colorectal Carcinomatosis

The level 1 evidence on the use of HIPEC for colorectal peritoneal carcinomatosis includes two RCTs [5-7], one of which is currently available as an abstract only [5]. These trials diverged in their conclusions but also had notable methodological differences. In the Verwaal et al. trial [6,7], the control group did not undergo CRS and the comparator was the combination of CRS and HIPEC. It is unclear, therefore, if the survival advantage in this group can be attributed to the CRS, HIPEC, or the combination of the two. Moreover, the control arm received 5-fluorouracil and leucovorin chemotherapy, standard of care at that time (1998 to 2001). Current day palliative systemic regimens include irinotecan, oxaliplatin, and targeted agents, such as cetuximab and bevacizumab, with significantly improved OS rates. Indeed current survival rates with systemic chemotherapy alone are in the range of 2 years, similar to the experimental arm of the Verwaal study. In PRODIGE 7 [5], a more contemporary study (2008 to 2014) currently published in abstract form, the addition of HIPEC to CRS was evaluated in patients with a PCI score ≤25 and a complete or optimal cytoreduction (≤1 cm residual disease). While this trial failed to demonstrate a survival advantage in the HIPEC group, the inclusion of patients with a high (>15) PCI score (30.1% in the HIPEC arm and 20.5% in the non-HIPEC arm), the short duration of HIPEC infusion (30 minutes versus the standard 90 minutes in other trials), and the use of oxaliplatin, as compared to MMC in the Verwaal trial, may affect the generalizability of the result. An unplanned subgroup analysis suggested an improvement in OS when HIPEC is added to CRS in patients with an intermediate PCI (11 to 15), but because the study was not designed to answer this question, these results should be interpreted with caution. The 36.7% five-year OS following CRS observed in this trial has led to speculation that the major benefit of CRS and HIPEC is in the optimal surgical debulking rather than the HIPEC, at least in the setting of contemporary systemic chemotherapy. When the full results of this trial are published, more information will be available.

Based on these two trials, neither of which had a control arm that is considered current standard of care (5-fluorouracil and leucovorin for the Verwaal study and CRS without HIPEC for the PRODIGE 7 study), the Working Group members concluded there is insufficient evidence to recommend HIPEC with CRS for patients with peritoneal cancer from metastatic peritoneal colorectal carcinomatosis. The differences in the chemotherapy used for HIPEC (MMC versus oxaliplatin) between the Verwaal and PRODIGE studies warrants further discussion. There may be biological rational for choosing MMC over oxaliplatin for HIPEC. The preclinical murine study by Cohen et al. directly compared single agent intraperitoneal chemotherapy with MMC versus oxaliplatin and confirmed that survival was improved with MMC [45]. Moreover, Ubink et al. [46] reported that peritoneal CRC was enriched (75% of peritoneal metastases) in the CMS4 molecular subtype (mesenchymal), and patients with the CMS4 subtypes did not benefit from systemic adjuvant oxaliplatin in the NSABP-C-07 trial [47]. However, retrospective clinical studies have not been able to confirm the superiority of MMC over oxaliplatin [48,49]. Despite this, the American Society of Peritoneal Surface Malignancies has recommended that HIPEC be standardized using MMC at 40mg dose and a temperature of 42 degrees Celsius, for a total duration of perfusion of 90 minutes [50].

In addition, there are two RCTs [8,9], one available in abstract form, that evaluated the use of adjuvant HIPEC in patients with high risk of developing peritoneal recurrence, such as those with T4 or perforated tumours or with minimal resected peritoneal disease. These two studies differ slightly in design. In the ProphyloCHIP trial [9], patients were randomized to second look and HIPEC (with oxaliplatin) versus observation alone following adjuvant systemic chemotherapy, while in the COLOPEC trial [8], patients were randomized to HIPEC (with oxaliplatin) at the time of initial curative resection and patients in both groups also received adjuvant systemic chemotherapy subsequently. Importantly, both trials used oxaliplatin for HIPEC infusion, raising similar issues as those discussed above. Based on these two studies, the

Working Group members concluded that there is insufficient evidence to recommend HIPEC with CRS for the prevention of peritoneal carcinomatosis in CRC but that there is sufficient evidence to recommend against HIPEC with oxaliplatin for this indication. There are five randomized phase III trials that are currently ongoing with study completion dates ranging from June 2019 to April 2024 (Appendix 6, Table A6-2) which will help clarify which components of the treatment and which patients are most likely to yield benefit from CRS and/or HIPEC in this disease.

Gastric Peritoneal Carcinomatosis

HIPEC combined with CRS is not routinely performed in North America for the treatment and prevention of peritoneal dissemination from gastric cancer but it is considered the standard of care in some Asian countries, including China [51]. The only level 1 data include a small (n=68) RCT evaluating the use of CRS plus HIPEC versus CRS alone for patients in China with isolated peritoneal carcinomatosis from gastric cancer, which demonstrated an improvement in median survival from 6.5 months to 11 months (p=0.046) with HIPEC [10]. The study was deemed to have a low risk of bias with the certainty of the evidence being moderate due to the effect estimate coming from one small study. Differences in epidemiology [52,53], including incidence, etiological factors, histological subtypes, response to therapies [54], and overall cancer outcomes, have led some experts to conclude that the biology of gastric cancer differs fundamentally between Asian and non-Asian patients. European and North American cohort studies [55,56] have shown that CRS plus HIPEC has been associated with a prolonged disease-free interval in up to 11% of patients. While provocative, the Working Group members felt that a single RCT, which included only 68 Asian patients, and where the control arm (CRS only) is not the current North American standard of care for peritoneal dissemination of gastric cancer, provided insufficient evidence to recommend the use of CRS and HIPEC in this clinical setting.

In the prophylactic setting for high-risk gastric cancer, four RCTs were included (three from Japan and one from China) [11-14]. While three of the four studies [11-13] reported a survival advantage with the addition of HIPEC to primary gastric cancer surgery, the methodologies of the published trials are unclear resulting in an unclear risk of bias. As mentioned above, the results may not be generalizable to non-Asian patients with gastric cancer. Currently, there are nine randomized phase III trials ongoing with study completion dates ranging between July 2019 and May 2025 (Appendix 6, Table A6-3), which may help determine the use of HIPEC combined with CRS for patients with peritoneal carcinomatosis from gastric cancer.

Mesothelioma

Given the rarity of primary mesothelioma within the abdominal cavity, it is not surprising that high-quality clinical trial data are not available. In the absence of level 1 and comparative evidence, cohort studies that included the use of CRS/HIPEC in a multivariable analysis were sought, which yielded one study [15]. While this study demonstrated significant differences in survival between those receiving CRS plus HIPEC and CRS alone, chemotherapy alone, and observation, no significant differences were found when compared with those who received CRS with chemotherapy. There are no randomized trials currently ongoing in this patient population for the use of HIPEC. The Working Group members acknowledge the challenges that exist in trying to obtain level 1 evidence for the use of HIPEC for this indication; however, standardized treatment approaches at high-volume centres engaged in multi-institutional collaborations will provide survival benchmarks and feasibility data for future comparative studies.

Appendiceal Mucinous Neoplasms

The terminology for appendiceal mucinous neoplasms has changed over the past three decades and differentiating the intraperitoneal mucinous spread originating from a ruptured cystadenoma (low- or high-grade appendiceal mucinous neoplasm) of the appendix from a mucin-producing invasive adenocarcinoma of the appendix is imperative because of the substantial difference in prognosis between these two clinical entities [57]. Unfortunately, many studies include both entities in one review, subsequently confirming that histological variant is a prognostic factor. For the purposes of this review, the Working Group members attempted to evaluate the evidence for the use of CRS and HIPEC for appendiceal mucinous neoplasm with DPAM, often clinically referred to as PMP. While peritoneal spread is generally considered metastatic disease, in these patients the non-invasive histology dictates that this be considered loco-regional disease, confined to the abdominal cavity. These patients have limited options as this relatively indolent disease is poorly responsive to chemotherapy and biologics.

There are no randomized phase III data comparing either CRS alone or systemic chemotherapy to CRS plus HIPEC in PMP. Of the three retrospective studies included, all had a moderate risk of bias and the comparative analysis had a high risk of bias, making the level of certainty for their conclusions low. The data are currently insufficient to recommend CRS and HIPEC but, given the limited alternative treatment options, many patients are still treated with this regimen. Based on the current limited data, the Working Group members strongly encourage high-volume centres to consider participating in clinical trials, particularly isolated to DPAM.

CONCLUSIONS

Peritoneal malignancies include cancers that arise from the lining of the peritoneal cavity (primary peritoneal malignancy, including mesothelioma and serous carcinoma of the peritoneum) and those that have spread to the peritoneum from a primary cancer site within the abdominal cavity (secondary peritoneal malignancy). In order to improve both the survival and QoL for patients, aggressive peritoneal therapies, including CRS and HIPEC, have been introduced. However, there remains a paucity of level 1 evidence in support of this aggressive therapeutic approach within each disease site. Patients with primary epithelial cancer have the most established data resulting in a recommendation. For patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, HIPEC should be considered for those with partial or complete response following neoadjuvant chemotherapy and complete or optimal interval CRS; there is insufficient evidence to recommend the addition of HIPEC with primary CRS when performed outside of a clinical trial. For patients with recurrent ovarian cancer, colorectal or gastric peritoneal carcinomatosis, mesothelioma, or disseminated mucinous neoplasms, there is insufficient evidence to recommend HIPEC with CRS outside of a clinical trial or research protocol. There are currently many ongoing RCTs evaluating the role of HIPEC with CRS in ovarian, colorectal, and gastric cancers with peritoneal dissemination; centres involved in treating patients with peritoneal mesothelioma and disseminated mucinous neoplasms are encouraged to publish treatment data.

Indications for Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 20 members of the GDG Expert Panel, 18 members voted, for a 90% response rate in May 2019. Of those who voted, 16 approved the document (89%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
Draft recommendation: *For patients with newly diagnosed primary, advanced epithelial ovarian cancer, HIPEC should be considered for those with at least stable disease following neoadjuvant chemotherapy at the time of interval CRS if complete or optimal cytoreduction is achieved. There is insufficient evidence to recommend the addition of HIPEC when primary CRS is performed.*	
1. A few reviewers noted that whenever mentioned, ovarian cancer should include ovarian, fallopian tube, and primary peritoneal carcinoma as all three of these entities are treated the same and included in the trial by van Driel et al.	We have modified Recommendation 1 to include fallopian tube and primary peritoneal carcinoma.
2. A suggestion to use the word "may" rather than "should" be considered and to specify this is for newly diagnosed stage III ovarian cancer.	We have decided to keep the recommendation worded as 'should be considered' due to the evidence available but have modified it to specify stage III patients.
3. There needs to be some clarity on when HIPEC should be performed in relationship to CRS, is it being suggested to perform CRS and then come back another day for HIPEC?	We have split Recommendation 1 into Recommendation 1a and Recommendation 1b and believe that will add clarity.
4. It may be useful to add uterine cancer and the role of CRS with HIPEC. There are currently no RCTs but there have been a few reports on this for advanced and metastatic uterine cancer and sarcomas. Numbers are very small so that you cannot comment further on how useful this procedure would be.	This guideline focuses on ovarian cancer and uterine cancer is outside the scope.
5. It may be worth adding that there is an ongoing trial of CRS with HIPEC in patients with primary and secondary peritoneal cancers. ClinicalTrials.gov Identifier: NCT03604653.	We have now included this trial in the Ongoing Trials sections.

6. HIPEC should be still offered as part of clinical trial, as debate remains and further investigations are needed. If no trial is available, HIPEC may be considered in this specific population as described in the recommendations but offered by a dedicated trained team and data should be collected rigorously.	We have added the following in the Implementation Considerations section, "HIPEC should be offered by a dedicated team and patients should be presented at a multidisciplinary cancer conference to ensure they meet the appropriate criteria." We have also specified that HIPEC with CRS is not recommended outside of a clinical trial or a research protocol within the recommendations for each site.
7. Do we know what centres in Ontario are doing HIPEC for ovarian cancer? Will this be a change in practice?	We have added the following in the Implementation Considerations section, "Currently, HIPEC is performed for primary ovarian cancer in Ontario as part of a study protocol. Most often HIPEC is performed in Ontario for patients with peritoneal colorectal carcinomatosis and other high- and low-grade gastrointestinal cancers. A small number of peritoneal mesothelioma cases are performed each year."
Draft recommendation: *There is insufficient evidence to recommend CRS with HIPEC in patients with recurrent ovarian cancer.*	
8. What makes the results of the RCT by Spiliotis et al. put into question? This RCT shows benefit for HIPEC and oncology drugs with less absolute benefit have been approved. Further explanation and details as to why the significant difference does not count is needed.	We have modified the Key Evidence for this recommendation to read, "Although this trial reported itself as a phase III RCT, it presents unclear methods and statistical analyses questioning its validity; results should be interpreted with caution. Further, it was not found in any clinical trial registry."
Draft recommendation: *There is insufficient evidence to recommend CRS with HIPEC in patients with metastatic colorectal cancer.*	
9. The Verwaal et al. 2003 study is quite outdated and in the PRODIGE 7 abstract it is stated that patients with low-volume peritoneal disease should just have cytoreduction – does this give the green light for centres where there is expertise to proceed with cytoreduction in patients where there is low PCI metastases? A comment can be made that a PCI score of greater than 15 is too high and may not get benefit and this would be in line with the many cohort studies that have already shown that a PCI greater than 20 has a poor outcome.	This guideline does not evaluate the role of CRS alone in these patient populations, but rather the role of HIPEC with CRS. We have inserted a note clarifying this. Data from the PRODIGE 7 trial are currently only available in abstract form and data from abstracts are insufficient to inform recommendations. The relative difference in benefit depending on PCI score is reviewed in the Discussion.
Draft recommendations: *There is insufficient evidence to recommend CRS with HIPEC for the treatment of gastric peritoneal carcinomatosis.*	

There is insufficient evidence to recommend CRS with HIPEC for the prevention of gastric peritoneal carcinomatosis.	
10. Gastric cancer in the Asian population is very different than the Canadian population but we do not exactly know why or how just yet and so there may be some Asians in Canada that may benefit and again some very highly selected Canadians that may benefit?	It has been shown in previous studies that once individuals from Asia move to North America that their response to therapy and incidence rates of gastric cancer are more in line with what is observed in North American populations. As a result, we have decided to keep the statement as is.
Draft recommendation: *There is insufficient evidence to recommend CRS with HIPEC in patients with peritoneal mesothelioma.*	
11. I would hate to go back to the days where these patients no longer get referrals to expert centres that should still be evaluating this and potentially providing good care on a case-by-case basis, especially in this rare disease where there will likely never be a RCT. It would be false to say there is no effective option in this patient population when we have seen many that have had benefit. Would the Working Group be willing to provide some qualifying statements about review at multidisciplinary cancer conference and referral to expert centres in these cases?	We have added the following qualifying statement to this recommendation, "The Working Group members recommend prospective research protocols with standardized treatment approaches at high-volume centres as this will provide survival benchmarks and feasibility data for future comparative studies." We have also modified the recommendation to read, "There is insufficient evidence to recommend HIPEC with CRS in patients with malignant peritoneal mesothelioma as a standard of care; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol." Further, we have also added the following in the Implementation Considerations section, "HIPEC should be offered by a dedicated team and patients should be presented at a multidisciplinary cancer conference, or at AGOC for ovarian cancer, to ensure they meet the appropriate criteria."
Draft recommendation: *There is insufficient evidence to recommend CRS with HIPEC in patients with disseminated mucinous neoplasm in the appendix.*	
12. The evidence for mucinous tumours is quite similar to the evidence for mesothelioma and for mucinous tumours the Working Group has a qualifying statement saying it can be considered despite a lack of an RCT but they do not feel the same way for mesothelioma?	We have modified the qualifying statement to this recommendation, "The Working Group members recommend prospective research protocols with standardized treatment approaches at high-volume centres as this will provide survival benchmarks and feasibility data for future comparative studies." We have also modified the recommendation to read, "There is insufficient evidence to recommend HIPEC with CRS in patients with disseminated mucinous neoplasm in the appendix as a standard of care; however, patients should be referred to HIPEC specialty

	centres for assessment for treatment as part of an ongoing research protocol."
General Comments	
13. For most areas of surgery including this topic, there is insufficient evidence in terms of randomized trials or similar to recommend intervention, yet these treatments are the standard of care. For example, liver or lung resection of colorectal metastases is the standard of care when possible despite no RCTs. In an area such as CRS and HIPEC, I do feel this therapy should still be considered on a case-by-case basis in a specialized centre (e.g., in this case Toronto) where there is follow-up of outcomes.	It was decided a priori for the methodology of this guideline that recommendations would be based on the best available evidence. The initial search would be for RCTs, and if no RCTs were found then a search would be conducted for prospective and retrospective comparative studies, where confounders are controlled for with ≥30 participants.
14. If other metastasectomy guidelines utilize evidence weaker than RCTs for recommendations (for example, liver resection in colorectal cancer), this guideline should be the same.	It was decided a priori for the methodology of this guideline that recommendations would be based on the best available evidence. The initial search would be for RCTs, and if no RCTs were found then a search would be conducted for prospective and retrospective comparative studies, where confounders are controlled for with ≥30 participants.
15. A few reviewers provided references of cohort studies stating that those could provide more meaningful information in informing recommendations.	It was decided a priori for the methodology of this guideline that recommendations would be based on the best available evidence. The initial search would be for RCTs, and if no RCTs were found then a search would be conducted for prospective and retrospective comparative studies, where confounders are controlled for with ≥30 participants.
16. Abstracts should not be used to serve as evidence, even if they are for RCTs. Unless the data are published it should not be used as evidence to inform recommendations.	The Working Group members agree and have not used data from abstracts of RCTs to make any recommendations. The results of the abstract are reported as they were found in the systematic review search. As the full publication becomes available, the guideline will be updated.
17. For most of the cancer types (except ovarian) the guideline says there is not enough evidence to recommend CRS with HIPEC. To me this also means there is not enough evidence to recommend against it. In all of these cases it seems more evidence is needed. I suggest the guideline be revised to include both i.e., there is not enough evidence to recommend for or against CRS and HIPEC for colorectal cancer (as one example).	The Working Group members discussed this and have decided to keep the existing wording as for or against means one could perform it as a standard of care treatment and the Working Group concluded that the data was insufficient to support that recommendation. We have added that HIPEC with CRS is not recommended outside the context of a clinical trial/research protocol within the recommendation to place an emphasis on rigorous evaluation of the therapies.

RAP Review and Approval

Three RAP members reviewed this document in May 2019. The RAP approved the document in May 2019. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. For recommendation 3 and 4 there are signals that some populations (i.e., those who are Asian) may benefit. HIPEC is offered in Toronto where there are a million plus Asians (by birth they lived there, or first generation, or later). A do-not-recommend statement would apply if population differences can be linked to lifestyle or diet versus genetics/biological variation as a function of race/culture. Do we know anything about that? Is the recommendation statement unintentionally risking health inequities because North American population is conceptualized as primarily western European?	It has been shown in previous studies that once individuals from Asia move to North America that their response to therapy and incidence rates of gastric cancer are more in line with what is observed in North American populations. As a result, we have decided to keep the statement as is.
2. The framing of the recommendations for ovarian cancer somewhat difficult to follow.	We have split Recommendation 1 into Recommendation 1a and Recommendation 1b and believe that will add clarity.

Patient and Caregiver-Specific Consultation Group

Five patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its

comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Consultation Group.

Comments	Responses
1. The Consultation Group felt the Working Group took into consideration the issues and outcomes that would be important to patients as many factors aside from the results were looked at when forming recommendations.	Thank you for your comment.
2. The Consultation Group felt that the "insufficient evidence" recommendations are left open to interpretation by physicians.	The Working Group has added that HIPEC with CRS is not recommended outside the context of a clinical trial/research protocol within the recommendation for each of the sites to add clarity.
3. The Consultation Group noted that many acronyms were not defined in Section 2 making it difficult for the non-clinicians to read.	The Working Group has now defined all acronyms used in Section 2.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Seven targeted peer reviewers from Ontario, Quebec, Nova Scotia, Europe and the United States who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 1). Two responses were received. Results of the feedback survey are summarized in Table 5-4. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the Targeted Peer Reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	1	0	0	1
2. Rate the guideline presentation.	0	0	0	1	1
3. Rate the guideline recommendations.	0	1	0	0	1
4. Rate the completeness of reporting.	0	0	1	0	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	1	0	0	0	1
6. Rate the overall quality of the guideline report.	0	1	0	0	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	1	0	0	1
8. I would recommend this guideline for use in practice.	0	1	0	0	1
9. What are the barriers or enablers to the implementation of this guideline report?	None were stated by the reviewers.				

Table 5-5. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	**Responses**

1. Decisions made a priori on types of studies to include and exclude do not reflect the totality of the literature on this topic and impose a higher standard of evidence for this surgical procedure than any other surgical procedure and requires a level of data that will never be achieved.	It was decided a priori for the methodology of this guideline that recommendations would be based on the best available evidence, which is the same process/methodology that we follow for all current guidelines, including any with surgical procedures. The initial search would be for RCTs, and if no RCTs are found then a search would be conducted for prospective and retrospective comparative studies, where confounders are controlled for with ≥30 participants. Compared with the number of trials included, the number of ongoing trials is large and as such the recommendations will be reviewed annually as newer evidence becomes available.
2. In the colorectal section, much emphasis is placed on PRODIGE 7 (available only in abstract form) and its negative outcomes but not enough on the limitations of the study. Similarly, the conclusion that HIPEC as a whole is not recommended based on a study that used one regimen of HIPEC is too sweeping (one would never say systemic chemotherapy as a whole is not recommended based on one negative study of one regimen).	Within the Discussion, the limitations of the PRODIGE 7 trial, from what is available from the abstract, are discussed. Based on the two trials available for peritoneal colorectal cancer, the recommendation is not negative; it is recommending that if HIPEC/CRS is performed then it should be done within the context of a clinical trial.
3. In the Key Evidence for Recommendation 4, one of the two bullet points refers to a single patient in a single study that developed peritoneal sclerosis. How can one single patient in one study be emphasized as "key evidence" informing a recommendation?	These were the only available data regarding adverse events available in the abstract and as a result were placed under the Key Evidence; however, the reviewer's concern is noted and the bullet point has been removed.
4. The reviewer does not feel it is appropriate that the conclusions of the Verwaal study (in colorectal) are completely discounted because contemporary systemic chemotherapy was not used.	The Working Group disagrees as the survival rates in the control group in the Verwaal study were not what is expected with current systemic treatment. Given improvements in survival with current best systemic chemotherapy, it is only appropriate to compare new interventions with best practice.
5. Adding that the results of combining HIPEC and interval cytoreduction surgery following neoadjuvant chemotherapy should be registered would enable an evaluation of this new therapeutic approach.	The Working Group agrees and has added the following Qualifying Statement to the recommendation, "The Working Group members recommend prospectively collecting data on these patients to evaluate real world outcomes and applicability."
6. The statement "patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol" should be	The Working Group disagrees as conducting an RCT for colorectal, gastric and ovarian is feasible given the number of patients. For peritoneal mesothelioma and disseminated

attached to all the recommendations (including colorectal, gastric and ovarian), not just mesothelioma and appendiceal mucinous neoplasms, rather than suggesting a clinical trial for colorectal and gastric.	mucinous neoplasm in the appendix, it is not feasible to conduct a clinical trial and as a result outcome data can be collected as part of an ongoing research protocol.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All surgical oncologists and medical oncologists in gastrointestinal cancers and clinicians with an interest in ovarian cancers or mesothelioma in the PEBC database were contacted by email to inform them of the survey. Seventy-six professionals were contacted, all of which practice in Ontario. Fourteen (18.4%) responses were received. Three stated that they did not have interest in this area or were unavailable to review this guideline at the time; one stated they were now retired; and one did not want to participate in Professional Consultation. The results of the feedback survey from nine people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	N=9 (11.8%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	1	1	7
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	1	0	3	5
3. I would recommend this guideline for use in practice.	0	0	2	2	5
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers • Resources and availability • Timely access to the doctors who perform the procedure • Education for patients and families				

Table 5-7. Summary of the Working Group's responses to comments from professional consultants.

Comments	**Responses**
1. This may become one of the more	Thank you for your comment.

politicized guidelines given the current status of HIPEC utilization in Ontario. That said, this is the evidence and the guidelines are objective.	
2. Regarding the recommendations for peritoneal colorectal and gastric carcinamatosis, the position that CRS/HIPEC is not recommended outside of a clinical trial has a number of issues: 1) Across Canada CRS/HIPEC is available, 2) Is it realistic that new trials will actually happen in this area, and 3) From a clinician point of view, the guideline says clinical trial, but the reality is this is happening in Ontario at present. The guideline needs to conclude what the available evidence provides, but also needs conclusions that may actually impact practice.	While there are no clinical trials in Canada, there are a large number of trials happening around the world as noted in the Ongoing Trials section. As these data become available, the recommendations will be updated appropriately. Canadian centres are encouraged to participate in these ongoing trials or start their own.
3. The term 'surgery' seems to be used Interchangeably with 'CRS' in places, but this is not the case.	The guideline reports interventions in the same manner as the journal articles. Appendix 5 provides details of the studies selected for inclusion.
4. For the peritoneal colorectal carcinomatosis recommendation, under Interpretation of the Evidence, the statement, "Recommendations could not be made since the control arms of both trials are not representative of current oncological practices resulting in outcomes that are not generalizable to current practice." – is a comment the reviewer strongly disagrees with as much of what is done is based on evidence that is from a prior era when different backbone chemotherapy drugs were used. If evidence was only applied from contemporary co-interventions, there would be little evidence for anything.	The Working Group disagrees as the survival rates in the control groups would not be what are expected with current systemic treatment. Given improvements in survival with current best systemic chemotherapy, it is only appropriate to compare new interventions with best practice.
5. For the recommendations regarding peritoneal mesothelioma and disseminated mucinous neoplasm in the appendix, the Qualifying Statement "recommend prospective research protocols with standardized treatment approaches at high-volume centres" – the reviewer feels this should be applied to all of the other areas where the group has concluded there is insufficient evidence and that patients should be encouraged to	The Working Group disagrees as conducting an RCT for colorectal, gastric and ovarian is feasible given the number of patients. For peritoneal mesothelioma and disseminated mucinous neoplasm in the appendix, it is not feasible to conduct a clinical trial and as a result outcome data can be collected as part of an ongoing research protocol.

enrol in trials for all areas where there is insufficient evidence.	

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table A1-1: Working Group Members

Name	Affiliation	Conflict of Interest
Rebecca Auer Surgical Oncologist	Ottawa Hospital Ottawa, ON	Published an article in the Ottawa Citizen on regional chemotherapy with no strong opinion which is peripherally related to this guideline
Jim Biagi Medical Oncologist	Cancer Centre of Southeastern Ontario Kingston, ON	No conflict of interest declared
James Conner Pathologist	Mount Sinai Hospital Toronto, ON	No conflict of interest declared
Erin Kennedy Surgical Oncologist	Mount Sinai Hospital Toronto, ON	Provided the dissenting opinion on Recommendation 3; works at Mount Sinai Hospital which is the Provincial Program for Peritoneal Disease, however does not perform HIPEC and CRS in her current clinical practice.
Taymaa May Gynecologic Oncologist	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Duvaraga Sivajohanathan Health Research Methodologist	Program in Evidence-Based Care, Cancer Care Ontario McMaster University Hamilton, ON	No conflict of interest declared

Table A1-2: Report Approval Panel

Name	Affiliation	Conflict of Interest
Melissa Brouwers Professor & Director	School of Epidemiology and Public Health University of Ottawa Ottawa, ON	No conflict of interest declared
William (Bill) Evans Medical Oncologist	Oncosynthesis Consulting Inc.	No conflict of interest declared
Jonathan Sussman Scientific Director Radiation Oncologist	Juravinski Cancer Centre Program in Evidence-Based Care, Cancer Care Ontario McMaster University Hamilton, ON	No conflict of interest declared

Table A1-3: Expert Panel Members

Name	Affiliation	Conflict of Interest
Tim Asmis Medical Oncologist	Ottawa Hospital Toronto, ON	No conflict of interest declared
Fady Balaa Surgical Oncologist	Ottawa Hospital Toronto, ON	No conflict of interest declared
Genevieve Bouchard-Fortier Gynecologic Oncologist	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Laura Donahoe Surgeon	Toronto General Hospital Toronto, ON	No conflict of interest declared
Laurie Elit Surgical Oncologist	Juravinski Cancer Centre Hamilton, ON	No conflict of interest declared
Lua Eiriksson Gynecologic Oncologist	Juravinski Cancer Centre Hamilton, ON	No conflict of interest declared
Wylam Faught Gynecologic Oncologist	Ottawa Hospital Toronto, ON	No conflict of interest declared
Sarah Ferguson Gynecologic oncologist	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Valerie Francescutti Surgical Oncologist	Hamilton General Hospital Hamilton, ON	Has been the principal investigator (PI) of a study assessing the patient experience for patients that had previously undergone the CS/HIPEC procedure to assess any area for improvement in patient education, patient pathways, etc., through qualitative interviews. The study is closed and has already been presented.
Prafull Ghatage Gynecologic Oncologist	Tom Baker Cancer Centre Calgary, AB	No conflict of interest declared
Erika Haase Surgical Oncologist	Edmonton, AB	No conflict of interest declared
Calvin Law Surgical Oncologist	Odette Cancer Centre Toronto, ON	Has received $5,000 or more in a single year to act in a consulting capacity for Amgen, Novartis and Ipsen; has received $5,000 or more in travel expenses supported by Taiho; is Chief of the Odette Cancer Program, where faculty staff have received support from Amgen and Elekta
Stephanie Lhereux	Princess Margaret Hospital Toronto, ON	Co-investigator of several clinical trials in gynaecological cancers; primary

Medical Oncologist		investigator of clinical trials of relevance from Roche, Astra-Zeneca
Lloyd Mack Surgical Oncologist	Tom Baker Cancer Centre Calgary, AB	Has been the PI for a clinical trial involving the objects of study and has been a co-author on a guideline article published regarding the use of HIPEC. 1. Hyperthermic intraperitoneal chemotherapy + early postoperative intraperitoneal chemotherapy versus hyperthermic intraperitoneal chemotherapy alone: assessment of survival outcomes for colorectal and high-grade appendiceal peritoneal carcinomatosis. Lam JY, McConnell YJ, Rivard JD, Temple WJ, Mack LA. Am J Surg 2015;210(3):424-30 2. Dubé P, Sideris L, Law C, Mack L, Haase E, Giacomantonio C, Govindarajan A, Krzyzanowska MK, Major P, McConnell Y, Temple W, Younan R, McCart JA. Curr Oncol 2015; 22(2): e100-12
Donna Maziak Surgeon	Ottawa Hospital Toronto, ON	No conflict of interest declared
Andrea McCart Surgical Oncologist	Mount Sinai Health System Toronto, ON	Professionally income may increase or decrease by substantially more than $10,000 per year depending on the outcome of the guideline and whether it changed referrals to the program; has been a co-author on a guideline article published regarding the use of HIPEC and has provided an overview of the program via an interview to The Toronto Star regarding the Peritoneal Malignancy Program. 1. Dubé P, Sideris L, Law C, Mack L, Haase E, Giacomantonio C, Govindarajan A, Krzyzanowska MK, Major P, McConnell Y, Temple W, Younan R, McCart JA. Curr Oncol 2015; 22(2): e100-12 2. https://www.thestar.com/life/health_wellness/2015/04/05/mount-sinai-offers-novel-treatment-for-abdominal-cancer.html
Jacob McGee Gynecologic Oncologist	London Health Sciences Centre London, ON	Has received $5,000 or more in a single year from Astra Zeneca in speaker fees and as a member of the drug advisory board;

		owns shares valued at $50,000 or more in Oncolytics Biotech; has received a grant as a PI or co-PI from Astra Zeneca to conduct a validation study of tumour testing
Carolyn Nessim Surgical oncologist	Ottawa Hospital Toronto, ON	No conflict of interest declared
Marc de Perrot Surgeon	Princess Margaret Hospital Toronto, ON	Has received grants or other research support as a PI or co-PI from Bayer for pulmonary hypertension
Frances Wright Surgical Oncologist	Surgical Oncology Program, Cancer Care Ontario Toronto, ON	No conflict of interest declared

Table A1-4: Members of the Patient Consultation Group

Name	**Conflict of Interest**
Lise Craig	No conflict of interest declared
Marissa Myers	No conflict of interest declared
Lauri Petz	No conflict of interest declared
Bob Tuck	No conflict of interest declared
Laurel Warr	No conflict of interest declared

Table A1-5: Targeted Peer Reviewers

Name	**Affiliation**	**Conflict of Interest**
Anand Govindarajan Surgical Oncologist	Mount Sinai Health System Toronto, ON	Is unsure if professional income can increase or decrease by substantially more than $10,000 per year as he surgically treats peritoneal malignancies; has been the PI of a study and is currently the PI of another study that includes patients who have undergone CRS-HIPEC; and is a co-author on a Canadian consensus guideline on the application of CRS-HIPEC.
Willemien J van Driel Surgical Oncologist	Netherlands Cancer Institute Amsterdam, Netherlands	Has been the PI for a clinical trial involving the objects of study (OVHIPEC 1) and will be the PI for the OVHIPEC 2 trial beginning in 2020 with funding by the Dutch Cancer Foundation; has authored a publication based on the OVHIPEC 1 trial; and has been involved in writing the evidence-based guidelines on HIPEC in the Netherlands 1. Van Driel WJ, Koole SN, Sikorska K, SchagenvanLeeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230-40

Appendix 2: Literature Search Strategy

MEDLINE
1 (systematic adj (review: or overview:)).mp. (123133)
2 (meta-analy: or metaanaly:).mp. (157266)
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (9477)
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (120180)
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (172345)
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
(38199)
7 or/1-6 (333659)
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic:quality).ab. (63562)
9 (stud: adj1 select:).ab. (21282)
10 (8 or 9) and review.pt. (42750)
11 7 or 10 (338032)
12 (guideline or practice guideline).pt. (30609)
13 exp consensus development conference/ (10967)
14 consensus/ (8862)
15 (guideline: or recommend: or consensus or standards).ti. (142211)
16 12 or 13 or 14 or 15 (161971)
17 11 or 16 (490852)
18 HIPEC.mp. (1433)
19 ((hyperthermic or heated) adj3 intraperitoneal adj3 chemotherapy).mp. (1711)
20 (intraperitoneal adj2 chemohyperthermia).mp. (66)
21 (thermochemotherapy adj3 intraperitoneal).mp. (3)
22 ((hyperthermic or chemohyperthermic) adj3 (perfusion or chemoperfusion)).mp. (850)
23 18 or 19 or 20 or 21 or 22 (2721)
24 exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp. (934714)
25 23 and 24 (283)
26 25 not 17 (244)
27 (comment or letter or editorial or news or newspaper article or patient education handout or case reports or historical article).pt. (3829016)
28 26 not 27 (231)
29 exp animals/ not humans/ (4464699)

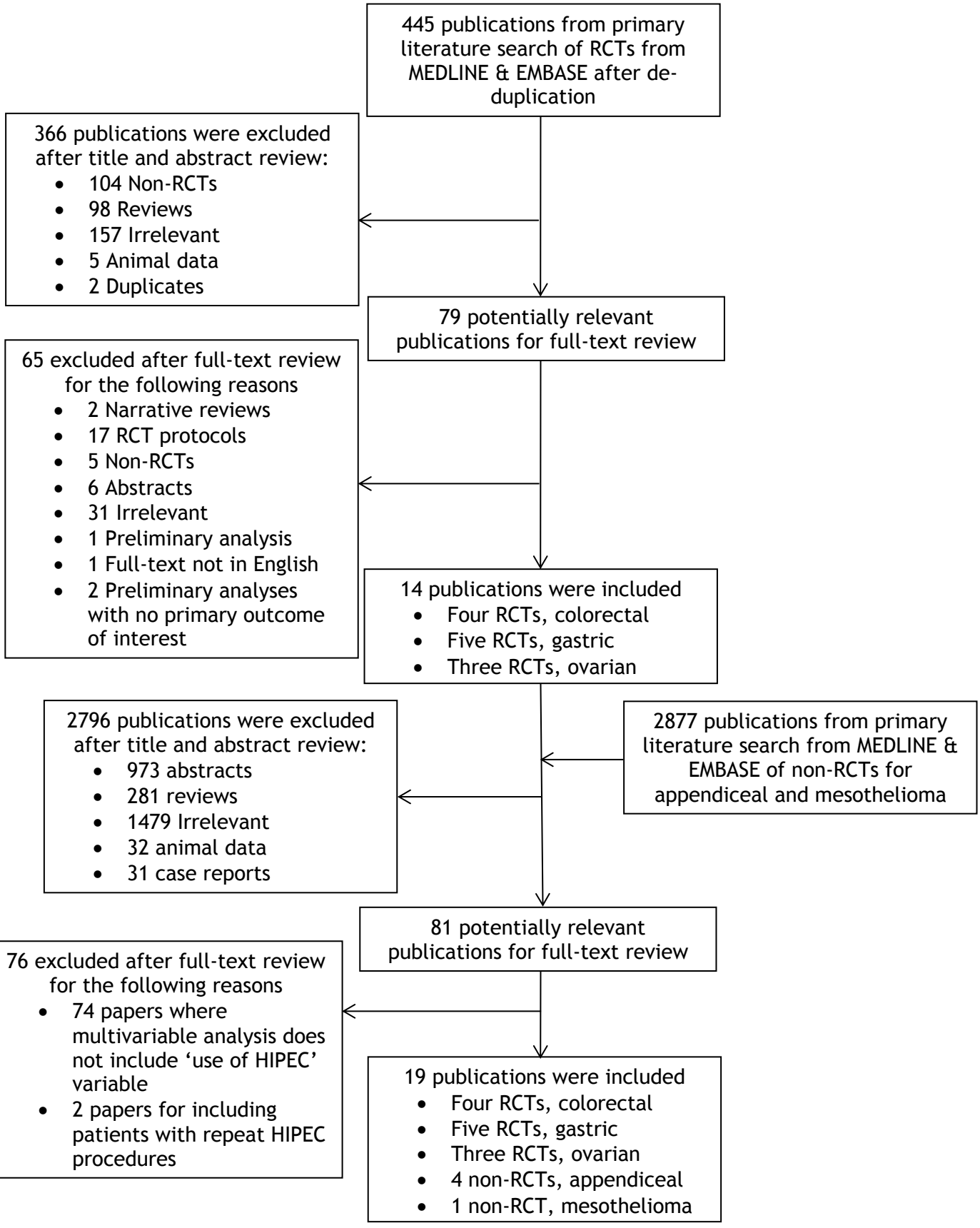
30 28 not 29 (222)
31 limit 30 to (english language and yr="1985 -Current") (195)

EMBASE

1 (systematic adj (review: or overview:)).mp. (230997)
2 (meta-analy: or metaanaly:).mp. (234581)
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (14522)
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (159400)
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (211835)
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. (47143)
7 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (80817)
8 (stud: adj1 select:).ab. (26234)
9 (7 or 8) and review.pt. (38349)
10 or/1-6 (474975)
11 9 or 10 (479455)
12 consensus development conference/ (22865)
13 practice guideline/ (339072)
14 *consensus development/ or *consensus/ (8334)
15 *standard/ (4377)
16 (guideline: or recommend: or consensus or standards).kw. (44492)
17 (guideline: or recommend: or consensus or standards).ti. (179755)
18 or/12-17 (476684)
19 HIPEC.mp. (2458)
20 ((hyperthermic or heated) adj3 intraperitoneal adj3 chemotherapy).mp. (2814)
21 (intraperitoneal adj2 chemohyperthermia).mp. (97)
22 (thermochemotherapy adj3 intraperitoneal).mp. (3)
23 ((hyperthermic or chemohyperthermic) adj3 (perfusion or chemoperfusion)).mp. (1150)
24 19 or 20 or 21 or 22 or 23 (4211)
25 exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp. (1271885)
26 24 and 25 (480)
27 (editorial or note or letter or short survey).pt. or letter/ or case study/ (2704230)
28 26 not 27 (454)
29 animal/ not human/ (1407692)

30 28 not 29 (452)
31 11 or 18 (922651)
32 30 not 31 (358)
33 limit 30 to (english language and yr="1985 -Current") (311)

Appendix 3: PRISMA Flow Diagram



Appendix 4: Risk of Bias and Quality Assessment

Table A4-1: Risk of Bias for Included Randomized Controlled Trials Assessed Using Cochrane's Risk of Bias Tool

Trial	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Ovarian Cancer							
Lim et al. (2017) [3] Abstract	?	?	-	-	?	+	+
Spiliotis et al. (2015) [4]	?	?	-	-	?	?	?
van Driel et al. (2018) [1]	+	?	-	-	+	+	+
Peritoneal colorectal carcinomatosis							
Klaver et al. (2019) [8] COLOPEC	+	+	-	-	+	+	+
Goere et al. (2018) [9] ProphyloCHIP Abstract	?	?	-	-	?	+	+
Quenet et al. (2018) [5] PRODIGE 7 Abstract	?	?	-	-	?	+	+
Verwaal et al (2003) [7] (2008) [6]	+	+	-	-	+	+	+
Gastric peritoneal carcinomatosis							
Yang et al. (2011) [10]	+	+	-	-	+	+	+
Cui et al. (2014) [11]	?	?	-	-	+	+	+
Yonemura et al. (2001) [12]	?	?	-	-	+	?	+
Fujimoto et al. 1998) [13]	?	?	-	-	+	?	+
Hamazoe et al. (1993) [14]	?	?	-	-	+	?	+

Table A4-2: Risk of Bias for Included Non-Randomized Studies Assessed Using Cochrane's ROBIN-I

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Mesothelioma								
Verma et al. (2018) [15]	Serious	Low	Moderate	Low	Moderate	Low	Low	Serious
Appendiceal								
Jarvinen et al. (2014) [16]	Serious	Low	Moderate	Low	Low	Low	Low	Serious
Sinukumar et al. (2019) [17]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Chua et al. (2012) [18]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Chua et al. (2009) [19]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Glehen et al. (2004) [20]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate

Table A4-3: Quality Assessment of Included RCTs

Study	Primary outcome	Randomization details	Statistical power and required sample size	ITT analysis	Baseline characteristics balanced	Loss to follow-up (# of pts)	Withdrawals	Industry funding	Terminated early
Ovarian cancer									
Lim et al. (2017) [3] Abstract	PFS, OS	Unclear	NR	NR	Yes	NR	NR	NR	No
Spiliotis et al. (2015) [4]	Mean OS	Randomized using GraphPad software into 2 groups with similar demographic, clinical and therapeutic features	Power analysis yielded a minimum of 33 patients	NR	Yes	NR	NR	NR	No
van Driel et al. (2018) [1]	RFS	Randomization was performed with the use of a minimization procedure with stratification according to previous surgery, surgical hospital, and number of involved regions in the abdominal cavity	80% power to detect 50% longer RFS in the surgery+HIPEC group than in the surgery group when α=0.05; 245 patients with sufficient follow-up for observation of 192 events of recurrence, progression or death	Yes	Yes	Three patients were lost to follow-up	One in the control group	No	No
Peritoneal colorectal carcinomatosis									
Klaver et al. (2019) COLOPEC [8]	18-mth PMFS	Block randomization was done centrally by CELK using a web-based randomization application, stratified by tumour characteristics (T4 or perforation), surgical resection of the primary tumour (laparoscopic or open), and age (<65 years or ≥ 65 years)	80% power to detect a 60% relative risk reduction (18-mth PMFS of 90% in the experimental group) when α=0.05 with a dropout rate of 5%; a minimum of 176 patients (88 in each group) needed	Yes	Yes	No	Two in the HIPEC arm	No	No
Goere et al. (2018)	3-year DFS	NR	NR	NR	NR	NR	NR	NR	No

Study	Primary outcome	Randomization details	Statistical power and required sample size	ITT analysis	Baseline characteristics balanced	Loss to follow-up (# of pts)	Withdrawals	Industry funding	Terminated early
Prophylo CHIP [9] Abstract									
Quenet et al. (2018) [5] PRODIGE 7 Abstract	OS	Unclear, stratified by centre, complete macroscopic resection (R0/1 vs R2) and neoadjuvant systemic therapy	80% power to show a gain in median OS from 30 to 48 mths (HR=0.625) when α=0.046; 264 patients required	NR	Yes	NR	NR	NR	No
Verwaal et al (2003) (2008) [6,7]	DSS	Randomized centrally by computer and stratified for presentation (primary or recurrence) and site (appendix, colon or rectum).	80% power to detect a 20% absolute difference in survival with $p<0.05$; 100 patients required	Yes	Yes	None	Five in control group and one in the HIPEC group	No	No
Gastric peritoneal carcinomatosis									
Yang et al. (2011) [10]	OS	Computer-generated randomized	80% power to show a gain in median OS from 30 to 48 mths (HR=0.625) when α=0.046; 264 patients required	Yes	Yes	No	None	NR	No
Cui et al. (2014) [11]	OS and PFS	NR	NR	Yes	Yes	4 patients	No	NR	No
Yonemura et al. (2001) [12]	OS	NR	NR	Yes	Yes	No	No	NR	No
Fujimoto et al. (1998) [13]	OS	NR	NR	Yes	Yes but serosal invasion was significantly more advanced in HIPEC arm (p=0.0405)	No	No	NR	No
Hamazoe et al.	OS	Random sampling	NR	Yes	Yes	No	No	NR	No

Study	Primary outcome	Randomization details	Statistical power and required sample size	ITT analysis	Baseline characteristics balanced	Loss to follow-up (# of pts)	Withdrawals	Industry funding	Terminated early
(1993) [14]									

Abbreviations: DSS: disease-specific survival; HIPEC: hyperthermic intraperitoneal chemotherapy; ITT: intention-to-treat; mths: months; NR: not reported; OS: overall survival; PFS: progression-free survival: pts: patients; RCT: randomized controlled trial; PMFS: peritoneal metastases-free survival; RFS: recurrence-free survival

Appendix 5. Details of Included Studies

A5-1: Details of studies selected for the use of HIPEC with CRS in patients with ovarian cancer

Lim et al (2017) [3] Abstract	*Inclusion criteria:* Women with primary advanced (staged III and IV) epithelial ovarian cancer.
	Exclusion criteria: NR
	Treatment arms: Surgery + HIPEC versus surgery alone
	HIPEC regimen: NR
Spiliotis et al. (2015) [4]	*Inclusion criteria:* Women aged between 18 and 70 years with recurrent epithelial ovarian cancer; GOG PS 1-2; no evidence of disease beyond the abdomen; and no splanchnic metastasis.
	Exclusion criteria: GOG PS 3-4, evidence of pleural or lungs metastasis; more than 3 sites of bowel obstruction; and evidence of bulking disease in retroperitoneal or on the mesentery.
	Treatment arms: CRS + HIPEC + systemic therapy versus CRS + systemic chemotherapy
	HIPEC regimen: For platinum-sensitive disease: cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 delivered for 60 min at 42.5°C; for platinum-resistant disease: doxorubicin 35 mg/m^2 and (paclitaxel 175 mg/m^2 or mitomycin 15 mg/m^2) delivered for 60 min at 42.5°C. In 40 patients, HIPEC was performed using the open (coliseum) technique, while on the remaining 20 the closed technique was performed.
	Systemic chemotherapy regimen: NR
van Driel et al. (2018) [1]	*Inclusion criteria:* Newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer and were referred for neoadjuvant chemotherapy because abdominal disease was too extensive for primary CRS or because surgery had been performed but was incomplete; WHO PS 0-2; normal blood counts and adequate renal function.
	Exclusion criteria: NR
	Treatment arms: CRS + HIPEC versus CRS
	HIPEC regimen: HIPEC was administered with the use of the open technique. The abdomen was filled with saline that circulated continuously with the use of a roller pump through a heat exchanger. By circulation of the heated saline, an intra-abdominal temperature of 40°C (104°F) was maintained. Perfusion with cisplatin at a dose of 100 mg/m^2 and at a flow rate of 1 liter/minute was then initiated (with 50% of the dose perfused initially, 25% at 30 min, and 25% at 60 min). The perfusion volume was adjusted

	such that the entire abdomen was exposed to the perfusate. The HIPEC procedure took 120 min in total. To prevent nephrotoxicity, sodium thiosulphate was administered at the start of perfusion as an intravenous bolus (9 g/m^2 in 200 ml) followed by a continuous infusion (12 g/m^2 in 1000 ml) over 6 hours.
	Systemic chemotherapy regimen: Three cycles of carboplatin and paclitaxel after surgery.

Abbreviations: CRS: cytoreductive surgery; GOG: Gynecologic Oncology Group; HIPEC: hyperthermic intra-peritoneal chemotherapy; min: minute NR: not reported; PS: performance status; WHO: World Health Organization

Table A5-2: Details of studies selected for the use of HIPEC with CRS in patients with peritoneal colorectal carcinomatosis

Klaver et al. (2019) COLOPEC [8]	*Inclusion criteria:* Patients with resectable primary clinical or pathological T4N0–2M0 stage or perforated colon cancer between 18 and 75 years, adequate clinical condition for HIPEC (according to the evaluation of the physician), and intention to start adjuvant systemic chemotherapy.
	Exclusion criteria: Patients with neuroendocrine tumours and those with microsatellite instability stage II tumours.
	Treatment arms: CRS + adjuvant HIPEC with oxaliplatin + adjuvant systemic therapy versus adjuvant systemic therapy
	HIPEC regimen: HIPEC was done by either a laparoscopic or open approach. A bidirectional HIPEC protocol was used: fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) were delivered intravenously followed by HIPEC using oxaliplatin (460 mg/m^2) in a single dose for 30 min at a temperature of 42–43°C.
	Adjuvant systemic chemotherapy regimen: Six months of capecitabine and oxaliplatin every 3 weeks or fluorouracil and oxaliplatin every 2 weeks, which preferably started within 6–8 weeks, but no later than 12 weeks, after primary tumour resection.
Goere et al. (2018) ProphyloCHIP [9] Abstract	*Inclusion criteria:* Patients at high risk of developing colorectal peritoneal metastases defined as minimal colorectal peritoneal metastases resected with the primary, or history of ovarian metastases, or perforated primary tumour
	Exclusion criteria: NR
	Treatment arms: Surveillance versus Second-look surgery + HIPEC with oxaliplatin
	HIPEC regimen: Oxaliplatin
Quenet et al. (2018) PRODIGE 7 [5] Abstract	*Inclusion criteria:* Histologically proven and isolated PC, PCI ≤25
	Exclusion criteria: NR
	Treatment arms: CRS + HIPEC with oxaliplatin + systemic therapy versus CRS alone + systemic therapy
	HIPEC regimen: Oxaliplatin intraperitoneally during surgery and hyperthermia for 30 minutes
	Systemic chemotherapy regimen: Leucovorin calcium IV followed by FU IV over 30 minutes. Systemic chemotherapy continues for at least 6 months, before and after surgery.
Verwaal et al	*Inclusion criteria:*

(2003) (2008) [6,7]	Histologically proven peritoneal metastases of CRC or positive cytology of ascites, which were diagnosed either at first presentation or at recurrence of CRC. No signs of distant metastases (liver, lung) on CT scan of abdomen and chest x-ray were allowed. Patients had to be younger than 71 years and be fit for major surgery.
	Exclusion criteria: NR
	Treatment arms: CRS + HIPEC + systemic therapy versus Surgery + systemic chemotherapy
	HIPEC regimen: Perfusion was started with a minimum of 3 L of isotonic dialysis fluid, at 1 to 2 L/min, and an inflow temperature of 41°C-42°C. As soon as the temperature in the abdomen was stable above 40°C, MMC was added to the perfusate at a dose of 17.5 mg/m^2 followed by 8.8 mg/m^2 every 30 min. The total dose was limited to 70 mg at maximum. If the core temperature exceeded 39°C, the inflow temperature was reduced. After 90 min, the perfusion fluid was drained from the abdomen, and bowel continuity was restored.
	Systemic chemotherapy regimen: Leucovorin calcium IV followed by FU IV over 30 minutes. Systemic chemotherapy continues for at least 6 months, before and after surgery.

Abbreviations: CRC: colorectal cancer; CRS: cytoreductive surgery; CT: computed tomography; FU: fluorouracil; HIPEC: hyperthermic intra-peritoneal chemotherapy; IV: intravenous; MMC: mitomycin C; PC: peritoneal carcinomatosis; PCI: peritoneal cancer index; NR: not reported

Table A5-3: Details of studies selected for the use of HIPEC with CRS in patients with gastric peritoneal carcinomatosis

Yang et al. (2011) [10]	*Inclusion criteria:* Patients aged 20-75 yrs old with gastric peritoneal carcinomatosis, Karnofsky PS >50, life expectancy >8 weeks, normal peripheral blood WBC count ≥3500/mm^3 and platelet count ≥80,000/mm^3, acceptable liver and renal function, and cardiovascular pulmonary and other major organ functions can stand major operation.
	Exclusion criteria: Patients with any lung, liver or prominent retroperitoneal lymph node metastasis, serum bilirubin level >3 ULN, liver enzymes >3 ULN, and serum creatinine level >1.5 mg/dL.
	Treatment arms: CRS + HIPEC versus CRS alone
	HIPEC regimen: HIPEC was performed before closure of abdominal cavity to provide optimal thermal homogeneity and spatial diffusion, with 120 mg of cisplatin and 30 mg of mitomycin C each dissolved 6l of heated saline (drug concentration, cisplatin 20 μg/ml, MMC 5 μg/ml). An outflow tube for perfusion was placed in Douglas' pouch just before HIPEC. The heated perfusion solution was infused intothe peritoneal cavity at a rate of 500 ml/min through the inflow tube introduced from an automatic hyperthermia chemotherapy perfusion device. The perfusion in the peritoneal cavity was stirred manually with care not to infuse directly on the bowel surface. The temperature of the perfusion solution in peritoneal space was kept at 43.0 ± 0.5°C and monitored with a thermometer on real time. The total HIPEC time was 60–90 min.
Cui et al. (2014) [11]	*Inclusion criteria:* Patients aged 18-75 yrs old that had been diagnosed with advanced gastric cancer by gastroscopy biopsy and histopathological examinations with metastasis classification identifying the tumors as IIIA or IIIB without the presence of hepatic, pulmonary, cerebral or bone metastasis, the tumors were evaluated to be stage IIIA or IIIB by EUS and CT scans that revealed at least one measurable lesion and Karnofsky PS ≥60
	Exclusion criteria: Patients with residual gastric cancer or had undergone a laparotomy
	Treatment arms: Surgery alone versus preoperative neoadjuvant chemotherapy + surgery versus surgery + HIPEC versus preoperative neoadjuvant chemotherapy + surgery + HIPEC
	HIPEC regimen: Chemotherapy was performed for 90 min per day for four consecutive days. On day 1 and 4, the intraperitoneal hyperthermic perfusate consisted of 60 mg/m^2 cisplatin and 3000 mL normal saline, while on day 2 and 3, the perfusate consisted of 0.75 g fluorouracil and 3000 mL normal saline. In addition, 10 mg dexamethasone and 10 mL lidocaine (2%) were routinely added to the perfusate in order to reduce peritoneal reactions. The perfusion machine, circulation pump and heater were powered at 38°C, which was reached prior to therapy. The temperature of the perfusate was then elevated to and stabilized at 41–43°C using a temperature control system that lasted for 90 min.
Yonemura et al. (2001) [12]	*Inclusion criteria:* Patients under 75 years with advanced GC showing macropscopic serosal invasion (T3 or T4) with no established peritoneal metastasis, WBC count ≥3000 u/L, platelet count ≥150,000 u/L.

	Exclusion criteria: Those with active liver disease, renal dysfunction, or severe metabolic disease
	Treatment arms: Surgery + CHPP vs. CNPP vs. surgery alone
	HIPEC regimen: For CHPP, abdominal cavity was filled with 8-10 L of heated saline at 42°C containing 30 mg of MMC and 300 mg of high-dose cisplatin (CDDP). The saline was circulated for 60 min at a rate of 10L/min. For CNPP, 8L of 37℃ saline containing the same doses of MMC and CDDP as CHPP was introduced into the peritoneal cavity and was circulated by controlling the peritoneal temperature at 37℃ for 60 min.
Fujimoto et al. (1998) [13]	*Inclusion criteria:* Patients with gastric carcinoma who underwent macroscopic curative surgery.
	Exclusion criteria: GC patients with macroscopic peritoneal, ovarian, and/or hepatic metastases or cardiorespiratory lesions.
	Treatment arms: IHCP + surgery + postoperative adjuvant chemotherapy vs. Surgery + postoperative adjuvant chemotherapy
	HIPEC regimen: IHCP system allowed perfusate circulation with a variable dynamic flow of 500 to 30,000 mL/min and hyperthermic capability ranging between 38-48°C. Approximately 3 to 4 L of perfusate containing MMC, 10 µg/mL is circulated for 120 min at the inflow and outflow temperatures of 44.5 to 45.0°C and 43.0 to 44.0°C, respectively.
Hamazoe et al. (1993) [14]	*Inclusion criteria:* Patients with macroscopic serosal invasion but no macroscopic peritoneal metastasis, who were scheduled to undergo curative surgery for gastric cancer.
	Exclusion criteria: NR
	Treatment arms: CHPP + surgery versus surgery alone
	HIPEC regimen: CHPP with physiologic saline that contained 10 µg/mL MMC was performed only once, immediately after surgical resection. The perfusate, which had been heated to 48 to 50°C, was infused into the peritoneal cavity through an intrapelvic tube attached to a pump. Thin Teflon-coated microthermocouples were placed in the inflow and outflow tubes at the entrances to the abdominal cavity. The inflow and outflow temperatures were maintained between 44 to 45℃ and 40 to 42°C, respectively.

CDDP: cisplatin; CHPP: continuous hyperthermic peritoneal perfusion; CNPP: continuous normothermic peritoneal perfusion; CRC: colorectal cancer; CRS: cytoreductive surgery; CT: computed tomography; GC: gastric cancer; HIPEC: hyperthermic intra-peritoneal chemotherapy; IHCP: intraperitoneal hyperthermic chemoperfusion; IV: intravenous; L: litres, min: minutes; MMC: mitomycin C; NR: not reported; ULN: upper limit of normal

Table A5-4: Details of studies selected for the use of HIPEC with CRS in patients with mesothelioma

Verma et al (2018) [15]	***Inclusion criteria:*** Patients with newly diagnosed, histologically confirmed non-metastatic MPM with the primary site in the peritoneum from the National Cancer Database (NDCB) Participant User File from 2004-2013.
	Exclusion criteria: Cases with missing information on M classification and/or treatment details, those who had undergone palliative-intent treatment and patients receiving non-definitive local surgical therapy methods that were not cytoreductive in nature.
	Treatment arms: Chemotherapy alone versus CRS alone versus CRS + chemotherapy versus CRS + HIPEC versus observation
	HIPEC regimen: NR

Abbreviations: CRS: cytoreductive surgery; HIPEC: hyperthermic intra-peritoneal chemotherapy; MPM: malignant peritoneal mesothelioma; NR: not reported

Table A5-5 – Details of studies selected for the use of HIPEC with CRS in patients with disseminated mucinous neoplasms of the appendix

Jarvinen et al. (2014) [16]	***Inclusion criteria***: *Debulking era*: Consecutive patients with PMP who were treated at Helsinki University Central Hospital by serial debulking between 1984 and 2008. *HIPEC era*: Patients with PMP starting in January 2008 regardless of the actual treatment received.
	Exclusion criteria: NR
	Treatment arms: Debulking era versus HIPEC era
	HIPEC era regimen: Intraperitoneal chemotherapy with MMC was administered using the modified coliseum technique after a score of either CC-0 or CC-1 was obtained. The standard dosage of MMC was 30 mg/m^2. The target temperature of the chemotherapeutic solution was 42–43°C, and the duration of the intraperitoneal chemotherapy was 90 min.
	Debulking era regimen: Complete tumour resection was attempted, when the disease was amenable to such a procedure. The patients did not undergo peritonectomy procedures on a large scale. Organ resections were performed sparingly. Subsequent debulking surgeries were mostly timed by symptoms.
Sinukumar et al. (2019) [17]	***Inclusion criteria***: Patients with PMP of appendiceal origin entered into the registry from March 2013 to December 2017.
	Exclusion criteria: NR
	Treatment arms: CRS alone versus CRS + HIPEC
	HIPEC regimen: HIPEC was performed at 42.5 °C using the closed abdomen or open abdomen technique. One of the following drugs were used for HIPEC, cisplatin (75 mg/m^2) for 60 min, mitomycin C (15 mg/m^2) for 90 min, or oxaliplatin (300 mg/m^2) for 30 min.
Glehen et al. (2004) [20]	***Inclusion criteria:*** Patients with the diagnosis of an epithelial peritoneal surface malignancy of appendiceal origin between May 1983 to February 2003 who underwent incomplete CRS and had residual tumor nodules more than 0.25 mm after surgery.
	Exclusion criteria: NR
	Treatment arms: CRS + IPCH versus CRS + IPCH + EPIC versus CRS + EPIC versus CRS alone
	HIPEC regimen: 12.5 mg/m^2 for males and 10 mg/m^2 for females of MMC were given in the operative room with 41 to 42°C heat and manual distribution of the chemotherapy solution.
	EPIC regimen:

	Normothermic MMC on postoperative day 1 at a dose of 12.5 mg/m^2 for males and 10 mg/m^2 for females. The 5-fluorouracil has always been given at 650 mg/m^2 on postoperative days 2 to 6 or 1 to 5.
Chua et al. (2012) [18]	***Inclusion criteria***: Histologically confirmed PMP from an appendiceal mucinous neoplasm with histopathologic subtype classified by either Ronnett's criteria or Bradley's criteria in patients treated between February 1993 and April 2011.
	Exclusion criteria: Colorectal malignancies, patients with extra-abdominal metastases, patients deemed medically unfit to undergo radical surgery based on preoperative medical assessment, and those patients whose disease was considered technically unresectable at the multidisciplinary team meeting.
	Treatment arms: CRS + HIPEC + EPIC versus CRS + HIPEC versus EPIC alone
	HIPEC regimen: HIPEC was administered at the completion of CRS using an open coliseum or closed technique depending on the individual unit's preference, with the chemoperfusate heated to achieve a temperature ranging between 40°C to 42°C. HIPEC with 10 to 12.5 mg/m^2 MMC is delivered over a 90-min period and 460 mg/m^2 oxaliplatin over a 30-min period.
	EPIC regimen: 650 mg/m^2 flurouracil is administered intraperitoneally on days one to five at room temperature.
Chua et al. (2009) [19]	***Inclusion criteria***: Patients with peritoneal carcinomatosis from appendiceal or colorectal cancer who underwent CRS and PIC between January 1996 and January 2011. Patients were >18 and ≤80 years old, with WHO PS ≤2 good performance status and had a confirmed histological diagnosis.
	Exclusion criteria: Presence of extra-abdominal metastasis, re-operative procedures and patients who had incomplete cytoreduction (CCR2/3).
	Treatment arms: CRS+HIPEC+EPIC versus CRS+HIPEC versus CRS+EPIC
	HIPEC regimen: HIPEC was performed by instillation of a heated chemoperfusate into the abdomen using the coliseum technique at approximately 42ºC for 90 min. The chemoperfusate was made up of the cytotoxic drug diluted in 3 L of 1.5% dextrose peritoneal dialysis. For gastrointestinal malignancies, MMC (10–12.5 mg/m^2) or oxaliplatin (460 mg/m^2) was used. In patients receiving oxaliplatin HIPEC, an intravenous perfusion of 5-FU (400 mg/m^2) with leucovorin (20 mg/m^2) was administered 30 min prior to commencing HIPEC
	EPIC regimen: HIPEC was performed EPIC was made up of 5-FU (650–800 mg/m^2 per day) in 1 L of 1.5% dextrose peritoneal dialysis solution. The intraperitoneal chemotherapy was allowed to dwell for 23 h before it was removed by closed suction drains over the course of 1 h. The next instillation was commenced once the abdomen was cleared of fluid as completely as possible. This was performed for 5 days.

Abbreviations: CRS: cytoreductive surgery; EPIC: early postoperative intraperitoneal chemotherapy; FU: fluorouracil; HIPEC: hyperthermic intraperitoneal chemotherapy; IPC: intraperitoneal chemotherapy; IPCH: intraperitoneal chemohyperthermia; MMC: mitomycin C; PIC:

perioperative intraperitoneal chemotherapy; PMP: pseudomyxoma peritonei; POIC: perioperative intraperitoneal chemotherapy; PS: performance status

Appendix 6: Details of Ongoing, Unpublished, or Incomplete Trials

Table A6-1: Ongoing, unpublished, or incomplete studies of HIPEC with CRS for ovarian cancer

A Phase III Clinical Trial of Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy With Lobaplatin in Advanced and Recurrent Epithelial Ovarian Cancer [HIPECOV]	
Protocol ID:	NCT03371693
Type of trial:	Phase III
Primary endpoint:	OS, 1- and 3-year survival rate
Accrual:	222
Sponsorship:	Zhongnan Hospital
Status:	Active, not recruiting
Date last updated:	December 13, 2017
Estimated study completion date:	December 30, 2020

A Phase III Multicenter Prospective Randomized Controlled Clinical Trial of HIPEC as NACT and Postoperative Chemotherapy After Interval Debulking Surgery in the Treatment of Advanced-Stage Epithelial Ovarian Cancer	
Protocol ID:	NCT03180177
Type of trial:	Phase III
Primary endpoint:	PR/SD rate, percentage of optimal debulking surgery, DFS
Accrual:	263
Sponsorship:	Shu-Zhong Cui
Status:	Not yet recruiting
Date last updated:	January 24, 2018
Estimated study completion date:	July 1, 2022

Assessment of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in First or Secondary Platinum-resistant Recurrent Ovarian Epithelial Cancer [HIPOVA-01]	
Protocol ID:	NCT03220932
Type of trial:	Phase III
Primary endpoint:	PFS
Accrual:	220
Sponsorship:	Hospices Civils de Lyon
Status:	Not yet recruiting
Date last updated:	July 18, 2017
Estimated study completion date:	December 31, 2022

A Phase III Randomized Study of Phase III Evaluating Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in the Treatment of Relapse Ovarian Cancer [CHIPOR]	
Protocol ID:	NCT01376752
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	444
Sponsorship:	UNICANCER
Status:	Recruiting
Date last updated:	November 1, 2017
Estimated study completion date:	December 2020

CARCINOHIPEC: Cytoreduction With or Without Intraoperative Intraperitoneal Hyperthermic Chemotherapy (HIPEC) in Patients With Peritoneal Carcinomatosis From Ovarian Cancer, Fallopian Tube or Primary Peritoneal Carcinoma: Randomized Clinical Trial [CARCINOHIPEC]	
Protocol ID:	NCT02328716
Type of trial:	Phase III
Primary endpoint:	DFS
Accrual:	32
Sponsorship:	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia
Status:	Recruiting
Date last updated:	December 13, 2017
Estimated study completion date:	December 2018

A Phase III Multicenter Prospective Randomized Controlled Clinical Trial of Hyperthermic Intraperitoneal Chemotherapy in the Treatment of Advanced-Stage Epithelial Ovarian Cancer After Cytoreductive Surgery	
Protocol ID:	NCT03373058
Type of trial:	Phase III
Primary endpoint:	DFS rate
Accrual:	214
Sponsorship:	Affiliated Cancer Hospital & Institute of Guangzhou Medical University
Status:	Not yet recruiting
Date last updated:	January 24, 2018
Estimated study completion date:	July 1, 2021

Hyperthermic Intraperitoneal Chemotherapy With Paclitaxel for the Treatment of Patients With Recurrent or Primary Advanced Ovarian Cancer : A Randomised Phase 3 Study [HIPECOVA]	
Protocol ID:	NCT02681432
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	60
Sponsorship:	Pedro Villarejo Campos
Status:	Recruiting
Date last updated:	August 21, 2018
Estimated study completion date:	December 2019

Phase III Randomized Clinical Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer Considering Two Different Settings: Primary Debulking Surgery (PDS) and Interval Debulking Surgery (IDS) [CHIPPI]	
Protocol ID:	NCT03842982
Type of trial:	Phase III
Primary endpoint:	DFS
Accrual:	432
Sponsorship:	Centre Oscar Lambret
Status:	Not yet ecruiting
Date last updated:	February 15, 2019
Estimated study completion date:	March 1, 2024

Phase III Randomized Clinical Trial for Stage III Epithelial Ovarian Cancer Randomizing Between Primary Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy [OVHIPEC-2]	
Protocol ID:	NCT03772028
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	538
Sponsorship:	The Netherlands Cancer Institute
Status:	Not yet recruiting
Date last updated:	February 27, 2019
Estimated study completion date:	April 1, 2025

Table A6-2: Ongoing, unpublished, or incomplete studies of HIPEC with CRS for colorectal cancer

Multicenter, Randomized Controlled Trial Designed to Evaluate the Efficacy and Safety of Adjuvant Hyperthermic Intraperitoneal Chemotherapy With Raltitrexed or Oxaliplatin Versus no HIPEC in Locally Advanced Colorectal Cancer [APEC]	
Protocol ID:	NCT02965248
Type of trial:	Phase III
Primary endpoint:	Peritoneal metastasis rate
Accrual:	147
Sponsorship:	Fudan University
Status:	Recruiting
Date last updated:	June 19, 2018
Estimated study completion date:	November 2023
Treatment of Peritoneal Dissemination in Stomach Cancer Patients With Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy	
Protocol ID:	NCT03348150
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	106
Sponsorship:	The Netherlands Cancer Institute
Status:	Recruiting
Date last updated:	November 20, 2017
Estimated study completion date:	October 1, 2022
Randomized Multicentric Phase III Trial Comparing Simple Surgery to Surgery Plus HIPEC With MMC in Colorectal Patients Who Have a High Risk of Developing Colorectal Peritoneal Carcinomatosis	
Protocol ID:	NCT02179489
Type of trial:	Phase III
Primary endpoint:	DFS
Accrual:	300
Sponsorship:	Zhejiang University
Status:	Recruiting
Date last updated:	January 23, 2018
Estimated study completion date:	October 2023
Clinical Study of the Impact of Hyperthermic Intraperitoneal Chemotherapy on Peritoneal Recurrence and Prognosis of Patients With Stage T4 Colorectal Cancer After Radical Surgery: A Multicentre Randomised Clinical Trial	
Protocol ID:	NCT03221608
Type of trial:	Phase III
Primary endpoint:	Incidence of endoperitoneal recurrence at 36 months
Accrual:	300
Sponsorship:	Sixth Affiliated Hospital, Sun Yat-sen University
Status:	Not yet recruiting
Date last updated:	July 18, 2017
Estimated study completion date:	August 1, 2024

Multicentre, Randomized Clinical Trial to Evaluate Safety and Efficacy of Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) With Mitomycin C Used During Surgery for Treatment of Locally Advanced Colorectal Carcinoma	
Protocol ID:	NCT02614534
Type of trial:	Phase III
Primary endpoint:	Locoregional control
Accrual:	200
Sponsorship:	Maimónides Biomedical Research Institute of Córdoba
Status:	Not yet recruiting
Date last updated:	July 18, 2017
Estimated study completion date:	October 2020

Table A6-3: Ongoing, unpublished, or incomplete studies of HIPEC with CRS for gastric cancer

D2 Resection and HIPEC in Locally Advanced Gastric Carcinoma, A Randomized and Multicentric Phase III Study [GASTRICHIP]	
Protocol ID:	NCT01882933
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	322
Sponsorship:	Hospices Civils de Lyon
Status:	Recruiting
Date last updated:	January 4, 2019
Estimated study completion date:	May 2025

Prospective Multicenter Phase III Trial Using CRS With/Without HIPEC After Preoperative Chemotherapy in Patients With Peritoneal Carcinomatosis of Gastric Cancer including Adenocarcinoma of the Esophagogastric Junction [GASTRIPEC]	
Protocol ID:	NCT02158988
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	180
Sponsorship:	Charite University, Berlin, Germany
Status:	Recruiting
Date last updated:	April 30, 2018
Estimated study completion date:	September 2020

A Phase III Study of Hyperthermic Intraperitoneal Chemotherapy Combined With Systemic Chemotherapy And Cytoreductive Surgery in the Treatment of Peritoneal Carcinomatosis From Gastric Cancer	
Protocol ID:	NCT03179579
Type of trial:	Phase III
Primary endpoint:	Median OS
Accrual:	88
Sponsorship:	Shu-Zhong Cui
Status:	Not yet recruiting
Date last updated:	June 7, 2017
Estimated study completion date:	August 1, 2022

D2 Radical Resection After Neoadjuvant Chemotherapy Combined With HIPEC for Advanced Gastric Cancer: a Prospective Randomized Controlled Trial	
Protocol ID:	NCT02960061
Type of trial:	Phase III
Primary endpoint:	Number of survival patients
Accrual:	640
Sponsorship:	Sixth Affiliated Hospital, Sun Yat-sen University
Status:	Not yet recruiting
Date last updated:	November 9, 2016
Estimated study completion date:	December 2019

Prospective Phase III Trial Using Radical Gastrectomy With/Without HIPEC in Advanced Gastric Cancer Patients Including Adenocarcinoma of the Esophagogastric Junction	
Protocol ID:	NCT02381847
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	60
Sponsorship:	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School
Status:	Not yet recruiting
Date last updated:	March 6, 2015
Estimated study completion date:	March 2020

A Phase III Study of Hyperthermic Intraperitoneal Chemotherapy in the Treatment of Locally Advanced Gastric Cancer after Radical Gastrectomy With D2	
Protocol ID:	NCT02356276
Type of trial:	Phase III
Primary endpoint:	5yr OS
Accrual:	584
Sponsorship:	Affiliated Cancer Hospital & Institute of Guangzhou Medical University
Status:	Recruiting
Date last updated:	October 31, 2017
Estimated study completion date:	January 2022

Multicenter Study on Cytoreductive Surgery Combined With Hyperthermic Intraperitoneal Chemotherapy and Chemotherapy for Gastric Cancer With Peritoneal Metastasis	
Protocol ID:	NCT03023436
Type of trial:	
Primary endpoint:	Median survival time
Accrual:	220
Sponsorship:	Nanfang Hospital of Southern Medical University
Status:	Recruiting
Date last updated:	February 7, 2017
Estimated study completion date:	June 2022

D2 Radical Resection After Neoadjuvant Chemotherapy Combined With HIPEC for Advanced Gastric Cancer: a Prospective Randomized Controlled Trial [PERISCOPE II]	
Protocol ID:	NCT03348150
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	106
Sponsorship:	The Netherlands Cancer Institute
Status:	Recruiting
Date last updated:	November 20, 2017
Estimated study completion date:	October 1, 2022

A Phase III Study of Hyperthermic Intraperitoneal Chemotherapy in the Treatment of Locally Advanced Gastric Cancer After radIcal Gastrectomy With D2 Lymphadenectomy	
Protocol ID:	NCT02240524
Type of trial:	Phase III
Primary endpoint:	OS
Accrual:	582
Sponsorship:	Affiliated Cancer Hospital & Institute of Guangzhou Medical University
Status:	Recruiting
Date last updated:	September 15, 2014
Estimated study completion date:	July 2019

Table A6-4: Ongoing, unpublished, or incomplete studies of HIPEC with CRS for appendiceal

[redacted]	
ICARUS: 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	
Protocol ID:	NCT01815359
Type of trial:	Phase II
Primary endpoint:	DFS
Accrual:	220
Sponsorship:	Memorial Sloan Kettering Cancer Center
Status:	Recruiting
Date last updated:	July 19, 2018
Estimated study completion date:	March 2019