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PRACTICE GUIDELINE

Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery: a clinical practice guideline

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ABSTRACT

Objective The purpose of the present review was to provide evidence-based guidance about the provision of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal cancers.

Methods The guideline was developed by the Program in Evidence-Based Care together with the Surgical Oncology Program at Ontario Health (Cancer Care Ontario) through a systematic review of relevant literature, patient- and caregiver-specific consultation, and internal and external reviews.

Results ***Recommendation 1a:*** For patients with newly diagnosed stage III primary epithelial ovarian or fallopian tube carcinoma, or primary peritoneal carcinoma, HIPEC should be considered for those with at least stable disease after neoadjuvant chemotherapy at the time that interval CRS (if complete) or optimal cytoreduction is achieved.

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

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

Recommendation 4: There is insufficient evidence to recommend HIPEC with CRS for the prevention of peritoneal carcinomatosis in colorectal cancer outside the context 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 the context of a clinical trial.

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

Recommendation 7: There is insufficient evidence to recommend HIPEC with CRS as a standard of care in patients with malignant peritoneal mesothelioma; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol.

Recommendation 8: There is insufficient evidence to recommend HIPEC with CRS as a standard of care in patients with disseminated mucinous neoplasm in the appendix; however, patients should be referred to HIPEC specialty centres for assessment for treatment as part of an ongoing research protocol.

Key Words Hyperthermic intraperitoneal chemotherapy, HIPEC, intraperitoneal chemotherapy, cytoreductive surgery, CRS, practice guidelines

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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). The rarity of primary peritoneal malignancies coupled with the time it takes to collect and report cancer data mean that Canadian and Ontario-specific incidence data are currently not available. An incidence rate of 0.2–3 per million has been reported for peritoneal mesothelioma in industrialized countries[1]. Secondary isolated peritoneal spread is relatively common with ovarian and gastrointestinal malignancies, including colorectal, appendiceal, and gastric. Survival rates vary depending on the histology and burden of disease, with the median ranging from months (gastric cancer)[2] to almost 5 years (ovarian cancer)[3].

Cytoreductive surgery (CRS) is a complex procedure that comprises a peritonectomy and resection of involved viscera as indicated, with the goal of leaving the patient with only microscopic residual disease[4]. A systematic approach toward comprehensive CRS was described in 1995 by Dr. Paul Sugarbaker[5], and that approach has generally been adopted. The addition of HIPEC to CRS was first evaluated in the 1980s. The biologic rationale for intraperitoneal delivery was based on studies demonstrating a pharmacokinetic advantage because the peritoneal–plasma barrier allows for a high concentration gradient of chemotherapeutic drugs between the peritoneal cavity and the systemic circulation[6] and because blood drainage from the peritoneal cavity occurs through the portal system, providing a "first-pass" effect through the liver, reducing systemic toxicity and simultaneously increasing intrahepatic concentrations[7]. 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[8]. Moreover, synergism between heat and the enhanced cytotoxicity of certain chemotherapeutics used during HIPEC has been well documented[9].

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 patients receiving those treatments have dictated that specialized centres be created for care delivery[10–12]. The use of HIPEC is an emerging field, and the current standard of care in Ontario for the relevant disease sites is systemic chemotherapy or best supportive care.

The Program in Evidence-Based Care (PEBC) together with the Surgical Oncology Program at Ontario Health (Cancer Care Ontario) developed the present guideline, which contains recommendations for the use of CRS with HIPEC. The guideline focuses on the use of HIPEC with formal CRS or in the prophylactic setting after resection of the primary tumour. It does not evaluate early postoperative intraperitoneal chemotherapy or sequential postoperative intraperitoneal chemotherapy, both of which have been explored in ovarian cancer.

METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[13,14]. The process for the present guideline included a systematic review, with interpretation of the evidence by the authors, who then drafted recommendations based on the evidence and expert consensus; internal review by content and methodology experts; and external review by clinicians and other stakeholders. The authors had expertise in surgical oncology, medical oncology, gynecologic oncology, pathology, and health research methodology.

Further details of the methods and findings of the systematic review that informed the guideline recommendations have been published elsewhere[15]. Briefly, MEDLINE, EMBASE, and the Cochrane Library were searched for randomized controlled trials (RCTs) comparing HIPEC in addition to CRS with either systemic chemotherapy, early postoperative intraperitoneal chemotherapy, sequential postoperative intraperitoneal chemotherapy, CRS alone, or any combination of the foregoing in adult patients with a diagnosis of mesothelioma or appendiceal (including appendiceal mucinous neoplasms), colorectal, gastric, ovarian, or primary peritoneal carcinoma. All RCTs were assessed for quality using components of the Cochrane Risk of Bias tool (Part 2, Section 8.5 in the *Cochrane Handbook for Systematic Reviews of Interventions,* downloadable from http://handbook.cochrane.org/); non-RCTs were assessed using the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool, downloadable from https://www.riskofbias.info/.

Patient- and Caregiver-Specific Consultation Group

A combination of patients, survivors, and caregivers participated as Consultation Group members. They reviewed copies of draft recommendations and provided feedback to the Working Group's health research methodologist about comprehensibility, appropriateness, and feasibility. The health research methodologist relayed the feedback to the Working Group for consideration.

Internal Review

Guidelines produced by the PEBC are reviewed by a panel of content experts (the Expert Panel) and a methodology panel (the Report Approval Panel).

The PEBC Report Approval Panel, a 3-person panel with methodology expertise, must unanimously approve the guideline document.

The Expert Panel for this guideline consisted of surgical, medical, and gynecologic oncologists. For a guideline document to be approved, 75% of the Expert Panel must cast a vote indicating approval of the document or must abstain from voting for a specified reason; of those that vote, 75% must approve the document.

The Working Group was responsible for incorporating the feedback from both panels.

External Review

The PEBC external review process is 2-pronged and includes a targeted peer review that is intended to obtain direct

feedback on the draft guidelines from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guideline to Ontario practitioners. In the professional consultation, feedback was obtained through a brief online survey of health care professionals and other stakeholders who are the intended users of the guideline. All surgical and medical oncologists with an interest in gastrointestinal cancers and any clinicians with an interest in ovarian cancers or mesothelioma in the PEBC database were contacted by e-mail.

RESULTS

The full systematic review[15] provides details of the methodologic characteristics of the evidence and clinical outcomes.

Patient- and Caregiver-Specific Consultation Group

Five individuals (patients, survivors, or caregivers) participated as consultation group members.

Internal Review

Three Report Approval Panel members, including the PEBC scientific director and two methodology experts, reviewed and approved the draft guideline in May 2019.

Of the 20 members of the Expert Panel, 18 members cast votes (90% response rate) in May 2019. Of those who voted, 16 approved the document (89%).

External Review

After approval of the document at internal review, the authors circulated the draft document to external review participants for review and feedback. Seven clinical experts from North America were identified by the Working Group as targeted peer reviewers. Three agreed to be reviewers; two responses were received. Table I summarizes the results of the review.

In the professional consultation, 76 individuals who practice in Ontario were contacted, and 14 responses (18.4%) were received. Three stated that they did not have interest in this area or were unavailable to review the guideline at the time; one stated that they were now retired; and one did not want to participate in the professional consultation. Table II summarizes the results of the survey responses from 9 professionals.

GUIDELINE

The target population for this guideline is adults (≥18 years of age) with a diagnosis of mesothelioma or appendiceal (including appendiceal mucinous neoplasms), colorectal, gastric, ovarian, or primary peritoneal carcinoma. The intended users of the guideline are clinicians involved in the care of such patients.

The guideline addresses the role of HIPEC with CRS and not the role of CRS alone. Although evidence to make recommendations for many of the target sites is lacking, many RCTs are noted to be ongoing. This guideline will be reviewed annually for any new evidence. When writing the 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 indicated that all of the outcomes mentioned would be important to them in making any treatment decisions.

Recommendation 1a

For patients with newly diagnosed stage III primary epithelial ovarian or fallopian tube carcinoma, or primary

TABLE I Responses to 9 items on the targeted peer reviewer questionnaire

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

TABLE II Responses to 4 items on the professional consultation survey

Question	Overall guideline assessment (*n*=9)				
	Lowest quality (1)	**(2)**	**(3)**	**(4)**	**Highest quality (5)**
Rate the overall quality of the guideline report.	0	0	1	1	7
	Strongly disagree (1)	**(2)**	**(3)**	**(4)**	**Strongly agree (5)**
I would make use of this guideline in my professional decisions.	0	1	0	3	5
I would recommend this guideline for use in practice.	0	0	2	2	5
What are the barriers or enablers to the implementation of this guideline report?	• Resources and availability • Timely access to the doctors who perform the procedure • Education for patients and families				

peritoneal carcinoma, HIPEC should be considered for those with at least stable disease after neoadjuvant chemotherapy at the time that interval CRS (if complete) or optimal cytoreduction is achieved.

Qualifying Statement

The Working Group members recommend prospectively collecting data relating to these patients to evaluate real-world outcomes and applicability.

Key Evidence

The evidence comes from one RCT[16,17] in which the overall certainty of the evidence for all outcomes is moderate.

The multicentre trial by van Driel *et al.*[16] compared patients with newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer who received interval CRS plus HIPEC using cisplatin [HIPEC/cisplatin (n = 122)] with interval CRS alone (n = 123). No upper age limit to enrol in the trial was imposed, but the oldest patient was aged 66 years. All women had at least stable disease after neoadjuvant chemotherapy and had complete or optimal cytoreduction at the time of surgery. Patients received an additional 3 cycles of carboplatin and paclitaxel after interval surgery. A significant difference in median OS was reported 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] 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). Exploratory subgroup analyses of OS and RFS did not reveal any specific subgroup (that is, age, histologic type, previous surgery, number of involved regions, or laparoscopy before surgery) that experienced better or worse outcomes with CRS and HIPEC or with standard treatment.

The OS probability at 3 years in the treatment and standard arms was 62% (95% CI: 54% to 72%) and 48% (95% CI: 39% to 58%) respectively. A p value was not reported. The RFS probability at 3 years in the treatment and standard arms was 17% (95% CI: 11% to 26%) and 8% (95% CI: 4% to 16%) respectively. A p value was not reported.

No significant differences between the groups were noted in the incidence of adverse events of any grade[16], and no significant differences in health-related QOL outcomes were reported over time[17].

Interpretation of the Evidence

In patients receiving neoadjuvant chemotherapy followed by interval CRS with HIPEC, the Working Group members determined that the benefits (that is, increased OS) outweighed the harms (that is, adverse events). Given the large survival benefit and the lack of significant differences in adverse events and QOL, patients with newly diagnosed advanced epithelial ovarian cancer would consider this treatment option to be acceptable.

This recommendation is generalizable to all patients with stage III primary epithelial ovarian or fallopian tube carcinoma, or primary peritoneal carcinoma, who have complete or optimal cytoreduction. It cannot be generalized to patients who have suboptimal cytoreduction.

Recommendation 1b

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

Key Evidence

The evidence comes from one RCT[18] available in abstract form, in which the overall certainty of the evidence for all outcomes is low.

The multicentre trial by Lim *et al.*[18], currently published in abstract form, compared patients with stage III or IV primary epithelial ovarian cancer who received primary CRS plus HIPEC/cisplatin (n = 2) with those receiving CRS alone (n = 92). Only patients who achieved optimal cytoreduction were included. This RCT showed no difference in 5-year OS (HIPEC/cisplatin arm, 51%; non-HIPEC arm, 49.4%; p = 0.574) or 5-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, no difference in

median OS ($p = 0.407$) or median PFS ($p = 0.137$) was observed between the two arms.

The most common adverse event was anemia, experienced by significantly more participants in the HIPEC/cisplatin arm (67.4%) than by those in the non-HIPEC arm (50%, $p = 0.025$). Elevation of creatinine was also significantly higher in the HIPEC/cisplatin arm ($p = 0.026$). No differences between the arms were observed for transfusion ($p = 0.432$), neutropenia ($p = 0.151$), and thrombocytopenia ($p = 0.136$).

Interpretation of the Evidence

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

Recommendation 2

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

Key Evidence

The evidence comes from one RCT[19] comparing patients who received surgery plus HIPEC with those who received surgery alone, where the overall certainty of the evidence for all outcomes is considered to be low. Although the trial reported itself as a phase III RCT, it presents unclear methods and statistical analyses, resulting in questions about 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 alone ($n = 60$, $p = 0.006$). In exploratory subgroup analyses, survival was significantly higher in patients with complete cytoreduction (no residual tumour, CC-0) who received HIPEC (30.9 months) than in those who received surgery only (16.9 months, $p = 0.038$). In patients who received surgery only, survival was longer in those with a CC-0 cytoreduction (16.1 months) than in those with a CC-2 cytoreduction (residual tumour 2.5 mm–2.5 cm; 6.7 months, $p = 0.002$). In a subgroup analysis by score on the peritoneal carcinomatosis index (PCI), survival was significantly higher for surgery plus HIPEC than for surgery alone both in patients with a PCI of 15 or less (30.4 months vs. 15.4 months, $p = 0.031$) and in those with a PCI of more than 15 (21.5 months vs. 9.2 months, $p = 0.049$).

No mortality, morbidity, or QOL data were presented.

Interpretation of the Evidence

There was agreement among the members of the Working Group that evidence with such unclear methods and statistical analyses is 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 the context of a clinical trial.

Key Evidence

The evidence comes from two RCTs[20–22], one fully published and the other available in abstract form, in which the overall certainty of the evidence for all outcomes is low.

The trial by Verwaal *et al.*[21,22] compared patients who received CRS plus HIPEC using mitomycin C (HIPEC/MMC) plus 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. The trial reported significant differences in disease-specific survival (22.2 months for CRS plus HIPEC/MMC vs. 12.6 months for standard therapy, $p = 0.028$) and PFS (12.6 months for CRS plus HIPEC/MMC vs. 7.7 months for standard therapy, $p = 0.020$) after a median follow-up of 94 months. However, the chemotherapy regimen administered in the standard therapy arm consisted of fluorouracil–leucovorin, which is not representative of current systemic chemotherapy regimens. Exploratory subgroup analyses did not reveal that any specific subgroup (that is, stratified by sex, age, site, or tumour origin) experienced better or worse outcomes with CRS plus HIPEC or with standard therapy.

Four patients (8%) died as a result of treatment, and two stopped adjuvant chemotherapy as a result of toxicity in the HIPEC/MMC arm; two stopped treatment in the non-HIPEC arm because of toxicity.

The PRODIGE 7 trial[20], currently published in abstract form, compared patients who received CRS plus HIPEC/oxaliplatin plus systemic chemotherapy ($n = 133$) with patients who received CRS and systemic chemotherapy ($n = 132$). The trial showed no difference in median OS (41.7 months for CRS plus HIPEC vs. 41.2 months for CRS only; HR: 1.00; 95% CI: 0.73 to 1.37; $p = 0.995$) or median RFS (13.1 months for CRS plus HIPEC vs. 11.1 months for CRS only; 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–leucovorin, which is not representative of current systemic chemotherapy regimens.

In a subgroup analysis of patients with a 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) for the HIPEC/oxaliplatin arm (HR: 0.437; 95% CI: 0.21 to 0.90; $p = 0.0209$).

No difference in the postoperative mortality rate was reported between the experimental and standard arms. The morbidity rates did not differ at 30 days, but at 60 days, significant differences in the rate of grades 3–5 morbidity were observed (24.1% for the HIPEC/oxaliplatin arm vs. 13.6% for the non-HIPEC arm, $p = 0.030$).

None of the studies reported QOL data.

Interpretation of the Evidence

The Working Group members noted that, although two RCTs were found (one currently available in abstract form), recommendations could not be made because the control arms of both trials were not representative of current oncologic practice, resulting in outcomes that are not generalizable to current practice.

The Working Group members determined that the evidence from an abstract of a RCT is insufficient to make

definitive recommendations about the use of HIPEC after CRS in this patient population.

One dissenting opinion emerged 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 the dissenting opinion was that the study by Verwaal *et al.*[21,22] showed a large difference in disease-specific survival for CRS plus HIPEC/MMC compared with the systemic chemotherapy consisting of fluorouracil–leucovorin used in the control arm. Although the best systemic chemotherapy was not used, it is uncertain whether use of the best systemic chemotherapy would completely negate the survival benefit reported with CRS plus HIPEC.

Recommendation 4

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

Key Evidence

The evidence comes from two RCTs[23,24] (one available in abstract form) in which the overall certainty of the evidence for all outcomes is moderate.

The multicentric COLOPEC trial by Klaver *et al.*[23] compared patients having T4 or perforated colon cancer who received adjuvant HIPEC plus CRS and adjuvant systemic chemotherapy ($n = 100$) with their counterparts who received adjuvant systemic chemotherapy alone ($n = 102$). Adjuvant HIPEC was performed simultaneously (9%) or within 5–8 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 differences between the experimental and control arms for 18-month disease-free survival [69.0% (95% CI: 60.0% to 78.0%) vs. 69.3% (95% CI: 60.3% to 78.3%) respectively, $p = 0.99$], 18-month OS [93.0% (95% CI: 87.9% to 98.1%) vs. 94.1% (95% CI: 89.6% to 98.6%), $p = 0.82$], or 18-month peritoneal metastases–free survival [80.9% (95% CI: 73.3% to 88.5%) vs. 76.2% (95% CI: 68.0% to 84.4%), $p = 0.28$].

The COLOPEC trial[23] reported that postoperative complications occurred in 14% of patients who received adjuvant HIPEC ($n = 87$).

The ProphyloCHIP trial by Goere *et al.*[24], currently published in abstract form, included patients with a high risk of developing colorectal peritoneal metastases after 6 months of adjuvant chemotherapy, randomizing them to a surveillance arm ($n = 79$) or to a systemic second-look surgery plus HIPEC/oxaliplatin arm ($n = 71$). The RCT showed no difference in 3-year disease-free survival ($p = 0.75$) or 3-year OS (p value not reported).

Interpretation of the Evidence

In patients with T4 or perforated colon cancer receiving adjuvant HIPEC plus CRS and adjuvant systemic chemotherapy, the Working Group members determined that the desirable effect of increased survival did not occur. Given the absence of a survival benefit, patients would not consider this treatment option to be acceptable.

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

Recommendation 5

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

Key Evidence

The evidence comes from one RCT[25] in which the overall certainty of the evidence for all outcomes is low.

The RCT by Yang *et al.*[25] showed a significant difference in median OS between the CRS plus HIPEC/cisplatin plus MMC arm (11.0 months; 95% CI: 10.0 months to 11.9 months) and the CRS-only arm (6.5 months; 95% CI: 4.8 months to 8.2 months; $p = 0.046$). Each arm included 34 patients. In subgroup analyses, the median OS was significantly greater for patients scored CC-0 to CC-1 than for patients scored CC-2 to CC-3 in both the HIPEC/cisplatin plus MMC arm ($p = 0.000$) and the non-HIPEC arm ($p = 0.000$). For patients with incomplete cytoreduction, OS was longer in the HIPEC/cisplatin plus MMC arm than in the non-HIPEC arm (8.2 months for HIPEC/cisplatin plus MMC vs. 4.0 months for non-HIPEC treatment, $p = 0.024$). Similarly, in subgroup analyses by score on the PCI, median OS for patients with a high score on the PCI was significantly longer in the HIPEC/cisplatin plus MMC arm (13.5 months; 95% CI: 8.7 months to 18.3 months) than in the non-HIPEC arm (3.0 months; 95% CI: 2.4 months to 3.6 months; $p = 0.012$); median OS was not different for patients with a low score on the PCI in either arm ($p = 0.464$).

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-0 or CC-1 score ($p = 0.003$), 6 cycles or more of chemotherapy ($p = 0$), and no serious adverse effects ($p = 0$) were identified as major independent prognostic factors for survival.

No significant differences in serious adverse events were demonstrated between patients receiving CRS plus HIPEC (14.7%) and those receiving CRS alone (11.7%, $p = 0.839$).

No QOL data were presented.

Interpretation of the Evidence

Although the benefits (that is, increased OS) outweighed the harms (that is, 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 the trial used 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 the results.

Recommendation 6

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

Key Evidence

The evidence comes from four Asian RCTs[26–29] (three from Japan, one from China) in which the certainty of the evidence for all outcomes is low. The trials present unclear methods and statistical analyses, which include providing no randomization details and not specifying the primary outcome (assumed to be OS) nor the outcomes of interest.

The trial by Cui *et al.*[26] reported that differences in median survival for patients who received surgery only (27 months), neoadjuvant chemotherapy plus surgery (33 months), surgery plus HIPEC/cisplatin (32 months), and neoadjuvant chemotherapy plus surgery plus HIPEC/cisplatin (36 months) were statistically significant ($p = 0.001$). The differences in median PFS between the four groups were also reported to be statistically significant ($p < 0.001$). Each arm included 48 patients.

The trial by Yonemura *et al.*[27] showed that survival was significantly better in patients who received continuous hyperthermic peritoneal perfusion with MMC plus cisplatin (5-year survival: 61%) than in patients who received continuous normothermic peritoneal perfusion (5-year survival: 44%; $p = 0.017$) or surgery alone (5-year survival: 42%; $p = 0.019$). The arms included 48, 44, and 47 patients respectively.

Similarly, Fujimoto *et al.*[28] reported that survival rates were significantly higher in the HIPEC/MMC arm (2-year survival: 88%; 4-year: 76%; 8-year: 62%) compared with the control arm (2-year survival: 77%; 4-year: 58%; 8-year: 49%; $p = 0.0362$). The arms included 71 and 70 patients respectively. Peritoneal recurrence was more frequent in the control arm ($p < 0.001$).

The final results of the RCT reported by Hamazoe *et al.*[29] found no significant differences in 5-year survival between the arm using continuous hyperthermic peritoneal perfusion with MMC (64.3%) and the arm using surgery only (52.5%, $p = 0.2427$), with 42 and 40 patients enrolled respectively. Median survival was reported to be 77 months with continuous hyperthermic peritoneal perfusion plus surgery and 66 months with control treatment.

All four RCTs[26–29] found no significant differences in adverse events between the experimental and control arms.

None of the studies reported QOL data.

Interpretation of the Evidence

Although the benefits (that is, increased OS) outweighed the harms (that is, adverse events) in the studies, the Working Group members concluded that confinement to Asian populations, lack of methodologic details, and low certainty of the evidence prevented the forming of recommendations.

Differences in the biology of gastric cancers between Asian and non-Asian patients limit the generalizability of the results.

Recommendation 7

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

Qualifying Statement

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

Key Evidence

To date, no randomized or comparative studies have compared the use of CRS plus HIPEC with other methods of oncologic management in patients with peritoneal mesothelioma. The evidence comes from one retrospective cohort study[30] ($n = 1547$), which conducted a multivariable analysis that included the use of CRS plus HIPEC as a variable. The certainty of that evidence is very low.

When compared with the CRS plus HIPEC cohort, cohorts receiving chemotherapy alone, CRS alone, or observation were independently associated with poorer OS ($p < 0.001$) in analyses controlled for age, sex, Charlson/Deyo score, insurance, and histology[30]. However, no statistically significant difference in OS was observed when comparing CRS plus HIPEC with CRS plus chemotherapy ($p = 0.397$).

Adverse events were not reported.

No QOL data were presented.

Recommendation 8

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

Qualifying Statement

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

Key Evidence

To date, no randomized studies have compared the use of CRS–HIPEC with other methods of oncologic management in patients with disseminated mucinous neoplasms. The evidence comes from one comparative study[31] that assessed the differences between patients treated during the debulking era ($n = 33$) and during the CRS plus HIPEC era ($n = 87$), and four retrospective cohort studies[32–35] that 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, peritoneal mucinous carcinomatosis, and hybrid histologies.

The comparative study by Jarvinen *et al.*[31] showed no significant difference in the 5-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 retrospective study by Sinukumar *et al.*[32] 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 to 9.8; $p = 0.016$).

In both studies by Chua *et al.*[33,34], 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; $p = 0.030$)[33]. In an exploratory subgroup analysis by histologic subtype, the use of HIPEC remained nonsignificant.

The study by Glehen *et al.*[35] 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.

In the study by Jarvinen *et al.*[31], 30-day mortality was not significantly different in the two groups. The four cohort studies[32–35] reported morbidity and mortality data in aggregate and not by treatment group.

None of the studies reported QOL data.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: TM reports personal fees received from ConMed and AstraZeneca outside the submitted work. The remaining authors (RCA, DS, JB, JC, and EK) have no conflicts to disclose.

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