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The relevance of intraperitoneal chemotherapy in preventing or treating neoplasms of the peritoneal surfaces - Peritoneal metastases secondary to ovarian cancer

English summary

Une production de l'Institut national
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Québec

SUMMARY

The relevance of intraperitoneal chemotherapy in preventing or treating neoplasms of the peritoneal surfaces - Peritoneal metastases secondary to ovarian cancer

Context

Peritoneal surface neoplasms (PSNs) comprise a heterogeneous group of cancers characterized by involvement of the abdominal cavity. They are most often secondary to intraperitoneal spread of tumours originating in the colorectum, ovaries, stomach, or appendix. Peritoneal metastases are associated with a poor prognosis, particularly due to the limited efficacy of systemic chemotherapy in this context.

The majority of ovarian cancer cases are diagnosed at an advanced stage, and peritoneal dissemination is common at diagnosis and during recurrence. Despite advances in systemic treatments, patient survival remains limited, which has sparked growing interest in complementary locoregional approaches.

Intraperitoneal (IP) chemotherapy, combined with cytoreductive surgery, aims to deliver cytotoxic agents directly into the peritoneal cavity to treat residual tumour microdeposits. Among the possible methods of IP chemotherapy administration, hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) have been the most studied in cases of advanced or recurrent ovarian cancer. However, IP chemotherapy remains rarely integrated into clinical practice due to surgical risks and uncertainty surrounding its optimal indications.

In this context, the Direction de la cancérologie of the ministère de la Santé et des Services sociaux (MSSS) has mandated the Institut national d'excellence en santé et en services sociaux (INESSS) to evaluate the clinical relevance of IP chemotherapy for the prevention or treatment of peritoneal metastases secondary to ovarian cancer, and to formulate recommendations, where appropriate, to support its optimal, equitable, and harmonized use across the Quebec healthcare network.

Methodology

A systematic review of the literature was conducted to assess the clinical relevance of IP chemotherapy for the management of peritoneal metastases secondary to ovarian cancer. The literature reviewed included phase III randomized controlled trials (RCTs). In addition, a narrative review of the economic literature specifically focusing on clinically recognized indications was conducted. Consultations with clinicians were also carried out. A permanent deliberative committee supported the development of findings and recommendations following the completion of the work.

Findings

By integrating scientific, contextual, and experiential data, the following findings were identified:

Health needs

- In 2023, 633 new cases of ovarian cancer were diagnosed in Quebec, about two-thirds of which were at an advanced stage. This disease caused 463 deaths in 2021, ranking as the fifth deadliest cancer among women.
- Peritoneal dissemination is common (>70% at diagnosis) and is the main site of recurrence.
- Treatment for ovarian-origin PSN generally relies on a strategy combining complete or optimal cytoreductive surgery, platinum-based chemotherapy, and personalized maintenance therapies based on the patient's molecular profile. However, this approach is associated with limited patient survival.
- The development of locoregional strategies, such as IP chemotherapy, is generating interest as a means to improve disease control.

Current practice in Québec

- No comprehensive administrative or registry data allow characterization of HIPEC use in Québec.
- Based on consultations with various stakeholders, HIPEC is performed in Quebec at a limited number of specialized centers—five institutions—each treating an estimated annual volume of between 30 and 60 patients with advanced-stage ovarian cancer.
- Patients treated with HIPEC in Quebec undergo a rigorous selection process, based primarily on clinical, functional, and surgical criteria as well as evaluation by specialized teams, which limits the procedure to cases likely to benefit from it.

Assessment of the level of scientific evidence

- Eight RCTs were selected to evaluate the efficacy, safety, and quality of life associated with IP chemotherapy in the treatment of peritoneal metastases secondary to ovarian cancer. No study evaluated the use of IP chemotherapy for preventive purposes.
- Among the modalities evaluated, HIPEC has been the subject of the largest number of studies, whereas EPIC has been examined in only two studies.
- The selected studies are not readily comparable with one another and have certain methodological limitations (limited transferability, heterogeneity in follow-up, presence of confounding factors, insufficient statistical power for certain parameters) that must be taken into account when interpreting the results.

Efficacy, safety and quality of life

In the context of primary cytoreduction in patients treated for newly diagnosed resectable peritoneal metastases of ovarian origin:

- The administration of EPIC does not appear to compromise overall survival and progression-free survival in patients (level of evidence: low). This intervention increases grade ≥ 3 adverse events (without increasing the number of deaths) and leads to a decline in quality of life compared to systemic chemotherapy (level of evidence: moderate and high).
- The evidence remains limited and insufficient to draw conclusions regarding the efficacy, safety, and impacts on quality of life associated with the use of HIPEC in this context (insufficient level of evidence).
- International organizations generally do not recommend this clinical practice, or they limit its use to clinical research settings.
- The consulted clinicians believe that current evidence does not demonstrate any clinical benefit associated with the administration of IP chemotherapy in the context of primary cytoreduction.
- In Quebec, HIPEC is not administered in the context of primary cytoreduction. If it were to be used, its implementation would be hindered by several organizational, diagnostic, and clinical challenges, notably the frequent lack of histological confirmation prior to primary cytoreduction, as well as delays in accessing imaging and the operating room.

In the context of interval cytoreduction following neoadjuvant chemotherapy in patients treated for newly diagnosed resectable peritoneal metastases of ovarian origin:

- Administration of HIPEC improves progression-free survival, disease-free survival, and overall survival; it has no impact on the number of adverse events, regardless of grade, or grade ≥ 3 events (including mortality), and does not result in any deterioration in patients' quality of life compared with the same procedure without HIPEC (level of evidence: moderate to high).
- Most international organizations support the administration of HIPEC during complete or optimal interval cytoreduction following neoadjuvant chemotherapy (6 in favor, 1 against, and 5 recommending it only for selected patients; recommendations/consensus of varying strength)
- The patient populations considered candidates for locoregional therapy vary among organizations, particularly with regard to the type of ovarian cancer, the extent of cytoreductive surgery, extraperitoneal involvement, and the interval between the last dose of neoadjuvant chemotherapy and HIPEC.

- The treatment regimen used in the OVHIPEC study (cisplatin 100 mg/m² administered over 90 minutes at 42–43 °C) has the broadest consensus (4 professional associations, regulatory agencies, or expert groups) in the context of interval cytoreduction.
- Cost-efficacy analyses reported in the literature support the use of HIPEC in the context of interval cytoreduction. However, the magnitude of the benefits and the level of uncertainty vary depending on the assumptions and perspective adopted.
- The clinicians consulted believe that the evidence supporting the use of HIPEC in the context of interval cytoreduction is of high quality and readily applicable to the Quebec context.
- In Quebec, HIPEC is performed almost exclusively in the context of interval cytoreduction. In practice, Quebec centers follow the OVHIPEC-01 study protocol, which involves cisplatin-based HIPEC combined with thiosulfate to reduce renal toxicity.

In the context of secondary cytoreduction following recurrence after systemic treatment in patients treated for resectable peritoneal metastases of ovarian origin:

- Interpreting the evidence in the context of secondary cytoreduction is complex, as it is difficult to distinguish true recurrence from continued disease progression following suboptimal initial cytoreduction—an issue raised by the clinicians consulted.
- Available data suggest that the administration of HIPEC improves overall survival and does not increase grade ≥ 3 adverse events (including mortality) compared with the same intervention without HIPEC (level of evidence: high). However, data on quality of life remain limited (level of evidence: insufficient).
- International organizations generally do not recommend the administration of HIPEC in routine practice; its use is proposed only for certain selected platinum-sensitive patients or is limited to clinical research settings.
- Despite statistically significant results in some studies, the clinicians consulted believe that the observed benefits remain modest and of limited clinical relevance. Furthermore, the transferability of the results from the selected studies to Quebec practice is considered limited, particularly due to therapeutic strategies not used in Quebec, such as neoadjuvant chemotherapy preceding secondary cytoreduction.
- Based on this information and considering that safety appears to be maintained, the clinicians consulted believe that HIPEC could be considered on a case-by-case basis, but they emphasize that the available data remain insufficient to establish this approach in Quebec.

Environmental considerations

- The available data on the environmental impacts of HIPEC remain very limited. To date, no life cycle assessment of HIPEC in a hospital setting comparable to that of Quebec has been identified. Although the prolonged duration of surgery and the use of anesthetic gases are the main sources of GHG emissions associated with HIPEC, its specific environmental impact remains relatively marginal given the low volume of patients treated and the limited number of centers performing this procedure.

INESSS position and recommendations

In light of all the scientific, contextual, and experiential data collected, the findings presented, and the deliberation process conducted, INESSS issues the following recommendations:

In patients treated for peritoneal metastases of ovarian origin who undergo complete or optimal **primary cytoreductive surgery**:

- the administration of cisplatin- or carboplatin-based EPIC is not recommended.
- there is currently insufficient data to determine the appropriateness of routine administration of an HIPEC. Additional evidence is needed.

In patients treated for peritoneal metastases of ovarian origin who undergo complete or optimal **interval cytoreductive surgery following neoadjuvant therapy**:

- administration of cisplatin-based HIPEC should be considered.
- when considered, the preferred treatment consists of administering 100 mg/m² of cisplatin heated to 42–43 °C, delivered as 50 mg/m² at the start of the procedure, 25 mg/m² at 30 minutes, and 25 mg/m² at 60 minutes, for a total duration of 90 minutes.

In patients being treated for peritoneal metastases of ovarian origin who undergo complete or optimal **secondary cytoreductive surgery following a recurrence**:

- administration of cisplatin-based HIPEC may be considered.
- when considered, the preferred HIPEC protocol consists of administering cisplatin (100 mg/m²) heated to 40 °C for a total duration of 90 minutes.

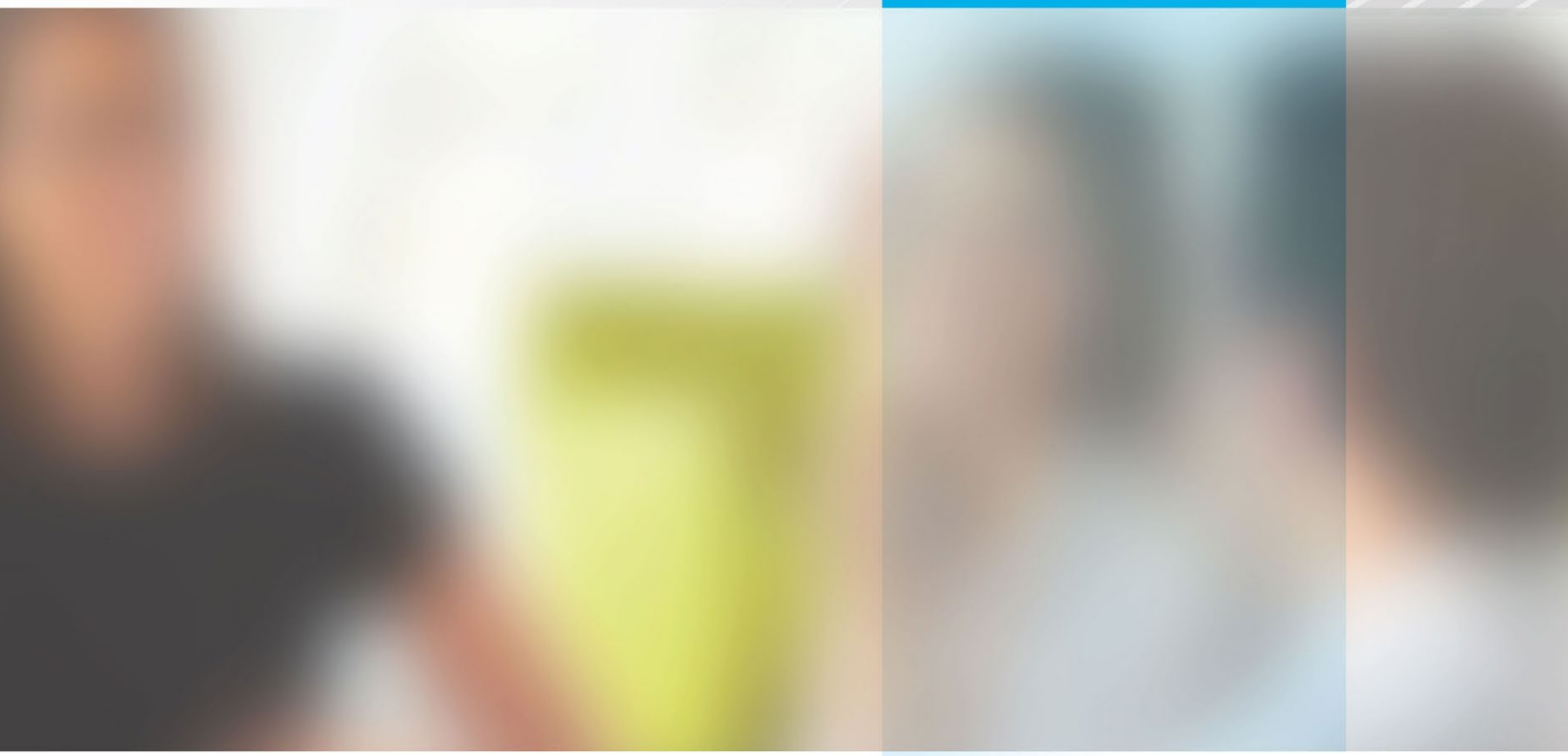
In support of these positions, INESSS has issued the following additional recommendations aimed at promoting optimal healthcare provision:

- Patients with peritoneal metastases of ovarian origin (whether resectable or not, and regardless of the presence or absence of extraperitoneal metastases) should be referred as soon as possible to a referral center with a multidisciplinary care team specializing in neoplasms of the peritoneal surfaces. The proposed comprehensive management plan (follow-up strategies, treatment options) should be discussed in a comité du diagnostic et du traitement du cancer (CDTC), regardless of whether locoregional treatment is being considered.
- The decision to resort to IP chemotherapy should be made in an informed manner and shared with the patient based on comprehensive and balanced information regarding the expected benefits, risks, and potential adverse effects, the uncertainties associated with the available evidence, as well as other relevant therapeutic options. This approach aims to support a choice consistent with the patient's values, preferences, and clinical situation.
- Since IP chemotherapy is a very little practiced intervention and evidence regarding its efficacy and safety is scarce, the collection and sharing of clinical data from specialized centers offering the treatment (regardless of the indication) should be encouraged to support the development of knowledge and evidence in actual healthcare settings in Quebec.

Recommendations update

The relevance of updating this opinion will be assessed and determined based on the availability of new data supporting any of the aspects evaluated in this statement, including the publication of studies, systematic reviews, meta-analyses, recommendations from international organizations, or national regulations.

Various studies are currently underway, including OVHIPEC-2 and CHIPPI-1808, which evaluate the addition of a cisplatin-based HIPEC to primary cytoreduction (expected primary completion date: April 2026 and August 2028), as well as the KOV-HIPEC-02 trial, which compares a doxorubicin- and mitomycin C-based HIPEC to systemic chemotherapy (at the physician's discretion) following secondary cytoreduction in the setting of recurrence (expected primary completion date: December 2029).



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