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Review Article

A guide to establishing a hyperthermic intraperitoneal chemotherapy program in gynecologic oncology

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HIGHLIGHTS

- Implementing hyperthemic intraperitoneal chemotherapy requires multi-disciplinary team, including anesthesia and nursing.
- Required equipment includes a pump for hyperthemic perfusate and personal protective equipment.
- Continuous monitoring and proactive patient management is imperative to decrease patient morbidity.

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ABSTRACT

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) may be used to treat peritoneal based malignancies, such as epithelial ovarian cancer (EOC). Despite results of clinical trials supporting an increasing indication for HIPEC in EOC, concerns have existed regarding morbidity and challenges with initiating HIPEC at an institutional level. The objective of this review is to describe evidence-based recommendations to guide implementation of a HIPEC program, following our experience at a high-volume tertiary care center. Establishing a HIPEC program requires building a multi-disciplinary team, including gynecologic oncologists, anesthesia, nursing, perfusionists and pharmacists. Team members require education regarding HIPEC protocols, toxic waste and spill management, and personal protective equipment (PPE). Required equipment includes chemotherapy certified PPE and a HIPEC pump which is connected to inflow and outflow catheters placed within the peritoneal cavity. During the procedure, 3–6 L of a hyperthermic perfusate, composed of a isotonic crystalloid vehicle and the chemotherapy of choice, is infused through the peritoneal cavity with goal temperature of 41–43 °C. Prior to HIPEC infusion, surgical teams must communicate with anesthesia and pharmacy. In patients receiving HIPEC with cisplatin, furosemide and mannitol should be administered one hour prior to chemotherapy to ensure adequate diuresis. Sodium thiosulfate may also be considered for renal protection (van Driel et al., n.d. [3]). We utilize a multi-agent pre-medication protocol prior to HIPEC infusion to reduce hypersensitivity reactions, renal toxicity and post-operative nausea and vomiting. Limited data exists to support the optimal regimen for HIPEC at the time of CRS in women with EOC. From our experience, we favor use of cisplatin 100 mg/m^2 alone or in combination with paclitaxel 135–175 mg/m2 with 90 min of total perfusion time. Close attention to temperature and glycemic control is essential during the procedure, as electrolyte derangements including hyperglycemia, lactic acidosis and hypokalemia may occur. Continuous patient monitoring and proactive management of abnormalities that arise during HIPEC is imperative to decrease patient morbidity and mortality.

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Contents

1. Introduction

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can be used to treat peritoneal based malignancies. For treatment of epithelial ovarian cancer (EOC) specifically, HIPEC has been evaluated for use at the time of CRS in patients with both primary and recurrent disease [1–5]. Recently, the addition of HIPEC at the time of interval CRS was associated with improved overall survival and progression free survival in women with optimally-debulked advanced EOC within an international, multi-center randomized trial [3]. Despite prior studies and upcoming clinical trials supporting the use of HIPEC in EOC, concerns have existed regarding patient morbidity and challenges with implementing and establishing a program to safely perform HIPEC procedures.

Establishing a HIPEC program requires a committed effort with dedicated teams and equipment to perform the procedure, appropriate training, and measures to safeguard the medical staff handling the cytotoxic drugs. The objective of this review is to describe evidence-based recommendations outlining the essential components required to implement a successful HIPEC program following our experience at a high-volume tertiary care center.

2. Pre-operative care and preparation

Building a multi-disciplinary team is essential to a successful HIPEC program. Key personnel include gynecologic oncologists and/or surgical oncologists, anesthesia and intensivists, nursing staff, perfusionists and pharmacists familiar with cytotoxic medications. All team members require education regarding HIPEC chemotherapy protocols and toxicities, waste and spill management, and personal protective equipment (PPE). Circulating surgical nurses should be familiar with management of the hyperthermia perfusion pump and should receive appropriate training. At our institution, we recommend a perfusionist to manage the HIPEC pump intra-operatively. The use of a dedicated perfusionist has streamlined HIPEC administration and has allowed for improved efficiency and troubleshooting.

The decision to proceed with HIPEC at the time of CRS follows an extensive discussion of risks and benefits with the patient. It is essential that patient age, cormorbidities including renal function, performance status, disease burden and the morbidity secondary to prolonged surgery, anesthesia time and intra-operative chemotherapy administration are considered [6]. In addition, prior randomized data supports increased rate of stoma formation among those undergoing HIPEC, and therefore, patients should be counselled accordingly and undergo stoma marking, if bowel exteriorization is anticipated [3]. Prior to surgery, appropriate medical clearance is important. In addition, serum studies must be carefully reviewed and similar parameters considered when administering intravenous chemotherapy should be followed for HIPEC.

3. Team and equipment

3.1. Hyperthermia delivery systems

Constant infusion of a hyperthermic perfusate is achieved during HIPEC through a continuous circuit generated by a system composed of a pump, heat exchanger, and temperature monitors. Historically, rapid infusion pump systems were re-purposed and augmented with hyperthermic capabilities [7]. However, as the number of HIPEC procedures increased, the delivery system was optimized. In 2013, the Federal Drug Administration (FDA) approved the first dedicated hyperthermic infusion system for use in HIPEC [8].

The HIPEC pump contains a heating system designed specifically for intraperitoneal use, with the ability to adjust from 36 to 47 °C in 1/10th degree increments. For the closed technique, two catheters are connected to the pump and placed within the abdominal cavity: 1) a Y-shaped inflow catheter within the pelvis and 2) an outflow catheter placed on the liver surface, after dividing the falciform ligament. The outflow catheter extracts the circulated perfusate and returns to the reservoir for heating and recirculation. The catheters are

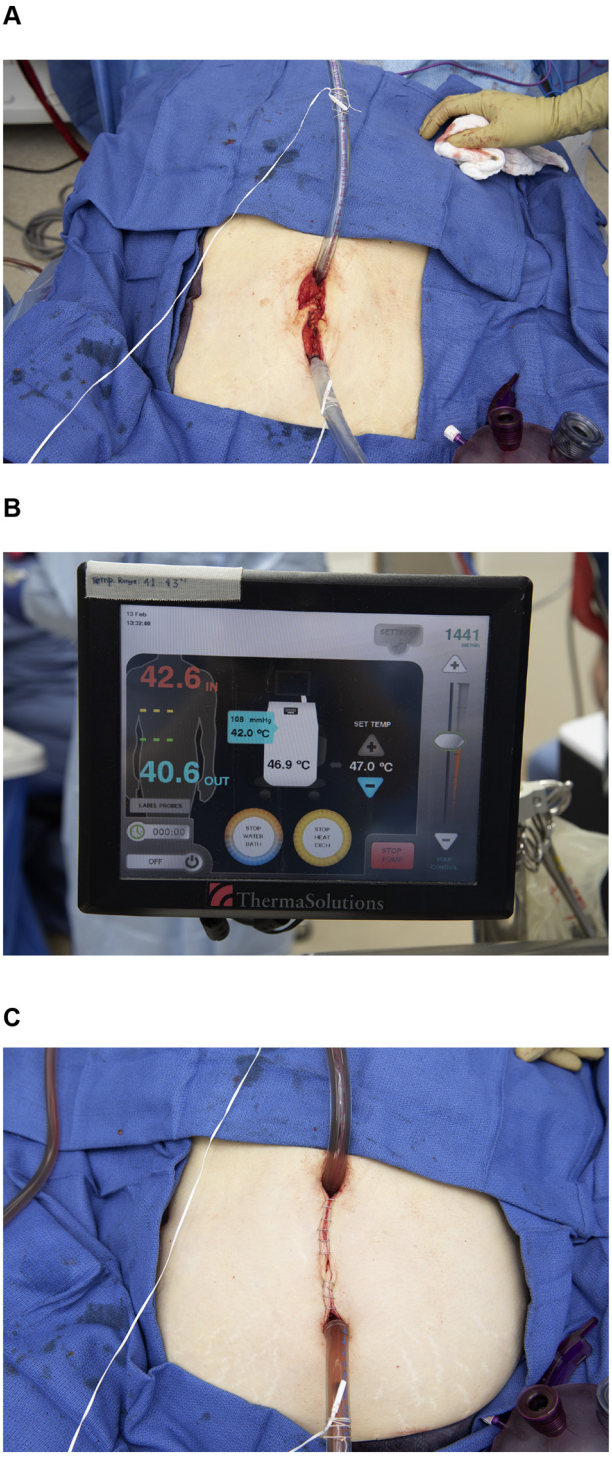

Fig. 1. Hyperthermic Intraperitoneal Chemotherapy System.

connected to probes that directly monitor the temperature of the perfusate entering and exiting the peritoneal cavity (Fig. 1).

3.2. Temperature and flow rates

HIPEC involves the infusion of 3–6 l of a hyperthermic perfusate, composed of a crystalloid vehicle and the chemotherapy of choice, through the peritoneal cavity following optimal CRS. Prior translational studies have indicated that malignant cells are selectively targeted and destroyed by hyperthermia in the range of 41–43 °C, which is therefore the goal temperature for HIPEC infusions [9–12]. Temperatures above 45 °C, usually resulting from inadequate circulation and pooling of the heated perfusate in dependent parts of the abdomen, may cause irreversible cellular damage through protein denaturation [13,14]. Higher flow rates, at a minimum of two liters/min, via the perfusion system can be used to mitigate this risk [15]. In addition, increasing the flow rates may decrease time to desired hyperthermic ranges, allowing for consistent intra-peritoneal temperatures. Gentle shaking of the abdomen during HIPEC by an assistant can assist in maintaining the perfusion circuit during infusion.

3.3. Delivery techniques

Multiple delivery methods of HIPEC therapy have been described. In 1999, Dr. Paul Sugarbaker described the open or “coliseum” technique using an inflow Tenckhoff catheter [16]. The coliseum technique is performed by maintaining an open abdomen and elevating the skin edges with an external self-retaining retractor, creating a funnel to bathe the peritoneal cavity. Suction drains are placed through the abdomen, in a water tight fashion, to extract and return the perfusate to the pump apparatus utilizing Tenckhoff catheters. Advantages of this technique include even distribution of hyperthermia within the peritoneal cavity without pooling and prevention of inflow catheter obstruction via direct visualization. However, limitations include dissipation of heat, difficulty in achieving consistent hyperthermia and safety concerns for operating room personnel, with the potential for increased exposure of the operative team to the chemotherapy perfusate [14].

Following this, the closed technique of HIPEC was developed, where large bore cannulas are placed through the abdominal incision and the skin with or without fascia is closed provisionally to ensure a water-tight seal (Fig. 1). Following completion of HIPEC infusion, the abdomen is re-opened to ensure hemostasis and perform bowel re-anastomosis, as needed. Advantages of this technique include short duration to achieve and maintain goal hyperthermia, decreased exposure of operating room personnel to the perfusate, and positive pressure to aid tissue penetration [14,17]. A limitation of this technique is the potential for uneven perfusion due to accumulation of perfusate in dependent areas of the abdominal cavity, which can may be mitigated with manual external agitation through a bedside assistant [18]. At present, there is insufficient evidence to suggest a superior method for HIPEC delivery [19]. In the absence of consensus, we employ the closed technique as utilized in randomized control trials in order to decrease exposure to the surgical team, as well as large bore catheters to ensure adequate and ample abdominal drainage to complete the circuit. Chemotherapy must only be perfused through the closed circuit after the integrity of the circuit is confirmed to have no leaks following abdominal wall closure.

3.4. Patient and operative team safety and personal protective equipment

Ensuring patient safety with administration of intra-operative chemotherapy is essential. Prior to surgery, the informed consent documents are verified with the patient by the operative team, including the administration of specific chemotherapy medications. HIPEC orders require authorization by two physicians and verification of dosing by a chemotherapy trained pharmacist in the electronic medical record. Intra-operatively, a two-step verification process occurs with the surgeon and circulating nurse that verifies the chemotherapy medication, dose ordered, dose received by pharmacy with the patient medical record number and date of birth.

It is imperative that all team members receive appropriate training and education, including necessary credentialing. Credentialing of the gynecologic oncologist can be streamlined in a health system that currently has surgeons with HIPEC privileges. When developing a de novo program, we highly recommend the whole team, including surgeons, nursing staff, perfusionists and pharmacy, attend a course dedicated to administering HIPEC or visit a high volume center to observe

HIPEC procedures. In addition, it is advised the surgeon partner with the administration at their institution to determine the criteria to obtain credentialing. At de novo centers, proctoring by a visiting gynecologic oncologist with expertise in HIPEC is recommended. We advocate for a monitored mentor program for a prescribed number of cases with periodic review. After successful completion, the surgeon may be granted HIPEC privileges. We recommend careful case selection and review of surgical outcomes, complications and morbidity to help identify adverse outcomes and address areas of concern.

Safety for the intraoperative team is essential and must be prioritized during chemotherapy infusion. Although a dilute solution of a crystalloid carrier and chemotherapy is formed to create the perfusate, certain safety measures should be observed to minimize exposure to hazardous materials. All operative personnel should be informed of these safety measures and strict adherence is imperative.

1. The surgical field and patient should be arranged with impervious drapes. Use of non-disposable fabric drape should be avoided. During HIPEC infusion, use of an additional anti-microbial translucent barrier drape over the incision may decrease exposure to patient's skin and operating room personnel.
2. During the administration of HIPEC, operating room traffic must be limited to essential personnel and doors labeled with signage advising that HIPEC is in progress.
3. Chemotherapy certified gowns, eyewear and gloves should be provided to all operative personnel who may come in contact with the perfusate and should be up to USP 800 standard as per guidelines provided by the American Standards and Testing Measures (ATSM). Gloves should be changed every 30 min when in direct contact with the perfusate.
4. Rigid yellow containers should be available and labeled clearly indicating cytotoxic contents. These containers should be used to place any items that may have come into contact with the perfusate, including drapes, gowns, gloves, shoe covers, towels, tubing, and syringes. These waste containers should be disposed of per regulations provided by individual states and institutional Occupational Health and Safety Management team. In addition, a chemotherapy spill kit must be immediately available.
5. Due to reproductive health and safety concerns reported with cytotoxic drugs, including congenital malformations, miscarriage and infertility, pregnant women, those who wish to become pregnant and nursing women should avoid handling chemotherapy and surgical procedures with HIPEC [20].
6. Patient excreta (including drain contents and urine) should be treated as contaminated for 48 h following surgery and handled with extra precautions, including chemotherapy safe gowns and gloves [20]. Teams caring for the patients in the post-operative period should be advised of these risks.

4. Hyperthermic intraperitoneal chemotherapy protocol

4.1. Premedication protocol

Prior to starting the HIPEC infusion, it is essential that the surgical team communicates with both anesthesia and pharmacy to ensure that appropriate medications are administered, baseline labs are obtained and the chemotherapy is prepared. In patients receiving HIPEC with cisplatin, furosemide and mannitol should be administered one hour prior to chemotherapy to ensure adequate diuresis. In addition, sodium thiosulfate may be administered to avoid nephrotoxicity at the time of starting HIPEC infusion [3]. At our institution, we utilize an evidence based multi-agent pre-medication protocol prior to HIPEC infusion to reduce hypersensitivity reactions, renal toxicity and post-operative nausea and vomiting [3,21] (Table 1). Once it is determined that the patient can be optimally cytoreduced, the surgeon should alert the circulating nurse to call pharmacy to mix the chemotherapy medications. Ample time (30–45 min) should be given to allow the pharmacist to prepare the chemotherapy and ensure the medications arrive to the operating room shortly after completing the cytoreductive procedures.

Table 1
Premedication Protocol for Hyperthermic Intraperitoneal Chemotherapy.

Medication	Administration Instructions
Furosemide 40 mg IV	Given one hour prior to cisplatin with goal urine output of 100 cc/h.
Fosaprepitant 150 mg IV	Given 30 min prior to chemotherapy
Dexamethasone 10 mg IV	Given 30 min prior to chemotherapy
Diphenhydramine 50 mg IV	Given 30 min prior to chemotherapy
Famotidine 20 mg IV	Given 30 min prior to chemotherapy
Potassium chloride 20 mEq	To be given with Paclitaxel
Sodium Thiosulfate	9 g in 200 mL at the start of infusion, followed by a continuous infusion (12 g in 1000 mL) for 6 h

IV, intravenous.

4.2. Chemotherapy agents

The cytotoxic effects of HIPEC are hypothesized to result from a synergistic effect of local intraperitoneal chemotherapy administration and hyperthermia [10,11,14,22,23]. Intraperitoneal administration allows for a high concentration of cytotoxic drug to be delivered to the tumor, with reduced systemic absorption and toxicity due to slowed absorption of drug from the peritoneal cavity [22,23]. Systemic exposure is further reduced by hepatic clearance and renal excretion based upon the peritoneal-to-plasma ratio based on the specific pharmacokinetics of the chemotherapy agent [22,23]. High peritoneal to plasma ratio ensures extended exposure of the cytotoxic agent within the peritoneal cavity. Delivery of drug to the peritoneal cavity allows for high intraperitoneal and low systemic concentrations due to slow absorption of drugs into the systemic circulation.

Choice of vehicle solution for the delivery of cytotoxic agents should not be overlooked, as it can impact drug absorption and pharmacokinetics. An ideal perfusate provides durable exposure of the tumor to high levels of chemotherapy, slow clearance from the peritoneal cavity, and is safe for prolonged peritoneal exposure [22]. For this reason, use of isotonic solutions is favored [22,24]. Hypotonic solutions have demonstrated increased cisplatin accumulation in tumor cells in vitro, but in vivo have been associated with an increase in unexplained post-operative intraperitoneal bleeding [24]. In addition, while hypertonic solutions may theoretically slow the clearance from the peritoneal cavity, they have been shown to dilute the drug concentration from resultant fluid shifts [24].

Historically, 5% dextrose solutions were recommended for HIPEC with oxaliplatin due to concerns of possible chemical instability in chloride containing solutions. However, it has since been demonstrated that oxaliplatin has minimal degradation in chloride-based solutions, and use may potentiate cytotoxicity [25]. When dextrose-based solutions are used, a 1.5% dextrose solution is preferred due to risks of hyperglycemia, hyponatremia and metabolic acidosis with 5% concentration [26]. In a study of patients receiving HIPEC with 1.5% dextrose peritoneal dialysate, 86% of patients developed intraoperative hyperglycemia within one hour of perfusion initiation. Blood glucose values reached as high as 651 mg/dl and 66% of patients required insulin therapy [25]. Based on this data, we currently favor the use of isotonic saline as our vehicle solution.

In general, chemotherapy agents that are efficacious in the treatment of peritoneal based malignancies with HIPEC share similar characteristics [22–34]. First, they must be heat stable, cell-cycle non-specific and should not require conversion or metabolism to an active form [22–24]. In addition, high molecular weight therapies are favored due to the decreased absorption from the peritoneal cavity, resulting in a desirable high peritoneal to plasma ratio [22–24]. Significant variability exists regarding the depth of tissue penetration for cytotoxic medications [22]. For example, studies have demonstrated that both carboplatin and cisplatin can penetrate tissue to a depth of 5 mm, but other agents, including doxorubicin, are only able to penetrate a few cell layers [22] (Table 2).

Platinum agents, including cisplatin, represent the most active class of cytotoxic medications for EOC treatment. Use of cisplatin with HIPEC achieves a high peritoneal concentration with a penetration depth of 3-5 mm. In addition, several translational studies have a demonstrated that the addition of heat to cisplatin leads to increased DNA adduct formation resulting in a synergistic anti-tumor effect [22,27]. Therefore, many centers, including our own, favor the use of cisplatin with HIPEC for EOC based upon favorable pharmacokinetic profile and anti-tumor activity. Best evidence supports administration of cisplatin at a dose of 100 mg/^{2} [3,22,27].

While cisplatin toxicities include nephrotoxicity and electrolyte imbalances, including hypokalemia and hypomagnesemia, intraperitoneal administration results in substantially decreased systemic concentrations of drug. Specifically, pharmacokinetic data demonstrates that only a small fraction of chemotherapy is absorbed systemically following peritoneal administration, with concentrations 10–36 times higher than plasma levels [22]. Therefore, risk of significant hematologic and renal toxicities is low following peritoneal administration [3,22,27]. To that end, in the randomized trial by Van Driel et al., administration of HIPEC with cisplatin did not increase any grade 3 or 4 complications, including renal or hematologic toxicities. Alternatively, carboplatin has also been employed with favorable pharmacokinetics and less nephrotoxicity. Unfortunately, carboplatin has decreased penetration depth compared to cisplatin, which is therefore the preferred platinum in this setting [22].

Paclitaxel may be considered for use at the time of HIPEC given its known activity in EOC and favorable pharmacokinetic profile, with high peritoneal to plasma ratio and large molecular weight [22]. Unfortunately, studies have shown that paclitaxel has limited thermal synergism and penetration depth limited to approximately 80 cell layers [22]. A variety of doses of paclitaxel, from 60 to 175 mg/m2 have been reported [22]. Data for the toxicity of paclitaxel in the setting of HIPEC is limited, and is largely extrapolated from studies on intraperitoneal chemotherapy, where fatigue, pain, hematologic, gastrointestinal, metabolic, or neurologic toxic effects are commonly reported [31].

Limited data exists to support the optimal chemotherapy regimen for HIPEC at the time of CRS in women with EOC. From our experience, we favor use of cisplatin (100 mg/m^2) alone for a of 90 min of perfusion time, per the protocol published in the randomized trial by Van Driel et al. [3]. However the dose of cisplatin may be individualized based on patient's age, co-morbid conditions, including poorly controlled diabetes mellitus, chronic kidney disease and myelosuppression during neoadjuvant chemotherapy. Studies are ongoing at our institution to further understand the optimal dosing regimen for women with EOC, and specifically whether addition of paclitaxel (135 mg/m^2) at the time of HIPEC with cisplatin will improve outcomes in women with EOC. In the absence of clinical trials data supporting superiority of one regimen, the HIPEC regimen utilized should be at the discretion of the prescribing surgeon [3]. For HIPEC with cisplatin alone, drug may be administered all at one time, or doses divided over 30–45 min. Similarly, if utilizing paclitaxel, it is infused first for 45 min followed by addition of cisplatin for an additional 45 min.

5. Anesthesia considerations

Hemodynamic, metabolic and hematologic disturbances occur to varying degrees during CRS with HIPEC. Ongoing communication with anesthesia, patient monitoring and proactive management of abnormalities that arise during HIPEC is imperative to decrease the risk of morbidity and mortality to the patient.

5.1. Monitoring devices

Appropriate patient monitoring during CRS with HIPEC requires multiple invasive and non-invasive devices. Standard monitoring is recommended with a blood pressure cuff, pulse oximetry, end-tidal carbon dioxide (CO2) censor, electrocardiogram, core-body temperature probe and urinary catheter for output monitoring. In addition, patients undergoing CRS with HIPEC should have arterial line and/or central venous line(s) placed for accurate hemodynamic monitoring and to ensure laboratory parameters, including electrolytes, glucose and platelets can be checked as clinically indicated [26,35,36].

5.2. Fluid management

The loss of blood and ascites during CRS, in addition to increased capillary leakage following HIPEC, can result in extensive fluid loss, with the potential for hemodynamic instability [36]. In anticipation of these losses, aggressive resuscitation is often undertaken by anesthesia providers to avoid hypovolemia. Unfortunately, non-specific large volume infusions can result in fluid overload, tissue edema and severe postoperative morbidity, including cardiac and pulmonary complications [37]. Providing balanced intraoperative fluid management during CRS with HIPEC allows for adequate oxygen supply while avoiding overload.

Randomized studies evaluating intraoperative fluid replacement regimens in patients undergoing abdominal surgery without HIPEC have shown a decrease in perioperative morbidity with restrictive fluid regimens [38,39]. Conversely, higher intraoperative infusion volumes have been associated with increased adverse outcomes in patients undergoing CRS with HIPEC. In a one retrospective study of 133 patients undergoing CRS with HIPEC, patients receiving fluid volumes above the mean of 15.7 mL/kg/h demonstrated a 43% increase in post-operative complications [32]. Additional retrospective data has demonstrated that patients who receive excessive fluid volumes during CRS with HIPEC experience longer hospital stays, extended intensive care unit (ICU) admissions and increased grade 3 or 4 complications [40].

The introduction of standard operating procedures (SOP) for CRS with HIPEC has been associated with improvement peri-operative outcomes [37] (Supplemental Document 1). In one study, introduction of a SOP was associated with reduced morbidity, including increased rate of extubation in the operating room and reduction in other major complications. Importantly, on multivariate analysis, use of greater than two liters of colloid was associated with major morbidity [37]. Based on evidence of negative outcomes with over resuscitation during CRS with HIPEC, standardized restrictive fluid protocols seem to be of value and are routinely used at our institution with success.

5.3. Electrolytes and acid-base abnormalities

CRS with HIPEC frequently results in abnormalities of sodium, chloride, potassium, calcium, magnesium, and phosphate levels. Hyperglycemia and hyponatremia may occur during HIPEC due to peritoneal exposure to chemotherapy perfusate solutions and physiologic stress response from hyperthermia. Chemotherapy vehicle solution usually consists of isotonic saline, but dextrose-based solutions have been historically used with high incidence of subsequent hyperglycemia [25]. Hyperglycemia may also result from premedication with dexamethasone prior to HIPEC administration. It is important to note that the

Table 2
Chemotherapy Drugs for Hyperthermic Intraperitoneal Chemotherapy.

Agent	Molecular Weight	MTD	Depth of Penetration	Heat synergy	AUC ratio	Toxicity
Mitomycin C	334.3	35 mg/m²	2–5 mm	Y	13–80	Neutropenia, poor wound healing
Oxaliplatin	397.3	460 mg/m²	1–2 mm	Y	16	Intra-abdominal bleeding
Cisplatin	300.1	300 mg/m²	1–5 mm	Y	12–22	Hypomagnesemia and nephrotoxicity
Doxorubicin	580.0	15 mg/m²	4–6 cell layers	Y	162–230	Fatigue, nausea, vomiting, abd pain
Carboplatin	371.3	800 mg/m²	0.5 mm	Y	15–20	Poor data
Paclitaxel	853.9	120-180 mg/m²	>80 cell layers	N	550–2300	Fatigue, pain, GI, hematologic
Gemcitabine	299.6	Not determined	Not assessed	Y	791–847	Limited data

MTD, maximum tolerated dose; AUC, area under curve.

osmotic effect of hyperglycemia can lead to excessive diuresis, which can exacerbate hyponatremia. With the use of isotonic low molecular weight carrier solutions hyponatremia can result due to the ease of absorption of these solutions from the peritoneal cavity. A rare complication leading to death from cerebral edema from acute changes in sodium levels has been reported, emphasizing the importance of careful attention to electrolyte and fluid management [21].

Additional considerations for electrolyte monitoring are dilutional hypomagnesemia, transfusion induced hypocalcemia as well as normal saline induced hyperchloremia and metabolic acidosis [26]. Transient lactic acidosis may occur during CRS with HIPEC and evidence suggests patients who do not have at least partial recovery of this base excess in the immediate post-operative period are at increased risk for complications [41]. Appropriate monitoring and correction of these abnormalities is warranted throughout the procedure. Our protocol includes obtaining baseline arterial blood gas prior to HIPEC and every 15–30 min during infusion. Close attention should be paid to blood glucose monitoring with low threshold to begin insulin therapy intraoperatively to treat hyperglycemia.

5.4. Renal perfusion and acute kidney injury

Renal dysfunction has been reported in up to 48% of patients who undergo CRS with HIPEC [26,35]. Risk factors for acute kidney injury (AKI) in CRS with HIPEC include preexisting renal dysfunction, high body mass index, preoperative hypoalbuminemia, long operative time, hyperglycemia, platinum chemotherapy, hypertension, blood product transfusion and excessive blood loss [26]. Strategies to avoid AKI are furosemide and mannitol to aid in cisplatin diuresis, optimization of intravascular volume, goal directed fluid replacement in high risk patients and avoidance of nephrotoxins [26,42]. In addition, administration of sodium thiosulfate may be considered to decrease nephrotoxicity. Specifically, sodium thiosulfate can be started at the start of HIPEC infusion (9 g in 200 mL), followed by a continuous infusion (12 g in 1000 mL) for 6 h [3]. When using urine output as a surrogate marker for renal perfusion, reasonable targets are 0.5 mL/kg/h during CRS and 2-4 mL/kg/h during HIPEC infusion.

5.5. Temperature management

Fluctuations in temperature during CRS with HIPEC can have significant physiologic effects on coagulation, inflammation and metabolic status [26]. Maintaining relative normothermia can help to mitigate these downstream effects [26]. During CRS patients are prone to hypothermia due to exposed surfaces and intravenous infusions, which can lead to impaired platelet function and clotting factor dysregulation [21]. However, during HIPEC, body temperature will then increase with the infusion of the heated perfusate into the peritoneal cavity. Hyperthermia can lead to increase in metabolic demand with increased heart rate and end-tidal CO_2, resulting in a metabolic acidosis [21,26]. Therefore, active patient cooling to normothermia is important, with infusion of cooled IV fluids, use of cooling blankets, ice packs or cooling mattresses, when necessary [26,35]. Efforts to maintain normothermia are imperative as data suggests that as the difference between the lowest and highest intraoperative temperature increases, the risk for prolonged ICU stay also increases [43].

5.6. Coagulation monitoring and blood product transfusion

Coagulopathy is not uncommon in patients undergoing CRS with HIPEC and its development is likely multifactorial related to fluid shifts, blood loss, temperature dysregulation, chemotherapeutic toxicity and blood product transfusion. [26] Periodic intra-operative monitoring of coagulation parameters with frequency based on estimated blood loss is recommended [26]. Early management of coagulopathy can aid in prevention of ongoing blood loss and decrease morbidity [26,35]. Prompt reversal of coagulopathy can decrease the need for large volume blood product transfusion. This is beneficial because data suggests increased risk of post-operative complications after CRS/HIPEC with increasing volume of blood products [40,44–46].

6. Surgical considerations

6.1. Surgical planning

Our recommendation is all HIPEC cases be scheduled at the beginning of the day, and with adequate planning, to ensure availability of all available team members. After careful exploration of the abdomen and extent of disease is known, HIPEC can be considered after optimal cytoreduction is complete. It is essential to consider the hemodynamic stability of the patient following cytoreduction, as administering HIPEC to a patient with a clinically tenuous status would be contraindicated [3]. General technique focuses on optimal visualization, meticulous hemostasis, and ongoing communication with anesthesia [47]. Assessment of the upper abdomen first, followed by mid-abdomen and pelvis, allows for a structure approach to cytoreduction. Dividing the falciform ligament allows for appropriate visualization of the diaphragmatic surfaces and also is crucial for positioning of the outflow HIPEC tubing. Drains, including Jackson Pratt, are discouraged, however if deemed clinically indicated should be handled with chemotherapy safe PPE for 48 h.

6.2. Bowel resection

In optimal debulking surgeries, bowel resections are often performed to achieve microscopic residual disease. Anastomotic leak rates following EOC cytoreduction is estimated at approximately 6% [48]. There are reports of an increased incidence of anastomotic leak after low colorectal resection with the addition of HIPEC, with one study noting an increase from 6% to 20% [49]. Anastomotic failure after cytoreductive surgery, including those with HIPEC, is associated with worse outcomes, with longer hospital stays, more readmissions, greater postoperative mortality and shorter overall survival [50].

Typical surgical techniques to reduce anastomotic leaks, including tension-free anastomosis, adequate blood supply, and stapling

technique, should be employed during CRS with HIPEC [48]. In a review of patients who underwent CRS with HIPEC, factors significantly associated with anastomotic failure included left-sided colorectal resection and low pre-operative albumin. Timing of anastomosis did not impact the leak rate, with reported anastomotic failure rate of 6% vs 8.6% when HIPEC was administered before versus after anastomosis ($p = .26$) [50]. In a preclinical animal model assessing effects of hyperthermia on timing of bowel anastomoses, rats were randomized to control without HIPEC, anastomosis before HIPEC administration and anastomosis after HIPEC administration. Anastomotic sites were found to have reduced tensile strength in both HIPEC groups, without significant difference in anastomotic site integrity whether HIPEC was administered before or after anastomosis [51]. At our institution, anastomosis is generally performed after HIPEC procedures. Notably, choice of chemotherapy has not resulted in significantly different anastomotic leak rate [50,52,2]. Cisplatin has been used as the cytotoxic agent in women with EOC undergoing CRS with HIPEC without worsened outcomes upon bowel anastomosis [3,53,54].

The necessity of a diverting ostomy in CRS with HIPEC for EOC is debated. Ostomy creation tends to be favored in higher risk patients, such as the elderly or those with poor nutritional status [48,55]. Surgical considerations for diverting ostomy include a very low anastomosis, positive air leak test, and multiple bowel anastomoses [48,56–58]. While diverting ileostomy is traditionally performed to reduce anastomotic leak rates and associated complications in colorectal cancer surgeries, studies in women with EOC undergoing CRS with large bowel anastomosis have demonstrated no difference in leak rate, major complications, or interval to postoperative chemotherapy with or without diverting stoma [58,59]. Studies that have demonstrated that oversewing at the anastomotic site at the time of CRS with HIPEC may lead to decreased leak rates in patients without ostomy creation [57,60]. VonBreitenbuch et al. reported that after changing their surgical technique to include oversewing rectal anastomoses, the rate of diverting protective ileostomies decreased from 65 to 20%, with low anastomotic leak rates of 5% [60]. Ultimately, meticulous surgical technique is essential, and individualized assessment of patient and surgical risk factors, including surgeon experience, should guide intra-operative decision making for ostomy creation. Drains, including Jackson Pratt, are discouraged, however if deemed clinically indicated should be handled with chemotherapy safe PPE for 48 h.

6.3. Abdominopelvic viscera

Optimal cytoreduction often requires resection or repair of other pelvic viscera in addition to bowel. In retrospective studies of patients who underwent CRS with HIPEC, splenectomy was associated with higher incidence of major complications including post-operative infection, pancreatic leak and longer length of stay [61,62]. Splenectomy should be performed if necessary, however should be avoided if spleen is uninvolved given the inferior perioperative outcomes [61,62].

Other important resections include omentectomy, diaphragm and pelvic peritonectomies, and partial bladder resection. At time of surgery, if diaphragm is entered, this should be repaired with suture prior to HIPEC administration to avoid hydrothorax and optimize ventilation if the chest cavity is not involved with disease. There are reports supporting that concurrent perfusion of the chest and abdominal cavities is both safe and feasible [63]. If bladder is entered or partially resected, this should also be repaired prior to HIPEC to appropriately monitor urine output and reduce bleeding [47]. Sites of repair should be carefully evaluated after completion of HIPEC to ensure hemostasis and appropriate approximation.

6.4. Troubleshooting

Given that CRS with HIPEC is a complex procedure, there may be issues that arise with HIPEC equipment or chemotherapy administration that require troubleshooting [24]. To reduce obstruction of the HIPEC tubing, the surgeon must ensure meticulous hemostasis and copiously irrigate the peritoneal cavity prior to HIPEC administration. Appropriate placement of tubing is paramount, with outflow tubing draped over the liver and directed toward patient's feet to ensure adequate outflow. The skin, with or without fascia, is reapproximated with monofilament suture temporarily in the closed HIPEC technique, with additional interrupted sutures as needed to prevent leak. Temperature probes are placed at or beneath the base of the in- and outflow tubing, given placement external to the body cavity can cause discrepant values during HIPEC administration. Despite these preventive measures, intraoperative issues with flow and chemotherapy administration may arise, whereby the assistance of a qualified perfusionist is key in further troubleshooting.

A concern during administration of HIPEC is maintenance of suture integrity. In one study, six different absorbable sutures were incubated in saline, mitomycin C, or oxaliplatin at 37 and 45 degrees Celsius, then tested for tensile breaking force and elongation rate. While Maxon was found to have the strongest tensile breaking force at baseline, all six suture types had similar strength with hyperthemic incubation, indicating heated chemotherapy does not significantly affect suture properties [24]. While this is reassuring, visceral repairs and reinforcements should be evaluated to ensure integrity after HIPEC application.

7. Post-operative considerations

7.1. ICU admission

Patients with EOC who undergo CRS with HIPEC need to be monitored closely post-operatively due to increased risk for hemodynamic instability, electrolyte abnormalities and post-operative complications. Post-operative care in the ICU may be necessary for some patients based on inability to extubate in the operating room or intraprocedural events that require post-operative critical care. Any ABG abnormalities should be addressed intra-operatively and followed to resolution prior to transfer to regular nursing floor.

Historically, due to the high morbidity and mortality after CRS with HIPEC, post-operative admission to the ICU was standard of care. However, with improvements in patient selection, anesthesia methodology and surgical technique, many patients no longer require ICU admission. In a retrospective study assessing safety of non-ICU management, patients directly admitted to the floor had less minor morbidity and unchanged major morbidity compared to those who were directly admitted to ICU requiring <48 h of ICU care [64]. Factors associated with ICU admission in this study were worse performance status, higher Clavien-Dindo score, increased blood loss, older age and higher surgical complexity [64]. Currently no data supports admission of all patients to ICU post-operatively as routine practice [64]. Importantly, since rates of serious complication after CRS with HIPEC are estimated between 12 and 54%, patients should be monitored closely on an experienced surgical floor in a center with rapid access to clinicians who are familiar with post-operative care following CRS with HIPEC [6,65].

8. Summary

In conclusion, implementation of a successful HIPEC program in gynecologic oncology requires a multidisciplinary team involving surgeons, anesthesia and intensivists, nursing, perfusionists and pharmacy and appropriate education to all involved. While CRS with HIPEC has the potential for increased post-operative morbidity, meticulous surgical technique and prompt care to correct electrolyte, hemodynamic and temperature abnormalities can significantly improve recovery outcomes.

Declaration of Competing Interest

The authors have no relevant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.06.487.

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