Developing a hyperthermic intraperitoneal chemotherapy (HIPEC) gynecologic oncology program: a Canadian experience

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ABSTRACT
Hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment option for epithelial ovarian cancer following cytoreductive surgery. The intraperitoneal spread of the disease makes the peritoneal cavity an ideal target for drug delivery. HIPEC has shown promising results in improving overall survival in epithelial ovarian cancer patients when performed during interval cytoreductive surgery. Recent studies have provided level 1 evidence supporting increased overall survival in stage III ovarian cancer patients treated with HIPEC during interval cytoreduction. Meta-analyses have further confirmed the survival improvement in women receiving HIPEC. Despite its inclusion in guidelines, many centers have been hesitant to implement HIPEC programs due to perceived obstacles, such as increased morbidity, cost, and resource requirements. Studies have shown that morbidity rates are acceptable in selected patients, and the addition of HIPEC to cytoreductive surgery is cost effective. Therefore, the main barrier to implementing HIPEC programs is related to resource requirements and logistics, but with proper preparation, these challenges can be overcome. Establishing a successful HIPEC program requires institutional support, a knowledgeable and dedicated team, adequate resources and equipment, and proper training and audit. This review aims to provide evidence based information to guide the development of successful HIPEC programs, including preoperative, anesthetic, and surgical considerations. It also reviews the different equipment and protocols for the perfusion and common postoperative events.

INTRODUCTION
Hyperthermic intraperitoneal chemotherapy (HIPEC) immediately after cytoreductive surgery has been performed and studied for several years. Epithelial ovarian cancer has the highest mortality among gynecological malignancies due to its advanced stage at diagnosis and high recurrence rate, despite aggressive treatment. Its intraperitoneal spread makes the peritoneal cavity an ideal target for drug delivery. For this reason, HIPEC has emerged as an interesting treatment option for ovarian cancer and has been studied in primary (upfront or interval debulking) and recurrent settings.

In 2018, level 1 evidence supporting an increase in overall survival of 11.8 months in stage III ovarian cancer treated with HIPEC during interval debulking surgery was published. In 2022, the final survival analysis of a Korean trial did not show an increase in overall or progression free survival in the intention-to-treat population. However, the subgroup analysis strictly evaluating HIPEC during interval surgery did show an increase in overall survival by 13.6 months. Since these publications, meta-analyses have confirmed the survival improvement in patients receiving HIPEC during interval cytoreductive surgery. Despite incorporating HIPEC in the National Comprehensive Cancer Network guidelines, many centers have not yet considered offering HIPEC to patients because of real or perceived obstacles to mounting such a program. The potential increased morbidity, as well as cost and resource requirements, have been cited as barriers to the implementation of HIPEC.

The perception of the high morbidity associated with HIPEC has been, in part, biased by the initial reports in ovarian cancer patients with the use of cisplatin without nephroprotective agents and the morbidity associated with high risk procedures, including multiple bowel resections. Morbidity appears to be proportional to the extent of cytoreduction and is acceptable in selected patients; the G3–G4 morbidity rate varied between 12.6% and 40%. A landmark trial in ovarian cancer demonstrated a similar G3–4 morbidity of 27% and 25% in the HIPEC and non-HIPEC arms, respectively. Regarding cost, the addition of HIPEC to cytoreductive surgery for ovarian cancer, after accounting for several variables, such as operating room expenses, drug costs, and postoperative care, is cost effective.

Resource requirements and logistical challenges remain potential barriers to implementing HIPEC. It is associated with an increase in the technicity level of the surgery and different intraoperative and postoperative challenges for the surgeon, anesthesiologist, and nursing team. However, with proper preparation, these are surmountable in a team already performing cytoreductive surgery.

Establishing a successful HIPEC program requires institutional support, a knowledgeable and dedicated team, resources and equipment, proper training and intermittent audit. This review aims to highlight the
different components and considerations to build a program with evidence-based information.

TEAM COMPOSITION AND RESOURCES
A multidisciplinary team is essential for the successful implementation of a HIPEC program. The team members should be interested in HIPEC, and support program development and improvement through data collection, audits, and research. Each center should develop a core team for most HIPEC procedures and provide the necessary training. There is a learning curve, and the surgical oncology literature demonstrated an increased rate of complete cytoreduction and a decrease in postoperative morbidity from 71.2% to 34.1% as the number of cases increased. Centers with the highest volume are more efficient, have a higher complete cytoreduction rate, and the lowest number of postoperative complications. Expert opinions recommend centralizing the cases to dedicated centers to maintain this expertise with tubings and pumps. They then worked in synergy to develop a consistent postoperative care plan on a joint floor unit.

The team is usually composed of one or two surgeons with oncological training (surgical and/or gynecologic oncologist), an anesthesiologist, a perfusionist (suggested), a lead nurse (perioperative nurse or nurse educator), an intensivist, and other professionals (physiotherapist, psychologist, pharmacist, dietician, and occupational therapist). Ideally, a perfusionist is present, but in most hospitals either the circulating nurse or someone from the surgical team is responsible for the perfusion pump, which does not interfere with their duty because surgery ceases during HIPEC perfusion. Most teams will include learners, such as residents and fellows and research personnel or nurses allocated to collect the data and provide audits to help implementation, improvement, and quality assurance. Education strategies include education in-service presentations, simulation exercises, and grand rounds presentations. The team should be recognized and supported by the institution.

SAFETY
All team members must undergo comprehensive training and education covering the program, chemotherapy handling, and safety measures to minimize exposure to hazardous materials. There is a risk to operating room personnel through direct or indirect contact (contact with a contaminated surface) or, less commonly, through inhalation of aerosols (more frequent with an open technique). Several studies have shown contamination on surgical gloves, shoes, floors around the operating room table, and surgical instruments. Studies have also shown that regardless of the technique chosen (open or close), if the appropriate surgical precautions were taken and with the use of personal protective equipment, there was no quantifiable contamination of operating room air and no measurable levels of chemotherapy agents in the blood or urine of operating room personnel. It is of the utmost importance to have appropriate safety measures, which include:

- Operating room doors should be labeled, indicating that an HIPEC procedure is ongoing and the personnel traffic should be limited.
- Use of disposable surgical field drapes, chemotherapy certified gowns, eyewear, gloves, shoe covers, and masks is required. Regular surgical masks are acceptable for closed method procedures whereas open method procedures may release hazardous aerosols, and N95 masks are recommended.
- Ensure chemotherapy containment during procedures to prevent spillage around the abdomen and onto the mattress and floor. Use adherent drapes with suction connected plastic pockets, place absorbent pads near the table and suction canisters, and train teams in spillage management. Maintain a spill kit (Box 1) and implement simulation scenarios for safety training about new hazards.
- Verify that chemotherapy syringes and all items in contact with the chemoperfusate (gown, gloves, tubing, drapes, and sponges) are disposed of in a rigid container clearly labeled containing cytotoxic agent.
- Teams must be educated on wearing proper personal protective equipment when handling a patient's blood and other body fluids during the procedure. For the first 5 days postoperatively, the patient excreta (drains and urinary catheter content) should be considered contaminated and handled with chemotherapy precautions (safe gowns and gloves).

PREOPERATIVE CONSIDERATIONS
Patient Selection
The oncological indications for HIPEC are continuously evolving. As a group starting a new program, we recommend adhering to stringent evidence-based protocol and patient selection. Once tumor biology and oncological characteristics have made the patient eligible for HIPEC, overall functional status and comorbidities should be assessed to determine fitness for surgery. Patients must be motivated and able to understand the procedure and its potential risks and benefits.

Several patient risk factors have been shown to increase the risks of complications, including age, hypoalbuminemia (<30), Eastern Cooperative Oncology Group performance status (>1), and high disease burden (peritoneal cancer index >30). Furthermore, significant cardiovascular disease, smoking, and poorly controlled diabetes may increase perioperative morbidities. Experienced surgical oncologists in Canada have also included body mass index

Box 1 Spill kit
- Chemical splash goggles
- Two pairs of gloves
- Utility gloves
- Low permeability gown
- 2 sheets (12″ × 12″) of absorbent material
- 250 mL and 1 L spill control pillows
- Two large waste disposal bags for cytotoxic drugs
- Small sharp container

May vary based on institutional occupational health and safety recommendations.
as a factor influencing eligibility. The combination of comorbidities more than each factor individually must be considered.

Cardiac, Pulmonary, and Renal Evaluation
An ECG should be ordered preoperatively. The patient’s underlying comorbidities guide the extent of the cardiac workup. This helps to optimize patient outcomes and decide the choice of monitoring during surgery. A chest X-ray or CT chest is obtained preoperatively to assess the presence of pulmonary atelectasis, pleural effusion, or underlying lung disease. Strategies can then be put in place to decrease the risk of postoperative complications. Renal function is assessed preoperatively because an acute renal injury is possible due to the fluid shift, hypoperfusion, and nephrotoxic nature of some chemotherapy agents.

Hematologic Assessment
Most patients will have received chemotherapy in the weeks prior to surgery, putting them at high risk of myelosuppression, including anemia, nutritional deficiency, and hypoalbuminemia. A complete blood count, albumin, prothrombin time, partial thromboplastin time, and type and screen should be ordered preoperatively. Anemia or any coagulation disorder should be corrected preoperatively. In the presence of neutropenia (absolute neutrophil count <1.5), consideration should be given to postponing the case.

Pain Management
A plan should be discussed preoperatively with the patient and put in place to manage pain perioperatively. Most patients choose to proceed with epidural analgesia which is consistent with early recovery after surgery recommendations.

Chemotherapy Orders
Standardized orders are adjusted based on accurate patient weight and body surface area. All medications ordered for the HIPEC should be verified by the oncology pharmaceutical team and prepared beforehand.

ANESTHETIC CONSIDERATIONS
Cytoreductive surgery with HIPEC is an extensive and lengthy procedure involving major abdominal/pelvic resection, creating corporeal thermal variation, with a potential for significant blood loss, fluid shifts, and electrolyte and acid–base disturbances.

Physiological Changes during HIPEC
Hyperthermia creates a hypermetabolic response that increases oxygen consumption, carbon dioxide production, and anaerobic glycolysis utilization for energy production. This results in increased serum lactate. Aerobic glycolysis can also be activated in response to stress via high epinephrine levels and its activity in skeletal muscle, further contributing to lactic acidosis. Elevation in lactate levels (up to 7–8 mmol/L range) is common and transitory. Usually, it resolves itself within 12 hours. The inflammatory reaction in response to drug induced cytokine release during chemoperfusion may cause changes in tissue perfusion secondary to the decrease in systemic vascular resistance and mean arterial pressure. There is also an increase in cardiac output and heart rate, similar to the physiological response to sepsis. Finally, the anesthesiologist must consider the surgical technique for chemotherapy circulation chosen by the team, because the closed technique increases central venous, intra-abdominal, and intrathoracic pressure, thus affecting ventilation pressures, ventricular preload, and afterload.

Pre-chemotherapy Medication and Antiemetics
Preventing postoperative nausea and vomiting is paramount because these side effects are more prevalent in women, in prolonged abdominal surgery cases, and certainly associated with platinum chemotherapy. Pre-chemotherapy medication standard protocols have been shown to reduce the risk of hypersensitivity reactions and nausea/vomiting. Several protocols have been described. The protocol used in our center is described in Table 1.

Monitoring
In addition to regular intravenous access, the patient should have an arterial line to allow for easy laboratory monitoring and accurate hemodynamic reading. Most patients will benefit from insertion of a central venous catheter, which helps in fluid management. The patient has a urinary catheter for measurement of urine output and regular standard monitoring devices (blood pressure cuff, five lead ECG, pulse oximetry, capnograph, and core body temperature probe). Some centers have reported improved patient related outcomes with adherence to goal directed fluid therapy using dynamic monitors of fluid responsiveness.

A baseline arterial blood gas sample is obtained during surgery and is then repeated every 15–30 min during the HIPEC infusion to monitor pH, lactate, electrolytes, hemoglobin and blood glucose.

### Table 1: Perioperative nausea and vomiting management

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant 40mg orally × 1</td>
<td>Consider TIVA (eg, TCI with propofol)</td>
<td>Dexamethasone 4 mg orally twice daily × 3 days</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20mg intravenously</td>
<td>Metoclopramide 10mg orally/intravenously every 6 hours as needed</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4–8mg intravenously</td>
<td>Ondansetron 8mg orally/intravenously every 8 hours as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine 10mg orally once a day at bedtime × 4 days (decrease to 5mg if aged &gt;65 years)</td>
</tr>
</tbody>
</table>

TCI, target controlled infusion; TIVA, total intravenous anesthesia (no volatile agent).
**Review**

**Epidural**
The use of an epidural local anesthetic infusion allows proper pain management intraoperatively and postoperatively. Ideally, it is started during the procedure as it decreases the quantity of opioids and other anesthetic agents during surgery. However, some may prefer to alter their dosing/rate or use the epidural only in the post-operative period due to the potential vasodilation and sympathetic blockade that may deepen the hypotensive state already created by the hyperthermia and fluid shift.

**Fluid Management**
Liberal use of large volume infusions was proven to be ominous and resulted in fluid overload, tissue edema, and increased pulmonary and cardiac morbidity. Therefore, goal directed fluid therapy is recommended. The adoption of standardized restrictive fluid protocols has demonstrated benefits, including reduced morbidity, fewer major complications, shorter stay in the intensive care unit and in hospital, and a higher rate of extubation in the operation room. In addition to fluid shifts, nephrotoxicity of the agent used may lead to acute kidney injury. This can be further decreased in renal perfusion if the closed abdomen technique is chosen.

Urine output is continuously monitored during the case, and while the recommendation suggests intravenous fluid administration at 9–12 mL/kg/h to counteract significant fluid loss, our experience shows that lower rates (3–8 mL/kg/h) effectively maintain urine output at a minimum of 0.5 mL/kg/h, ensuring adequate renal perfusion. Acute kidney injury is less common since the addition of sodium thiosulfate as a chelating renal protection agent and when it occurs, it is more likely due to hypovolemia than nephrotoxicity. Therefore, judicious fluid resuscitation combined with sodium thiosulfate is likely the best way to prevent nephrotoxicity.

Some centers use mannitol, dopamine, or furosemide to aid in cisplatin diuresis, or low dose dopamine to increase renal perfusion. However, there is no evidence supporting clinical differences in outcome, and there is evidence against their use in critical care.

**Temperature Management**
Maintaining normothermia is an important factor in decreasing complications; however, this can be challenging due to the tendency towards hyperthermia during the cytoreductive surgery (large exposed abdominal surface and significant intravenous fluid administration) and the iatrogenically induced hyperthermia during chemotherapy perfusion.

During cytoreductive surgery, fluid warmer and forced warm air blankets are used to maintain normothermia. Before the HIPEC perfusion, the patient’s central body temperature is lowered to 35°C. The warming blanket can be reversed to cool, a cooling mattress can be used, intravenous fluids are chilled, and occasionally ice packs to the neck or groins may be applied. A three way Foley catheter allows cold fluid bladder irrigation if necessary. Core body temperature is measured using a nasopharyngeal or esophageal thermometer and can rise up to 40.5°C during HIPEC, but the usual increase is in the range of 2–3°C. The temperature usually normalizes within 30 min after cessation.

**Electrolyte, Glucose, and pH Imbalance**
In addition to the physiological stress induced by the procedure, the use of intravenous dexamethasone and of dextrose based perfusate may contribute to the frequent occurrence of hyperglycemia during HIPEC. Transient intraoperative insulin infusion may be required, even in non-diabetic patients. Other common anomalies noted are hyponatremia, hypomagnesemia, hypokalemia, and hypocalcemia (if the patient receives a large amount of blood transfusion), hyperchloremia, and metabolic acidosis.

**Coagulopathy Monitoring**
Significant variations in core body temperature, amount of blood loss, and some chemotherapeutic agents used can all contribute to the development of coagulopathy. Coagulation parameters should be monitored frequently throughout the case. Pre-emptive administration of tranexamic acid 1 g intravenously may decrease blood loss and transfusion.

**SURGICAL CONSIDERATIONS**
The Canadian HIPEC guideline divides surgery into three phases. Assessment phase: the peritoneal cancer index is usually calculated on entry. Tumor distribution is determined within 13 regions. A score from 0 to 3 based on tumor size is assigned to each region for a maximum total score of 39. The score is helpful for documentation, audit, and research. It is also useful in clinical decision making as it has been linked to an increased risk of anastomosis leak and other complications.

Cytoreduction phase: surgeons proceed with cytoreduction surgery with the aim of achieving a complete or near complete cytoreduction. The degree of residual disease (null, <0.5 cm, <1 cm) should be well documented and described in the operative report.

HIPEC: infusion of the chosen chemotherapy, according to evidence based literature or to research protocol.

**Cytoreductive Surgery**
The procedure should be completed starting with the area at most risk of incomplete resection. It will serve as an indicator to decide on the completion or abortion of the remaining surgery if resection is impossible. All involved pelvic viscera should be resected if safely feasible, to achieve a complete cytoreduction. These often include selective peritoneectomy of the pelvic cul-de-sac, paracolic gutters, bladder, and diaphragm. If there is perforation of the diaphragm at the time of dissection, this should be repaired before HIPEC perfusion, and a chest tube should be considered. Although less studied, there has been some evidence for hyperthermic intraoperative chemotherapy when there is pleural involvement, but this is beyond the scope of this review.

**Stoma**
Following bowel resection, the best way to prevent an anastomotic leak is to have a meticulous surgical technique with tension free anastomosis and adequate blood supply. Despite no evidence in ovarian cancer that HIPEC is associated with an increased rate of anastomotic leak, a phase III trial showed a significant increase in diverting stoma in patients requiring bowel resection within the HIPEC arm compared with cytoreductive surgery alone (72% vs 43%). This may reflect a more protective surgical attitude in the...
context of chemohyperthermia.\textsuperscript{1} Intraoperative indocyanine green assessments have also been described to assess proper bowel perfusion. This may be associated with improved postoperative outcomes, lower leak rate, and fewer unnecessary ileostomy creations by improving surgeon reassurance.\textsuperscript{29}

Closed Versus Open Technique

According to a 2019 review,\textsuperscript{30} approximately half of the centers use a closed perfusion technique, 42% use an open technique, and 5% use alternative techniques. No trial has determined one approach to be superior. The coliseum technique, first described by Sugarbaker, maintains the abdomen open with retractors (Figure 2) to facilitate even distribution, direct visualization, and repetitive chemotherapy mixing in the peritoneal cavity. However, it has challenges in maintaining heat and poses potential exposure risks to surgical staff due to chemotherapy aerosols or spills.

In contrast, the closed technique provides advantages such as the ability to easily achieve and sustain target intraperitoneal temperatures, maintain stable hemodynamic parameters, and enhance chemopenetration into target tissue due to increased intra-abdominal pressure.\textsuperscript{31} This technique reduces the potential hazardous exposure to the operating room staff. However, it may be challenging to access cannulas and redistribute the heated chemotherapy evenly, preventing pooling in dependent areas. Based on the paucity of data comparing both methods and seemingly similar impact on oncologic outcomes, the HIPEC technique may be left to the discretion of the operating surgeon.

PROTOCOL FOR THE HIPEC PROCEDURE

Preparation for the Procedure

The patient’s central body temperature is lowered in anticipation of the hyperthermal infusion. In cases where cisplatin is used, sodium thiosulfate 9 g/m\textsuperscript{2} in 200 mL of D5\%NS0.45\% intravenously over 15–20 min is administered by the anesthetist immediately before HIPEC perfusion, followed by a 6 hour continuous infusion of sodium thiosulfate 12 g/m\textsuperscript{2} in 1 L of D5\%NS0.45\%.

HIPEC Equipment

A HIPEC perfusion system includes a heat generating device capable of heating liquid up to 44°C, a roller pump that can circulate fluid at flows up to 1 L/min, and a hard shell reservoir that can accommodate a volume of at least 4 L. The intraperitoneal temperature must be monitored, and this can be done via four probes and four monitor interface cables. Most HIPEC programs have dedicated intraperitoneal perfusion equipment. However, it is possible to use a modified extracorporeal circulation machine used for cardiac surgery. It is important to note that if the latter option is chosen, the perfusion temperature is often limited to 41°C as those machines are not designed to reach higher temperatures.

Closed Technique with Fascial Closure

This technique has gained popularity because of its safety and efficacy. The pump circulates the fluid via inflow and outflow tubing.
Each of them is connected via a Y-type connector to two cannulas. Therefore, there are two inflow cannulas, one in the left upper quadrant and one in the deep pelvis, and two outflow cannulas, one above the liver in the right upper quadrant (after dividing the falciform ligament) and one in the superficial pelvis. These cannulas are placed through the skin and fascia prior to closure. Drain(s) are inserted in a separate incision(s). These are clamped during the chemoperfusion but will be left in place until postoperative day 4 or 5, depending on output. There are then two options for performing the closed HIPEC technique: closing the skin (without fascial closure), placing four temperature probes (one in each quadrant), proceeding with the chemoperfusion, then reopening the incision for exploration of the peritoneal cavity, drainage of the abdomen, and creation of a diverting stoma, if required. Alternatively, if no stoma is required, the fascial layer can be closed in the usual manner with placement of the four temperature probes (one in each quadrant) at regular intervals in between the fascial running suture line (Figure 3). At the end of the procedure, the probes and cannulas are removed, and the abdomen remains closed unless the return perfusate is blood tinged, raising concerns for proper hemostasis. This is time saving and commonly performed at our center.

**Volume Injected and Perfusion**

The optimal volume is estimated at twice the patient’s body surface area (m²). The pump is used to fill the abdomen of the perfusate via two inflow cannulas. The two outflow cannulas are clamped to avoid flow back into the hard shell reservoir. Abdominal distention and ventilation pressures may be monitored to assess intraperitoneal cavity filling. Ventilation pressure should remain inferior to 25–30 mm Hg during filling and perfusion. Once the abdomen is filled, the perfusion may begin.

Different types of perfusate can be chosen based on the chemotherapy agent used. Isotonic saline or dextrose based peritoneal dialysis solutions are commonly chosen as perfusate. The carrier solution must keep the cytotoxic agent stable and have a slow clearance from the peritoneal cavity to enhance exposure to the peritoneal surface. Cisplatin with sodium chloride 0.9% as a carrier solution is a common choice for epithelial ovarian cancer.

The perfusion is started by removing the clamp on the abdominal outflow line. Some center uses a vacuum system to aspirate the perfusate back into the hard shell reservoir, but a second roller pump could also work. The desired flow is generally 1000 mL/min and the abdominal return is regulated to maintain approximately 400 mL in the hard shell reservoir. The flow can be increased up to 2000 mL/min to decrease time to the desired temperature range and limit the pooling of the heated perfusate in certain parts of the abdomen, causing irreversible cellular damage.32 The perfusion continues until we achieve a temperature of 40–42°C in at least two of the four probes. Lightly shaking the abdomen may help stabilize and make the temperatures uniform. The perfusion time needed to reach the desired intra-abdominal temperature varies on a case-by-case basis. The close technique makes this step quicker. Monitoring body temperature throughout the case and making sure it does not exceed 38°C is important. Throughout the case, the team must ensure that there is no leakage of the perfusate at the four cannulation points; in our experience, the best strategy to avoid leakage is making a small incision at the time of placement of the cannula with a tight fit of stretched skin around the cannula and avoiding sutures. However, in the case of a leak, skin sutures can be added as needed.

**Chemotherapy Perfusion**

The chosen chemotherapy is injected according to established pharmaceutical protocols. In our case, for interval debulking of ovarian cancer, cisplatin is injected in three stages via a syringe directly into the hard shell reservoir of the HIPEC perfusion system. The initial dose corresponds to a loading dose of cisplatin 50 mg/m². At T=30 min and T=60 min, respectively, second and third doses of 25 mg/m² each are administered similarly to the initial loading dose. The total chemotherapy perfusion time is 90 min.

**Chemotherapy Drainage and Completion of the Procedure**

Once the infusion is complete, the intra-abdominal perfusate is aspirated into the hard shell reservoir. If the abdomen is reopened, the perfusate can then be completely aspirated with a suction probe. In the case of a closed fascial technique, perfusate is maximally aspirated through the outflow cannulas before removing...
them. The drains remain secured to the skin and any remaining perfusate will be evacuated through them in the next few postoperative hours. Previous publications in gynecologic oncology have supported the use of intraperitoneal chemotherapy, making gynecologic oncologist surgeons more familiar and comfortable with incomplete intra-abdominal drainage. The remaining volume of fluid after maximal draining effort should be a collected data point that may help further our knowledge.

**POSTOPERATIVE CARE AND COMMON COMPLICATIONS**

**Postoperative Disposition**

Most patients are extubated before leaving the room. Occasionally, a patient will leave the operative room intubated to go directly to the intensive care unit. Proper fluid management with a goal directed approach facilitates early extubation.° Due to the historically high morbidity and mortality rate, when we started our HIPEC program all patients were sent to the intensive care unit to be monitored for hemodynamic instability, electrolyte anomalies, and postoperative complications. However, advancements in patient selection, anesthesia, surgical techniques, and the adoption of enhanced recovery after surgery protocols with goal directed fluid management have significantly improved outcomes.

Most contemporary studies have shown that with adequate nursing education and a proper nursing ratio, patients can be discharged directly to the floor or to a step-down unit and this has also been our experience.° These should be experienced surgical units with adequate monitoring and access to HIPEC knowledgeable physicians and have intensivist support available. The decision to transfer a patient to the intensive care unit should be individualized based on factors such as age, comorbidities, surgical complexity, need for ventilation support, hemodynamic status, persistent lactic acidosis, hyperglycemia requiring insulin, and significant blood loss.° The average length of stay in a step-down unit is 24–48 hours.° A universal policy for intensive care unit admission after the procedure is not required.

**Postoperative Complications**

Literature regarding complications inherent to HIPEC needs to be carefully interpreted. The distinction between adverse events attributed to cytoreductive surgery versus HIPEC is often imprecise. Nevertheless, a randomized controlled trial did not find significant differences in adverse events when comparing cytoreduction alone versus cytoreduction with HIPEC.° Common grade 3–4 adverse events include postoperative ileus, infections, gastrointestinal fistula or leak, and acute kidney injury. A large retrospective cohort study identified four factors directly correlated with adverse event occurrence: peritoneal cancer index >10, indications for the procedure, completeness of the cytoreduction, and use of cisplatin.° Furthermore, health related quality of life and symptoms burden showed no significant differences between cytoreduction alone or cytoreduction and HIPEC, with the only slightly more frequent symptom being loss of appetite, which was not clinically significant.°

Delayed Gastric Emptying

The occurrence of ileus varies widely (0–86%) and its duration correlates with the extent of cytoreduction, typically lasting 5–13 days in most studies.°° Prolonged nasogastric tube use can induce intestinal quiescence. Evidence suggests that surgical factors, rather than perfusion temperatures, have a significant role in reduced peristalsis. The routine use of a nasogastric tube after cytoreductive surgery is debated, especially when extensive lysis of adhesion, bowel manipulation, and fluid resuscitation are necessary. However, a Cochrane review showed that routine use of a nasogastric tube caused delayed bowel function recovery and food intake resumption.°°° It is also associated with an increased risk of postoperative respiratory infection and atelectasis.°°°° Therefore, nasogastric tube placement should be selective, based on risk factors for delayed gastric emptying.°°°°

Metabolic and Electrolyte Shift

The two main metabolic impacts induced by HIPEC are metabolic acidosis and hyponatremia. Other common issues are hyperglycemia, hypochloremia, and a state of lactic acidosis. Postoperative acidosis results from a dual etiology: (1) endogenous increase in lactic acid induced by the chemoperfusion medium and (2) inadequate compensatory mechanisms, such as digestive loss of bicarbonates, renal tubular acidosis, and occasionally mild respiratory acidosis from decreased ventilation during the closed HIPEC perfusion. Metabolic acidosis, when attributed to HIPEC itself, usually resumes spontaneously within 24 hours. Persistent elevation beyond this period warrants further investigations. Therefore, close follow-up of electrolytes, lactate, glucose, pH, and bicarbonates is required in the acute postoperative period.

Acute Renal Injury

Acute renal dysfunction is commonly reported, ranging from 0 to 18.6% following HIPEC due to its singular hemodynamics perioperative features and use of nephrotoxic drugs. This is usually transient and, although it can prolong the length of hospital stay by 3.5 days, it does not seem to impact overall survival.°°°°° Sodium thiosulfate is a sulfur containing compound that distributes rapidly in extracellular fluid and covalently binds to cisplatin, thereby reducing its nephrotoxicity and possibly its ototoxicity.°°°°° Close postoperative follow-up of intake and outputs and standard hydration protocol with judicious crystalloid response to oliguria <0.5 mL/kg/h is recommended. Liberal use of intravenous fluid has been shown to increase intratibial edema and bowel anastomosis leak.°°°°° Daily weight measurements (avoid weight gain by >3.5 kg on postoperative day 2°°°°°) hourly intakes and outputs recordings, and consider furosemide 20 mg intravenously every 8 hours as needed in case of a positive balance of 500 mL or more.

Bowel Complications

Fistula and anastomosis leaks are cited among the most common adverse events, mainly due to the large number of intestinal resections and carcinomatosis induced bowel wall weakening. Recent studies report fistula and perforation rates of 0–23% and 0–10%, respectively, with reoperative rates of 11.7–16.5%.°°°°° The leak rate following a cytoreductive surgery for ovarian cancer is estimated at approximately 6°°°° which is lower than the numbers reported in colorectal surgery. This may be due to tumor biology, location, and the type of vasculature compromised due to the different surgical resection plans. Other factors linked to an increase in anastomotic

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leak include low preoperative albumin, low anterior resection, positive air leak bubble test, and multiple bowel anastomosis.

Van Driel et al did not report an increased rate of anastomoses leakage when HIPEC was performed concomitantly with cytoreduction. However, it is supported by preclinical studies demonstrating that hyperthermia alone does not impair anastomotic healing. Additionally, the timing of the anastomosis (before or after HIPEC) was not shown to increase the risk of leak. No prospective clinical trials have addressed this question. Unproven theoretical risks of tumor cells being trapped between suture materials has been cited.

Bone Marrow Toxicity

Hematological toxicity grades 1, 2, and 3 have been reported as 13%, 26%, and 13% respectively. It is mostly dependent on the dose and type of agent used. Although leukopenia and thrombocytopenia taken independently are not significantly morbid, they tend to potentiate other surgical complications, such as bleeding and infections. Hemoperitoneum attributed to immune-mediated platelet dysfunction has been reported but remains rare. It is important to consider thrombocytopenia as it may affect the timing of the epidural catheter removal.

CONCLUSIONS

The field of research on HIPEC is presently flourishing, and several ongoing trials will come to completion within the next 3–5 years. As of now, the National Comprehensive Cancer Network mentions HIPEC as an option for all stage III ovarian cancers at the time of interval cytoreductive surgery. FRANCOGYN, a national French research group in oncological and gynecological surgery, made HIPEC a grade B recommendation, and current oncology in 2020 made it a Canadian recommendation. These recommendations will encourage physicians to offer this as an option for their patients and it is of the utmost importance that we have a strong, safe, and well-implemented program.

REFERENCES
