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PRACTICE GUIDELINE

Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms

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ABSTRACT

To meet the needs of patients, Canadian surgical and medical oncology leaders in the treatment of peritoneal surface malignancies (PSMS), together with patient representatives, formed the Canadian HIPEC Collaborative Group (CHICG). The group is dedicated to standardizing and improving the treatment of PSM in Canada so that access to treatment and, ultimately, the prognosis of Canadian patients with PSM are improved.

Patients with resectable PSM arising from colorectal or appendiceal neoplasms should be reviewed by a multidisciplinary team including surgeons and medical oncologists with experience in treating patients with PSM. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy should be offered to appropriately selected patients and performed at experienced centres.

The aim of this publication is to present guidelines that we recommend be applied across the country for the treatment of PSM.

KEY WORDS

Peritoneal surface malignancy, pseudomyxoma peritonei, carcinomatosis, colorectal cancer, appendiceal cancer, hyperthermic intraperitoneal chemotherapy, cytoreductive surgery, peritoneal metastasis

1. INTRODUCTION

A peritoneal surface malignancy (PSM) is a cancer arising from or spreading to the peritoneal surfaces. It can be a primary disease arising from the peritoneum (such as malignant peritoneal mesothelioma) or a secondary disease (such as metastasis originating from a primary malignant neoplasm). Primary PSM is rare; the most frequent forms are primary peritoneal mesothelioma and serous carcinoma of the peritoneum. Secondary PSM is by far the most frequent. Its origin is often cancers of the gastrointestinal tract, but it can frequently arise from ovarian cancer and breast cancer (mostly the lobular subtype). However, many cancers can metastasize to the peritoneum [1–7].

Surgical treatment of PSM is recent [8–10]. Before 1989, cures were anecdotal, and median survival was 9 months. Now, long-term survival is possible in 25%–85% of patients [1,2,4–6,8,11,12], depending on patient and disease characteristics [8,13–20]. Despite that success, a lack of agreement on many issues (drug, dose, duration) means that many questions remain, and few randomized controlled trials have provided comparative evidence.

In selected cases, optimal treatment of PSM consists of a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). This complex procedure requires a dedicated multidisciplinary team. Unfortunately, worldwide, philosophic and fundamental differences exist about issues ranging from patient selection to treatment approaches. Consequently, no accepted standard of care for the provision of this treatment has been developed.

A primary concern in the medical community regarding PSM treatment by CRS plus HIPEC is the paucity of phase III studies to support this modern therapeutic approach. The lack of studies is, in part, a result of the strong personal biases found among surgeons providing PSM care, the rapid increase in the number of centres offering this multimodal approach, and the relatively small number of patients at risk.

Well-selected PSM patients can clearly be treated with CRS and HIPEC. However, in the absence of a large body of level 1 evidence, Canadian surgical and medical oncologists should offer PSM patients a thoughtful, carefully integrated approach founded in surgical and biologic principles and supported by the available evidence. To that end, it is strongly recommended that all

patients with a PSM from a colorectal or appendiceal neoplasm be considered for referral to one of the HIPEC centres listed in Table I. Referrals should occur as a first-line metastatic cancer treatment intervention.

To meet the needs of patients and assure the highest possible standard of care, leading Canadian experts in the treatment of PSM, together with patient representatives, formed the Canadian HIPEC Collaborative Group (CHICG, Appendix A). This initiative is supported by the Colorectal Cancer Association of Canada (http://www.colorectal-cancer.ca/en/) and sponsorship from pharmaceutical companies.

2. METHODS

Before these guidelines were written, the literature in PubMed was searched using the key words "peritoneal carcinomatosis," "PC," "intraperitoneal chemotherapy," "HIPEC," "colorectal neoplasms" (or cancers), "colonic neoplasms" (or cancers), "rectal neoplasms" (or cancers), "pseudomyxoma peritonei," "debulking," and "chemohyperthermia." Descriptive studies and clinical trials (phase II and III) published between 1990 and 2013 were retained. As additional sources of information, published guidelines from national and international organizations were obtained:

- Society of Surgical Oncology (United States)
- 5th International Workshop on Peritoneal Surface Malignancy (Milan, Italy; December 4–6, 2006)
- 6th International Workshop on Peritoneal Surface Malignancy (Lyon, France; November 17–19, 2008)
- 7th International Workshop on Peritoneal Surface Malignancy (Uppsala, Sweden; September 8–10, 2010)
- 8th World Congress on Peritoneal Surface Malignancies (Berlin, Germany; October 31–November 2, 2012)
- L'Association Française de Chirurgie and Direction de la lutte contre le cancer (France)

Before the final revision, a census of the available Canadian resources (any combination of expertise, equipment, and time dedicated to HIPEC) was taken to align the guidelines with those resources.

Over the course of three full-day meetings and two teleconferences, surgical (PD, LS, CL, LM, EH, CG, AG, YM, WT, RY, JAM) and medical oncology (MKK, PM) experts in the treatment of PSM addressed 40 questions (referenced in this paper as Q1, Q2, and so on, and detailed in Table II). Each question was discussed by the CHICG membership, and conclusions were based on the level of evidence and the level of consensus among the CHICG members. The guidelines presented here focus on PSM of colorectal and appendiceal origin. Questions about peritoneal mesothelioma (Q13, Q24, Q39, Q40) and other secondary sites (Q26) will be discussed in future editions of the guidelines.

The evidence was graded using the five levels set out by the American Society of Clinical Oncology. Level 1 evidence is based on meta-analyses or multiple randomized trials (phase III). Level 2 evidence is based on 1–2 randomized trials. Level 3 evidence is based on nonrandomized trials (phase II). Level 4 evidence is based on observational studies, and level 5 is based on case reports or expert opinion.

The level of consensus (LOC) concerning each question was adopted from the approach described by Murphy *et al.* [21] as used by the Program in Evidence-Based Medicine of Cancer Care Ontario. The LOC A–D definitions were determined *a priori* by the CHICG members, based on a combination of the already defined levels of evidence, applicability (based on discussion and available resources), and vote of the members (Table III).

TABLE I Centres currently providing a hyperthermic intraperitoneal chemotherapy program in Canada

Centre	*University*	*Surgeon*	*Status*
Maisonneuve–Rosemont Hospital	Montreal	Pierre Dubé[a] Lucas Sideris	Open
Tom Baker Cancer Centre	Calgary	Walley Temple[a] Lloyd Mack	Open
Centre Hospitalier de l'Université de Montréal	Montreal	Rami Younan[a]	Open
QE II Health Sciences Centre	Dalhousie	Carman Giacomantonio[a]	Open
Cross Cancer Institute	Alberta	Erika Haase[a]	Open
Mount Sinai Hospital	Toronto	Andrea McCart[a] Anand Govindarajan	Open
Jewish General Hospital	Montreal	Tsafrir Vanounou[a]	Pending
Health Sciences Centre	Manitoba	Pamela Hebbard[a]	Pending
Vancouver General Hospital	British Columbia	Yarrow McConnell[a]	Open

[a] Director of program and contact.

TABLE II Questions addressed during the Canadian HIPEC Collaborative Group consensus process

Q1	Importance of provincial and national recognition
Q2	Need for an accreditation program
Q3	Strategies to improve peer recognition and support
Q4	Minimal training to perform hyperthermic intraperitoneal chemotherapy (HIPEC)
Q5	Minimal caseload per surgeon, team, and network
Q6	Optimal nursing support and qualifications
Q7	Maximum age for HIPEC
Q8	Maximum body mass index for HIPEC
Q9	Patient must participate in research
Q10	Definition of resectable disease as seen on preoperative work-up
Q11	Place of perioperative liver ultrasonography
Q12	Peritonectomy in pseudomyxoma peritonei
Q13	Peritonectomy in peritoneal mesothelioma
Q14	Strategies when the peritoneal carcinomatosis index (PCI) score is high
Q15	Indication for ostomy
Q16	Strategies to improve accessibility
Q17	Eligibility when a synchronous primary tumour accompanies low-grade disseminated peritoneal adenomucinosis (DPAM) or intermediate-grade peritoneal mucinous carcinomatosis (PMCA-I)
Q18	Eligibility when an unknown primary tumour accompanies DPAM or PMCA-I
Q19	Eligibility when a synchronous primary tumour accompanies grade 1 or 2I adenocarcinoma from the appendix
Q20	Eligibility in the case of a peritoneal surface malignancy (PSM) arising less than 6 months after surgery for a primary adenocarcinoma grade 1 or 2 from colorectal origin
Q21	Eligibility in the case of synchronous PSM and a primary adenocarcinoma grade 1 or 2 from colorectal origin
Q22	Eligibility in the case of PMCA or grade 3 adenocarcinomas originating from the appendix
Q23	Eligibility in the case of grade 3 adenocarcinomas originating from the colon
Q24	Eligibility in the case of sarcomatoid mesothelioma
Q25	Eligibility in the case of a primary from the rectum
Q26	Eligibility in the case of PSM arising from gastric cancer
Q27	Eligibility in the presence of extra-regional lymph node invasion in the case of DPAM or PMCA-I
Q28	Eligibility in the presence of liver invasion in the case of DPAM or PMCA-I
Q29	Eligibility when in the presence of extra-peritoneal invasion in the case of DPAM or PMCA-I
Q30	Eligibility in the presence of extra-regional lymph node invasion in the case of a PSM originating from a grade 1 or 2 appendiceal adenocarcinoma
Q31	Eligibility in the presence of liver invasion in the case of a PSM originating from a grade 1 or 2 appendiceal adenocarcinoma
Q32	Eligibility in the presence of extra-peritoneal invasion in the case of a PSM originating from a grade 1 or 2 appendiceal adenocarcinoma
Q33	Eligibility in the presence of extra-regional lymph node invasion in the case of a PSM originating from a grade 1 or 2 colorectal adenocarcinoma
Q34	Eligibility in the presence of liver invasion in the case of a PSM originating from a grade 1 or 2 colorectal adenocarcinoma
Q35	Eligibility in the presence of extra-peritoneal invasion in the case of a PSM originating from a grade 1 or 2 colorectal adenocarcinoma
Q36	Maximum PCI score in the case of DPAM or PMCA-I
Q37	Eligibility when the PCI score exceeds 20 in the case of PSM originating from a grade 1 or 2 appendiceal adenocarcinoma
Q38	Eligibility when the PCI score exceeds 20 in the case of a PSM originating from a grade 1 or 2 colorectal adenocarcinoma
Q39	Maximum PCI score in the case of epithelioid mesothelioma
Q40	The place of a completeness of cytoreduction score of 2 in the case of epithelioid mesothelioma

TABLE III Level of consensus system

Level of consensus	*Level of evidence*	*Applicability*	*Vote of agreement*	*Status of recommendation*
A	I or II	Discussion is completed; recommendation is applicable in all CHICG centres	>70%	Must be applied as part of the CHICG guidelines
B	II or III	Discussion is advanced; recommendation is applicable in most CHICG centres	50%–70%	Can be applied as part of the CHICG guidelines
C	II, IV, or V	Discussion has started	<50%	Could be applied as part of the CHICG guidelines, depending on the centre
D	Not applicable	Discussion has not occurred or recommendation is not applicable in most CHICG centres	Not applicable	Should not be used outside of a clinical trial and is not part of the CHICG guidelines

CHICG = Canadian HIPEC Collaborative Group

3. CENTRES

Currently, 8 centres in Canada have HIPEC programs (Table I). All are part of an academic university centre, and all are dedicated to the development of HIPEC therapy in Canada.

Centres involved in HIPEC in Canada should be recognized and supported by hospitals, universities, provincial agencies (Q1) and national organizations (Q2). This multilevel support is needed for further development: teaching, research, accessibility, and funding (LOC A).

The CHICG has developed criteria based on the CHICG LOC system, as defined in this guideline, that provincial and national agencies can use to help to coordinate development, improve efficacy, and promote accessibility of HIPEC therapy to Canadian patients (LOC A).

Accreditation will improve accessibility across Canada, because referring physicians will have to be convinced of the benefit of the proposed treatment before they will refer patients to CHICG centres (Q3, LOC A).

3.1 Resources

To create viable Canadian guidelines, a census of the resources available across Canada was taken. All centres have access to computed tomography imaging and modern diagnostic equipment, but access to positron-emission tomography imaging is limited in some areas. Most teams have dedicated intraperitoneal perfusion equipment, but some use a modified extracorporeal circulation machine dedicated to cardiac surgery (an important difference, because perfusion temperature is limited to 41°C with the latter machine). Finally, drug access is not the same across Canada: The choice of chemotherapeutic and dose is limited by some authorities. Oxaliplatin is used for HIPEC at some sites in Canada; mitomycin C is currently available at all sites.

4. TEAMS

Multi- and interdisciplinary teams are needed for the treatment of PSM patients [9,22,23]. Ideally, complex PSM patients should be discussed at local tumour boards (LOC A) [24].

4.1 Team Composition

The core team is composed of surgical oncologists, anesthesiologists, perfusionists (optional), pharmacists, nurses, supportive care professionals (physiotherapists, psychologists, nutritionists, and so on), fellows and residents, pathologists, intensivists, and research personnel (nurses, research coordinator, data manager, and so on). These members should be on site and available when needed. The surgeon directs the team (LOC A) [25]. Other team members (medical oncologists, gastroenterologists, and basic scientists) are ideally on site, but if they are not, they can be part of a network to ensure services and future development.

Surgeons must have surgical oncology training, including appropriate cytoreductive surgery and HIPEC training (Q4, LOC A) and a surgical and research practice dedicated to PSM patients. The rest of the team should have an interest in HIPEC, to support development and research (Q5, LOC B). The minimum number of cases handled each year per surgeon has not yet been defined, but a team or centre should handle at least 20 cases[a] each year (LOC B).

[a] This recommendation is based on recent recommendations from the Peritoneal Surface Oncology Group International. A new team should be handling at least 1 case each month, with the goal of treating 20 patients each year. Until a new team has the referral base to handle 1 case per month, consideration should be given to referring those patients to an existing centre.

Activities performed by each team should be part of the CHICG national research program—at a minimum with respect to quality assurance and contributing to the national prospective database.

One research coordinator and operating room nurse can be identified and dedicated to the development of HIPEC for each local team (Q6, LOC A). The team should be recognized and supported by the institution (hospital and university) (LOC A).

5. PATIENT SELECTION

Patient selection (Table IV) can be divided into patient-related criteria and disease-related criteria. Essentially, a patient must be fit enough to undergo a high-risk procedure, and the disease must demonstrate biologic behaviour that is potentially curable by a combination of CRS and HIPEC [7,26–34]. On occasion, palliative HIPEC for intractable ascites can be considered [35].

5.1 Patient-Related Criteria

Patients should not have any major comorbidities (LOC A), and their Eastern Cooperative Oncology Group performance status at the time of HIPEC should be 0 (LOC A). In selected patients, especially in those whose performance status is reversible, a performance status of 1 can be acceptable [27,36] (LOC A).

Physiologic age should be considered (Q7). When less than 65 years of age, all eligible patients are good candidates (LOC A). When 65 years of age and older, only carefully selected patients without comorbidities and with a low peritoneal carcinomatosis index (PCI) (Table V) and a low-grade tumour should be considered (LOC A) [37,38]. Body mass index should also be considered (Q8). A body mass index above 35 is a relative contraindication [39,40], and age, PCI, and tumour biology should be taken into consideration (LOC B). Patients must be motivated and must understand the extent, the risks, and the potential benefits of the procedure (LOC A). Finally, patients should be encouraged to participate in clinical trials and to be included in the CHICG database (Q9, LOC A).

5.2 Disease-Related Criteria

Disease classification is based on the primary tumour (origin), the tumour histology (and tumour biology), and the extent of disease [11,18,31,32]. Histology is documented by biopsy when feasible, because characteristics can change over time and might not match those of the primary tumour [19]. Extent of disease is evaluated during the preoperative work-up, at laparoscopy in some cases, and at laparotomy.

For PSM of colorectal and classical appendiceal adenocarcinoma origin [41], histology is based on differentiation. A well-differentiated classical adenocarcinoma is considered grade 1, an intermediate or moderate one is grade 2, and a poorly or undifferentiated tumour is grade 3.

For mucinous tumours of the appendix, the histologic classification is more complex and controversial, and thus multiple classifications are used.

TABLE IV Absolute and relative criteria for patient eligibility

Criterion	*Eligibility by origin (level of consensus)*	
	Colorectal	*Appendiceal*
ECOG performance status		
0	Yes (A)	Yes (A)
1	No (C)[a]	Yes (B)
2	No (A)	No (C)[a]
Patient age		
≤65 Years	Yes (A)	Yes (A)
66–74 Years	No (C)[a]	No (C)[a]
≥75 Years	No (B)[a]	No (B)[a]
Body mass index		
≤35	Yes (A)	Yes (A)
≥40	No (B)[a]	No (B)[a]
Histologic grade[b]		
Classical I or II	Yes (A)	Yes (A)
Classical III	No (B)[a]	
DPAM/LAMN/PMCA-I		Yes (A)
Classical III or PMCA		No (B)[a]
Interval from primary tumour to peritoneal carcinomatosis		
Any		Yes (A)
≥6 Months	Yes (A)	
Synchronous or <6 months	No (C)[a]	
Extraperitoneal disease[c]		
Present	No (A)	No (A)
Peritoneal carcinomatosis index		
Any		Yes (B)
≤20	Yes (A)	
>20	No (B)	
Predicted score for completeness of cytoreduction		
0	Yes (A)	Yes (A)
1	No (B)	Yes (A)
2	No (A)	No (C)[c]
3		No (A)

[a] Up to 3 resectable liver metastases can be considered.
[b] Classical signifies adenocarcinoma grades I–III.
[c] Generally, a relative contraindication, but can be considered depending on other patient and disease factors. Referral to a peritoneal surface malignancy treatment centre is advised.

ECOG = Eastern Cooperative Oncology Group; DPAM = disseminated peritoneal adenomucinosis; LAMN = low-grade appendiceal mucinous neoplasm; PMCA[-I] = peritoneal mucinous carcinomatosis[–intermediate].

TABLE V Terminology

Criterion	*Definition*
Peritoneal carcinomatosis index (PCI) [32]	The PCI index describes the extent of carcinomatosis before surgery. The abdomen is divided into 13 sections. Each section is assigned a score from 0 to 3: 0 = No tumour 1 = Tumour < 5 mm 2 = Tumour 5 mm–5 cm 3 = Tumour > 5 cm The sum of the scores for the 13 sections yields a total score out of 39.
Score for completeness of cytoreduction (CC)	Assessment of residual disease after cytoreductive surgery: CC0 = no visible macroscopic disease CC1 = residual disease < 0.25 cm CC2 = residual disease 0.25 cm–2.5 cm CC3 = residual disease > 2.5 cm
Pathology classification of appendiceal neoplasms [42,43]	Low-grade tumour = diffuse peritoneal adenomucinosis or low-grade appendiceal mucinous neoplasm Intermediate-grade tumour = peritoneal mucinous adenocarcinoma–intermediate High-grade tumour = peritoneal mucinous adenocarcinoma or mucinous adenocarcinoma

The presence of signet-ring cells in any group is a marker of a high-grade tumour (grade 3). The term pseudomyxoma peritonei is used more to describe the clinical presentation rather than the pathologic designation. Two main pathologic classifications have been described. In 1995, Ronnett *et al.* [42] divided these tumours into three main groups: namely, low-grade disseminated peritoneal adenomucinosis (DPAM), high-grade peritoneal mucinous carcinomatosis (PMCA), and intermediate-grade PMCA (PMCA-I). In 2003, Misdraji *et al.* [43] described another classification designating appendiceal tumours as either low-grade appendiceal mucinous neoplasms or high-grade mucinous adenocarcinomas. Knowing both of these classifications is important, because both are used in the literature. Both classifications essentially categorize appendiceal tumours into a low-grade or high-grade category. The categories are associated with different natural histories and thus different outcomes.

Extent of disease is reported using the PCI [2,32,44]. A PCI evaluation on preoperative work-up is suboptimal, but provides an indication of whether the PCI exceeds 20, which is usually a contraindication in the case of grade 1 or 2 adenocarcinomas (Q37, Q38). In certain selected cases with favourable patient and disease factors, a PCI exceeding 20 can be considered, depending on the type of resection required (LOC A). In the case of DPAM and PMCA-I (Q36), a high PCI is not a contraindication to proceed to HIPEC. It is important to emphasize that, currently, PCI can be accurately evaluated only at laparotomy [45].

Disease evaluation should be based on a recent work-up, which consists of

- an appropriate history and physical examination;
- appropriate blood tests (carcinoembryonic antigen in non-mucinous disease);
- total colonoscopy;
- computed tomography imaging of chest, abdomen, and pelvis [30,46,47];
- positron-emission tomography–computed tomography imaging (if available in cases of non-mucinous disease) [47];
- confirmation of disease (that is, pathology review, tissue biopsy, or progression on imaging); and
- other appropriate examinations, including laparoscopy as judged necessary by the investigator [48].

5.3 The Eligible Patient

Absolute contraindications as defined by the preoperative work-up (Q10) include

- extra-abdominal disease proven by histology [18,b,c] (Q29, Q32, Q35; LOC A);
- extraperitoneal disease, such as more than 3 liver metastases (Q28, Q31, Q34) [49], and N3 (retroperitoneal) lymph nodes (Q27, Q30, Q33)[d]; or
- unknown primary tumour (Q18)[e].

[b] Appropriate selection of patients is key and must be based on histopathologic examination. All material related to the current episode must be reviewed, and appendiceal adenocarcinoma must be classified according to a recognized classification system (LOC B).

[c] For example, supraclavicular nodes or histology-proven lung metastasis. If histology is not possible, reassessment over a 2- to 3-month period of observation with or without chemotherapy is a good option (LOC B).

[d] If clearly not peritoneal carcinomatosis.

[e] In the case of DPAM or PMCA-I, the patient is eligible for debulking plus HIPEC even if the primary is unknown, and chances of cure are good. In most patients, even women, the primary is the appendix.

At the time of HIPEC, patients should not have signs of bowel obstruction (LOC A), must be responding to neoadjuvant chemotherapy (if used to downstage the disease), and for adenocarcinoma, should have a tumour grade of 1 or 2 (Q22, Q23). Grade 3 adenocarcinoma (including signet-ring cells and PMCA) is a relative contraindication (Q22, Q23) [50,f]. In the case of a short interval (Q17, Q18, Q19, Q21) [46,g] between the primary adenocarcinoma and peritoneal carcinomatosis (synchronous or <6 months), patients should be carefully selected, and neoadjuvant chemotherapy is strongly recommended before CRS plus HIPEC so as to select patients who will benefit the most from this aggressive approach (for example, no development of extra-abdominal or unresectable disease) [13] (LOC B). Patients with up to 3 liver metastases responding to neoadjuvant chemotherapy could be eligible if all other patient and disease criteria are favourable (LOC A) [51,52].

The presence of a frozen pelvis secondary to a rectal cancer recurrence is a relative contraindication to HIPEC (Q25, LOC A).

6. SURGICAL CONSIDERATIONS

Cytoreductive surgery is divided into 3 phases:

- *Assessment Phase:* It is imperative to rule out extraperitoneal disease (for example, >3 liver metastases [49,51] or N3 lymph nodes [6,7,15,17,18]) and to evaluate if a resection is feasible. It is during this phase that the PCI is measured (LOC A). The decision to proceed—or not—is then made [53].
- *Cytoreduction Phase:* The goal is to proceed with the resection of all macroscopic disease [54]. After resection, the completeness of cytoreduction (CC) [27,29,55] is evaluated using the CC score (Table V).
- *HIPEC Phase:* Delivery of HIPEC is performed, followed by creation of diverting stomas (if required). The abdomen is then closed (LOC A). Reconstructions are performed either before or after HIPEC, per the surgeon's choice (LOC A).

6.1 Intraoperative Assessment

The goal of the intraoperative assessment is to confirm the results of the preoperative work-up and to determine the potential completeness of resection (LOC A). A laparotomy through a xyphopubic incision optimizes exposure, and a complete adhesiolysis is mandatory to allow for a meticulous visual inspection (LOC A). The role of laparoscopic exploration is controversial, but it can be of use when extensive miliary peritoneal carcinomatosis is suspected in the presence of a normal preoperative workup [48] (LOC B). Intraoperative ultrasonography is *not* recommended (Q11, LOC B). After adhesiolysis, the PCI score is calculated.

In the case of a high PCI discovered at laparotomy, or when a CC0 resection is not achievable, three subsequent strategies are possible:

- Close the abdomen and consider neoadjuvant systemic chemotherapy until the best tumour response has been achieved and then try again [56] (LOC B). This approach is encouraged in the case of grade 1 or 2 classical adenocarcinoma, when a CC0 resection seems hard to achieve as demonstrated by the assessment or when a very-high-risk resection seems the only way to achieve CC0.
- Proceed to a double cytoreduction with or without systemic chemotherapy between the procedures (LOC C). This approach is used mainly in the case of DPAM or PMCA-I with a PCI score exceeding 20. The goal of the first procedure is to remove all tumour from the upper or the lower abdomen; during the second procedure, the goal is to remove all remaining tumour and to proceed to the HIPEC phase.
- Close the abdomen and consider best supportive care if neoadjuvant systemic chemotherapy is not an option (LOC A).

If unexpected extraperitoneal disease is found during the exploration, the therapeutic plan must be revised (LOC B).

In the case of classical adenocarcinoma, a CC0 resection is required to proceed with HIPEC [57] (LOC A). In the case of DPAM and PMCA-I originating from the appendix [58], a CC0 resection should be the goal, but a CC1 resection could be beneficial and might improve survival (LOC A).

If, at any time, the situations that follow have to be considered to achieve cytoreduction, the treatment plan should be revisited by the team. A decision to go ahead with the procedure should be reserved for very motivated and highly selected patients (LOC B). The relevant situations are

- definitive end stoma with concomitant ileal bladder (pelvic exenteration),
- Whipple procedure,
- short-bowel syndrome, or
- major hepatectomy [34,59].

6.2 CRS

Cytoreduction should be planned according to the area at risk of incomplete resection [60]. The area of the abdomen at highest risk of incomplete resection should be addressed first, because it serves as an indicator—that is, the procedure should be stopped if the resection is not possible [28,61,62] (LOC B).

[f] In highly selected grade 3 cases, if other factors are favourable, HIPEC can be considered (LOC B).

[g] In the presence of DPAM, PMCA-I, or appendiceal adenocarcinoma grade 1 or 2, the primary tumour can be addressed at the same time as the peritoneal carcinomatosis (LOC B).

In selected cases of a high PCI score and DPAM or PMCA-I, performing the cytoreduction as two separate procedures is an option if complete cytoreduction is expected to last more than 10–15 hours, if blood loss is too high, or if surgical complications make proceeding with HIPEC a contraindication (Q15, LOC C). In such a situation, the infra-mesocolic area is addressed during the first surgery; the second surgery focuses on the supra-mesocolic cytoreduction and HIPEC. A complete adhesiolysis of the infra-mesocolic abdomen should be performed during the second procedure before HIPEC. An adhesiolysis of the upper abdomen can be more complex [63,64] (thus the recommendation to perform cytoreduction of the upper abdomen as the second procedure).

6.2.1 Peritonectomy

Selective peritonectomy is defined as disease-oriented peritonectomy. These procedures are selective when they are performed to remove macroscopic disease. They are indicated when a CC0 resection is performed for an adenocarcinoma of colorectal origin or when a CC1 resection is performed for a DPAM or PMCA (LOC B).

Radical peritonectomy is defined as the resection of all parietal, diaphragmatic, and near total mesenteric peritoneum. It can be indicated when a CC0 resection is performed for a DPAM or PMCA-I (Q12, LOC C).

6.2.2 Reconstruction

Bowel continuity is restored before or after HIPEC, per the surgeon's preference (LOC A). Stomas are performed after HIPEC (LOC B). Anastomoses should be created according to the usual principles and surgeon's preference (LOC A). Hand-sewn or stapled anastomoses are acceptable (LOC A).

Definitive stomas should be created for the usual reasons, but diverting stomas should be considered (Q15) for high-risk anastomoses such as left-sided anastomoses and low anterior resections (LOC A).

Total gastrectomy is occasionally necessary to achieve a CC0 resection or in the case of gastric devascularization. Although a standard reconstruction with a Roux-en-Y esophagojejunostomy is generally performed, the very high risk associated with that anastomosis has to be recognized, and early re-operation and drainage should be considered if a leak occurs (LOC A).

6.3 HIPEC

Delivery of HIPEC can be performed using an open or a closed technique [65]. Both techniques are performed across the country and are considered safe. The highest risk for chemotherapy exposure is during clean-up, which is the same for both procedures. Whichever technique is chosen, the dose, the duration, and the temperature of perfusion should not be modified (LOC B).

Oxaliplatin and mitomycin C are currently the most commonly used drugs. Doxorubicin, irinotecan, cisplatin, and others can be used for special indications [57,66]. The recommended dose of oxaliplatin is 460 mg/m^2 perfused for 30 minutes at 43°C [44,67–71] (LOC B). Systemic 5-fluorouracil and leucovorin can be administered by the anesthetist to potentiate oxaliplatin efficacy and should be considered for classical adenocarcinoma of colorectal origin (LOC B). The dose of 5-fluorouracil is 400–450 mg/m^2 administered over 30 minutes by the intravenous route, 30–60 minutes before HIPEC (LOC B). Leucovorin (20 mg/m^2) is given before the 5-fluorouracil, intravenously over 10 minutes. When mitomycin C is used [14,72], the U.S. guidelines suggest 40 mg as a fixed dose to be delivered in 2 syringes [73,74] (LOC B). Taking local habits, equipment, and funding into consideration, the ranges accepted in Canada are listed in Table VI. No concomitant systemic chemotherapy is given when mitomycin C is used for HIPEC (LOC A).

7. OUTCOMES

Overall survival varies from 20% to 90% at 5 years [70,72,75–79]. It is influenced [26,29,31,32,55,78] by origin of the PSM, histology, PCI score, patient comorbidities (performance status, body mass index, health problems), cancer-related symptoms, and surgical morbidity and mortality [79,80].

Good prognostic factors include appendiceal origin, DPAM and low-grade tumours, a low PCI score, and a patient who is asymptomatic and has no comorbidities [11].

Evaluation of outcomes is needed for the future development and funding of HIPEC programs [81]. To assess outcomes, all Canadian patients should be included in a prospective database, ideally with matched tissues (normal and cancerous).

Outcomes that should be measured include complications [79,80], overall survival [2,11,28,44,57,62,69,82–85], disease-free survival, quality of life [86,87], and cost-effectiveness [88].

8. RESEARCH

The priority of the CHICG research program is to maintain a national prospective database and matched-tissue tumour bank. All Canadian PSM patients should be included in a database, either locally or nationally, and have tumour, normal tissue, and blood stored in a local tumour bank, if available.

9. ACCESSIBILITY

9.1 Statistics

As published by the Canadian Cancer Society [89], 23,900 new colorectal cancer cases were expected in 2013, and up to 10% (n = 2390) would be expected to have peritoneal carcinomatosis. Of the latter group,

TABLE VI Administration of hyperthermic intraperitoneal chemotherapy

Drug	*Dose*	*Duration (minutes)*	*Intra-abdominal temperature (°C)*	*Concomitant intravenous therapy?*
Oxaliplatin	300 mg/m^2	30	40–43	5-Fluorouracil (400–450 mg/m^2)
	400 mg (fixed dose)	60	40–43	plus leucovorin (20 mg/m^2)
	460 mg/m^2	30	40–43	given 30–60 minutes before the oxaliplatin
Mitomycin C	10–30 mg/m^2	60–90	40–43	None
	30–40 mg (fixed dose)	60–90	40–43	None
	1 mg/kg (70 mg maximum)	60–90	40–43	None

30%–35% would be estimated to be eligible for HIPEC (approximately 800 patients). The incidence of pseudomyxoma peritonei (DPAM and PMCA-I) is 1 case annually per million population. In Canada, this incidence represents between 30 and 40 new cases annually, with most patients being eligible for CRS plus HIPEC.

9.2 Accessibility

After the CHICG census, it was estimated that the existing Canadian teams can treat 200–250 new patients annually—a number that doesn't come close to matching the number of predicted new cases. Ideally, a national coordinating centre should be created to improve accessibility (Q16).

10. SUMMARY

Given the increasing evidence that selected patients with PSM can benefit from an aggressive surgical approach combined with HIPEC, the guidelines presented here are intended to provide the physicians who treat these patients with the necessary tools to do so. The key messages to take from these guidelines are the importance of a multidisciplinary team approach, the need for strict patient selection, early referral to a centre with expertise in the surgical management of PSM, and close collaboration between medical and surgical oncologists to devise a treatment plan. It will be important to standardize the approach to these patients so that the benefits of CRS and HIPEC can be realized across the country and so that all eligible patients have the opportunity to receive treatment.

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12. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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APPENDIX A: THE CANADIAN HIPEC COLLABORATIVE GROUP

Mandate

Spearheaded by the Colorectal Cancer Association of Canada, the Canadian HIPEC Collaborative Group (CHICG) is a national network of interdisciplinary health professionals, patient advocates, and dedicated partners whose mission is to improve the lives of patients with peritoneal surface malignancy (PSM) by improving the accessibility of, and advancing the standard of care for, treatment involving hyperthermic intraperitoneal chemotherapy (HIPEC). The CHICG is dedicated to awareness, education, standards, research, and development of HIPEC treatment in Canada through our mission objectives.

Mission Objectives

- Creation of an interdisciplinary clinical pathway and dedicated network for the management of PSM patients
- Creation and maintenance of uniformity within and among Canadian institutions as it relates to the determination of quantitative prognostic indicators in PSM patient selection and case management
- Development and maintenance of a national database and research program to assist with the determination of optimal treatment options for patients with PSM
- Development and maintenance of standards based on current evidence, and evaluation of best practices

Structure

The CHICG coordinating committee (CHICG-CC) comprises one representative from each accredited Canadian team, plus one representative of the business committee. The CHICG-CC is responsible for scientific and strategic planning, and coordinates subcommittees on accessibility; data and tissue banking; standardization and guidelines review; basic and preclinical research; phase I, II, and III trials; technology evaluation; and quality control and audit.