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Relevance of intraperitoneal chemotherapy for preventing or treating neoplasms of the peritoneal surfaces

Peritoneal metastases secondary to colorectal cancer

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Québec

SUMMARY

Relevance of intraperitoneal chemotherapy for preventing or treating neoplasms of the peritoneal surfaces - Peritoneal metastases secondary to colorectal cancer

Context

Peritoneal surface neoplasms (PSNs) are a diverse group of cancers that most often show up as peritoneal metastases secondary to other tumours, especially colorectal, ovarian, gastric, and appendicular ones. People with PSN rarely achieve cure after systemic treatment alone. For resectable PSNs, one therapeutic option is to combine a systemic treatment with radical surgical resection of peritoneal metastases, which may be paired with intraperitoneal (IP) chemotherapy during or after surgery. The preventive use of intraperitoneal chemotherapy has also been studied in people at high risk of developing metachronous peritoneal metastases following surgical resection of their primary tumour.

In order to promote the judicious use of this intervention and harmonize the care of affected individuals, the Institut national d'excellence en santé et services sociaux (INESSS) has been mandated to issue an opinion on the clinical relevance of intraperitoneal chemotherapy for preventing or treating PSNs. This opinion is expected to specify the modalities of intraperitoneal chemotherapy to be recommended for recognized therapeutic indications, where applicable. This work is divided into five sections relating to the most common types of PSN encountered in clinical practice (peritoneal mesothelioma and peritoneal metastases of colorectal, ovarian, gastric, and appendicular origin).

This report focuses on the management of peritoneal metastases secondary to colorectal cancer.

Methodology

A comprehensive review of scientific literature and gray literature was conducted to identify scientific information on the clinical relevance of intraperitoneal chemotherapy for the management of colorectal-derived PSNs, both in a preventive and curative context. Information on population and sociocultural considerations surrounding the practice of the intervention was also extracted. The literature selected includes randomized clinical trials (7 publications from 5 studies) as well as international recommendations from health technology evaluation reports, clinical practice guidelines, and publications from expert groups (13 publications from 10 organizations).

Consultations were also conducted with clinicians who had experience with this modality, as well as with the Comité de l'évolution des pratiques en oncologie (CEPO) et le Comité délibératif permanent – Modes d'intervention en santé of INESSS.

Findings

The integration of scientific, contextual, and experiential data has led to the following findings and uncertainties:

Health needs and HIPEC practice in Quebec

- People with metastatic colorectal cancer that has spread to the peritoneum have a poor prognosis and significantly impaired quality of life;
- Treatment of colorectal-derived PSNs generally relies on systemic chemotherapy, which may be combined with palliative surgery if peritoneal tumour implants cause disabling or life-threatening symptoms (obstruction, malnutrition, etc.). However, these approaches offer patients only limited survival;
- Radical locoregional treatment with a curative intent may be considered in combination with systemic treatment when peritoneal metastases are considered completely resectable. It consists of complete cytoreduction of peritoneal tumour implants, with or without HIPEC. The aim of HIPEC is to bring cytotoxic agents into direct contact with the peritoneal surfaces in order to maximize the chemotherapy dose delivered to residual microscopic tumour implants after cytoreduction, while reducing systemic toxicity;

Assessment of the level of scientific evidence

- Few phase III RCTs have evaluated the clinical efficacy and safety of HIPEC in preventing or treating colorectal-derived PSNs. The studies selected did not evaluate quality of life in this context. They were considered to be of moderate methodological quality;
- The studies are not very comparable to each other due to heterogeneity in the clinical profile of the study populations, the completeness of information on the characteristics of the treatment groups, surgical procedures and protocols, the HIPEC and systemic adjuvant chemotherapy used and the timing of their administration, and the primary outcome measures;
- The populations studied are considered sufficiently representative of those targeted in Quebec. However, the care setting surrounding the administration of HIPEC for the prevention of PSN is different.

Efficacy and safety of HIPEC

In a preventive context in individuals treated for colorectal tumours with a high risk of metachronous peritoneal metastases:

- The administration of **mitomycin C**-based HIPEC (30 mg/m^2, 60 minutes) in an intraoperative adjuvant setting after primary tumour resection increases locoregional control (absence of relapse in the tumour bed or peritoneal surfaces) compared to primary treatment without HIPEC, without however altering overall

survival or disease-free survival. This HIPEC approach does not affect the frequency of serious complications (level of evidence: low);

- The administration of **oxaliplatin**-based HIPEC (460 mg/m^2, 30 minutes) in an adjuvant intraoperative or sequential setting after primary tumour resection does not alter peritoneal recurrence-free survival compared with primary treatment without HIPEC. The safety of this HIPEC approach is uncertain, but the risk of serious complications cannot be ruled out (level of evidence: insufficient to low);
- The administration of **oxaliplatin**-based HIPEC (300-460 mg/m^2 ± irinotecan 200 mg/m^2, 30 minutes) in a prophylactic context when second-look surgery is performed after primary tumour treatment does not alter disease-free survival compared to clinical/radiological surveillance. The combination of second-look surgery and HIPEC leads to serious adverse effects that are avoided with clinical/radiological surveillance (level of evidence: low);
- International organizations:
    - did not make any recommendations on the administration of HIPEC in an adjuvant or prophylactic setting in the presence of a primary colorectal tumour with a high risk of developing metachronous peritoneal metastases, with the exception of one organization that is not in favor of its use in this setting.
    - identified as a research priority the study of the efficacy of HIPEC in an adjuvant or prophylactic setting.

In a curative context in patients treated for resectable peritoneal metastases of colorectal origin:

- The administration of intraoperative mitomycin C-based HIPEC (35 mg/m2, in 3 fractions over 90 minutes) after cytoreduction of peritoneal metastases, in combination with postoperative systemic chemotherapy, increases progression-free survival and overall survival compared to systemic chemotherapy alone, but carries an increased risk of serious adverse effects. The observed clinical benefit is attributed to the combination of cytoreduction and HIPEC, as it is not possible to determine the respective contribution of these locoregional procedures (level of evidence: low);
- The administration of intraoperative oxaliplatin-based HIPEC (360-460 mg/m2, 30 minutes) after complete cytoreduction of peritoneal metastases, in combination with perioperative systemic chemotherapy, does not alter overall survival compared with complete cytoreduction without HIPEC in combination with perioperative systemic chemotherapy, but it increases the frequency of serious complications and the length of hospitalization (level of evidence: low);
- RCT results suggest that the absence of macroscopic residual disease after cytoreductive surgery is a key predictor of the efficacy of intraperitoneal treatment.

- International organizations:
    - Have varying opinions on the usefulness of intraoperative HIPEC after complete cytoreduction for the initial locoregional treatment of resectable peritoneal metastases (4 organizations against, 4 in favor, and 3 recommending it only for selected patients; recommendations/consensus of varying strength). Populations considered candidates for locoregional treatment vary between organizations, particularly with regard to the severity of peritoneal involvement, the risk of peritoneal recurrence, and extraperitoneal involvement;
    - do not recommend oxaliplatin-based HIPEC (PRODIGE 7 approach) due to its unfavorable efficacy and safety profile;
    - Those in favor of administering intraoperative HIPEC after complete cytoreduction favor a mitomycin C-based HIPEC protocol (Verwaal et al. approach or a variant thereof);
    - have identified as research priorities the study of the efficacy of complete cytoreduction combined with HIPEC compared to complete cytoreduction alone, as well as in relation to previous systemic treatments. A few studies are currently underway in this regard.

Perspective in the Quebec context

In a preventive context in individuals treated for colorectal tumours with a high risk of metachronous peritoneal metastases:

- The administration of HIPEC in an intraoperative adjuvant or sequential setting after primary tumour resection is not used in Quebec;
- Clinicians consider that the available evidence does not support the use of HIPEC in a prophylactic setting during second-look surgery or in an adjuvant setting after primary resection;
- In addition, adjuvant HIPEC approaches would be difficult to apply in the Quebec healthcare context for organizational reasons (coordination of peripheral and referral centers, waiting times for certain care and services, etc.).

In a curative context in people treated for resectable peritoneal metastases of colorectal origin:

- Oxaliplatin-based HIPEC (PRODIGE 7 protocol) is not used in Quebec;
- The administration of intraoperative mitomycin C-based HIPEC (a variant of the protocol developed by Verwaal et al.) after complete cytoreduction of colorectal peritoneal metastases, in combination with perioperative systemic chemotherapy, is used in Quebec to treat a small number of carefully selected patients in a few referral centers specializing in the management of PSNs. This approach is used after discussion within the comité du diagnostic et du traitement du cancer (CDTC) (cancer diagnosis and treatment committee);

- Clinicians have mixed opinions on the usefulness of mitomycin C-based HIPEC in a curative context after complete cytoreduction. Some believe that the available evidence is uncertain and does not allow for a conclusion to be drawn on the clinical relevance of adding mitomycin C HIPEC (compared to complete cytoreduction without HIPEC) during intraperitoneal therapy. Others believe that the effect of this intraperitoneal treatment is attributable to the combination of cytoreduction and mitomycin C-based HIPEC;
- Clinicians consider that the available evidence does not support the use of an oxaliplatin-based HIPEC protocol in a curative context after complete cytoreduction;
- Clinicians consider that the mitomycin C-based HIPEC protocol used in a curative context in Quebec causes far fewer serious adverse effects than the oxaliplatin-based HIPEC protocol.

INESSS Position and Recommendations

INESSS issues the following recommendations:

In individuals treated for colorectal cancer **with a high risk of developing metachronous peritoneal metastases**:

- Administration of oxaliplatin-based HIPEC is not recommended:
  - in an intraoperative or sequential adjuvant setting after primary tumour resection;
  - in a prophylactic setting when a second-look surgery is performed (in the absence of clinical or radiological signs of peritoneal recurrence);
- The administration of intraoperative adjuvant mitomycin C-based HIPEC after primary tumour resection is not recommended. Additional evidence is needed.

In patients **treated for peritoneal metastases** of colorectal origin undergoing complete cytoreductive surgery:

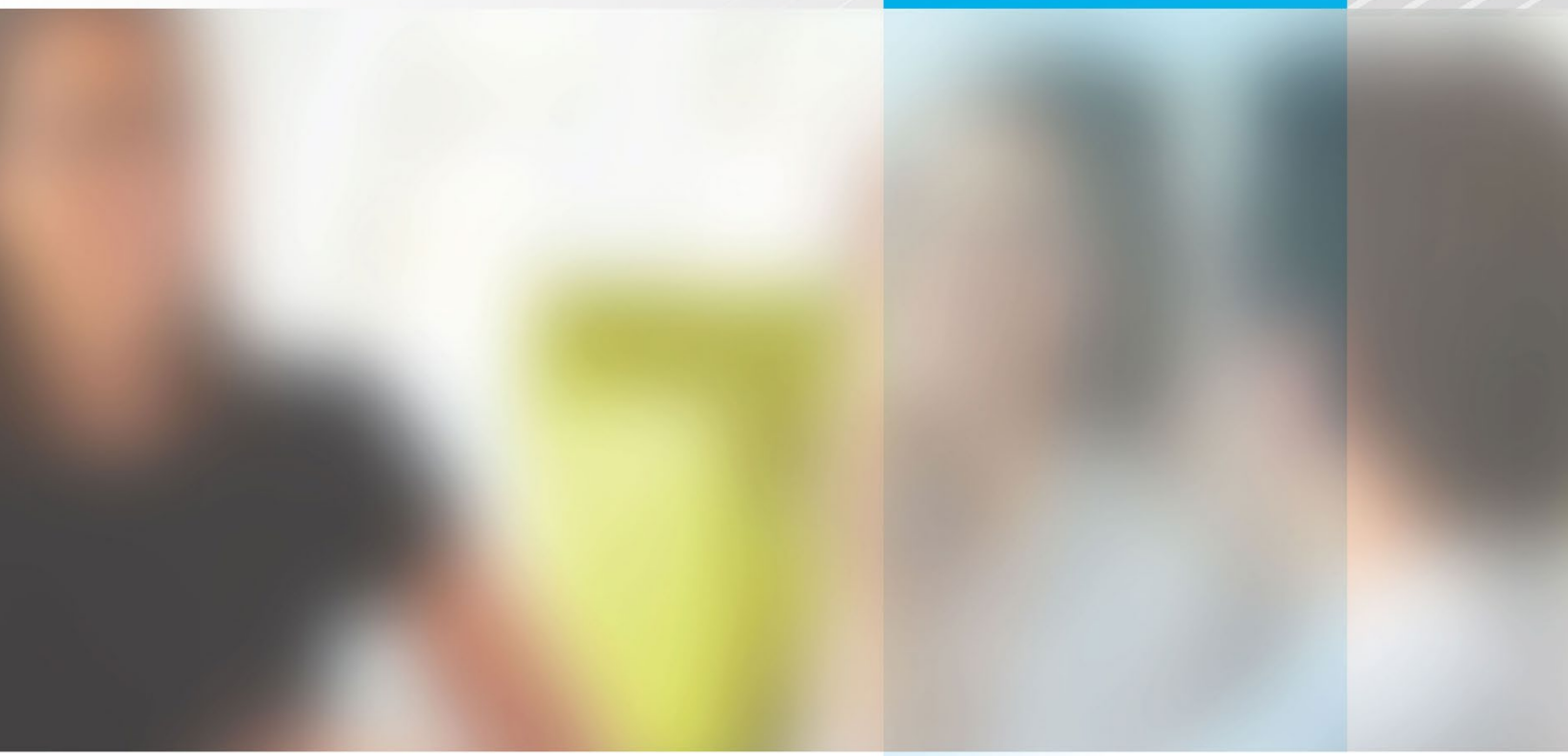
- The administration of intraoperative oxaliplatin-based HIPEC is not recommended;
- there is currently insufficient data to determine the relevance of routine administration of intraoperative mitomycin C-based HIPEC. Additional evidence is needed to determine the efficacy and safety of this approach, its impact on quality of life, and who is likely to benefit.

In support of this position, INESSS makes some additional recommendations aimed at promoting optimal healthcare provision:

- Individuals with colorectal tumours at high risk of developing metachronous peritoneal metastases, as well as those with colorectal peritoneal metastases (resectable or not, with or without extraperitoneal metastases) should be referred as soon as possible to a referral center with a multidisciplinary healthcare team specializing in peritoneal surface neoplasms.
    - the proposed overall management plan (follow-up strategies, treatment options) should be discussed in a CDTC meeting, regardless of whether locoregional treatment is planned;
    - a colorectal tumour should be considered at high risk for metachronous peritoneal metastases in the presence of synchronous peritoneal metastases, tumour perforation, or ovarian metastases;
    - in the presence of completely resectable peritoneal metastases, complete cytoreductive surgery should be considered in combination with systemic treatment.
- In the presence of synchronous peritoneal metastases not detected during preoperative clinical and radiological examinations, any cytoreductive surgery at the time of primary resection should be preceded by a consultation with a surgeon specializing in peritoneal surface neoplasms at a referral center;
- Decision to use IP chemotherapy should be made in an informed and shared manner with the person concerned, based on complete and balanced information regarding expected benefits, risks and potential adverse effects, uncertainties associated with the available evidence, and other relevant therapeutic options. This approach aims to support a choice that is consistent with the person's values, preferences, and clinical situation.
- Since IP chemotherapy is an intervention that is not widely used, for which evidence of its efficacy and safety is limited in terms of methodology, the collection and sharing of clinical data from specialized centers offering the treatment (regardless of the indication) is encouraged in order to support the development of knowledge and evidence in the real-world healthcare setting in Quebec.

Update of Recommendations

The relevance of updating this opinion will be assessed and determined based on the availability of new data supporting any of the dimensions evaluated in this opinion, including the publication of studies, systematic reviews, meta-analyses, recommendations from international organizations, or national regulations. Various studies are currently underway, including the GECOP-MMC study, which compares the administration of mitomycin C-based HIPEC after complete cytoreduction with complete cytoreduction without HIPEC for the locoregional treatment of resectable peritoneal metastases (estimated primary completion date: January 2027).



Siège social

2535, boulevard Laurier, 5e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563
inesss.qc.ca

Institut national d'excellence en santé et en services sociaux
Québec