Critical Care Management in a Patient of CRS and HIPEC

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39.1 Introduction

Cytoreductive surgery (CRS) along with Hyperthermic intraperitoneal chemotherapy (HIPEC) has been standard of care for a subset of patients with peritoneal surface malignancies (PSM) including primary peritoneal malignancies like mesothelioma and peritoneal involvement secondary to ovarian, colorectal, gastric and appendicular malignancies. As a first step, cytoreductive surgery (CRS) is performed after which chemotherapeutic agents heated to 41–43 °C are infused intraoperatively using a dedicated HIPEC machine. As chemotherapeutic drugs can penetrate the peritoneal membrane for a maximum of 3 mm, CRS is performed to increase the effect of these drugs [1]. CRS includes an amalgamation of multiple complex procedures like excision of the primary tumor, omentectomies, peritonectomies, bowel and other organ resections as considered necessary to achieve a macroscopically tumor free peritoneal cavity. Multiple factors decide the efficacy of HIPEC such as patient factors, clinical factors, treatment parameters, type of drug and techniques, drug concentration, carrier solution, perfusate volume, temperature and duration of treatment [2]. A high variability exists with regard to HIPEC treatment globally based on disease type and institutional protocols.

Blood loss and massive transfusions can frequently be a part of such major operations which can pose an added insult to the perioperative course. In general, this procedure involves prolonged duration of anesthesia, fluid and electrolyte shifts, thermal stress, along with toxic effects of chemotherapy and acid base disturbances. In a systematic review by Chua et al., including data from retrospective and prospective studies reporting CRS with HIPEC, authors reported a mean operative time ranging from 5 to 10 h and significant blood loss as high as 3.5 L [3].

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Perioperative and critical care management plays a very important role for optimal outcomes following CRS and HIPEC. This chapter will focus on the critical care management issues related to CRS and HIPEC.

39.2 Basic Surgical Concerns and Need for Admission in ICU

Multiple factors decide shifting the patients to ICU intubated or following extubation in the operating room. Some of the important ones are: existing major comorbidities of cardiac or respiratory system, blood loss, transfusion requirements, hemodynamics, metabolic factors towards end of surgery. Most of the time patients are shifted to ICU immediately after surgery (46–74%). In approximately 50% of cases endotracheal tube (ETT) is removed in the operating theatre (OT) [4]. Centers without ICU facilities can gain from experiences of high-volume centres on case selection or situations (e.g. Low volume disease, less blood loss etc.) where an ICU can be avoided. The following factors are important for a favorable postoperative outcome [5]

(a) Immediate or early extubation
(b) Epidural analgesia,
(c) Postoperative monitoring in ICU
(d) Immediate initiation of parenteral nutrition in postoperative period
(e) Stringent fluid status monitoring

Stress response in the postoperative period involves all major organ systems like cardiovascular, respiratory, coagulation, renal and endocrine system [6, 7]. During postoperative course patients may experience hyperthermia-related coagulopathy, hyperglycaemia, low-grade fever and mild pain. Besides these, secretory diarrhoea may occur in the first week. Other biochemical changes can be observed like transient severe hypophosphatemia (due to renal tubulopathy) and altered liver function tests (transaminitis following extensive electrocautery use on the liver capsule). Inflammatory markers like C-reactive protein and interleukins usually return to normal within 12–24 h. Total leukocyte count and platelet counts also decreases within a couple of weeks. Recommendations were laid down for postoperative care and ICU admission by the Society of Onco-anaesthesia and perioperative care and are described in Table 39.1 [5].

39.3 Monitoring in ICU (Hemodynamics/Coagulation Profile/Temperature/Electrolytes)

39.3.1 Haemodynamic Monitoring

These patients need invasive blood pressure monitoring and frequently also may require central venous pressure monitoring besides standard monitoring practices

Table 39.1 Postoperative and ICU care recommendations [5]

Sl no	Recommendation		Evidence available (yes/no)/consensus only
1	Should not routinely extubate the trachea on operating table		Yes
2	Attempting extubation in the operating room should be done in low-volume (low PCI) cases		Yes
3	Haemodynamically unstable patients should be transferred to ICU with endotracheal tube in situ		Consensus
4	Those patients undergoing massive blood loss, high arterial lactate and diaphragmatic striping may be considered for transfer to ICU with endotracheal tube in situ		Consensus
5	The decision to transfer patient to ICU with endotracheal tube in situ or with after tracheal extubation in patients who have undergone prolonged (>10 h) surgery, presence of preoperative bad pulmonary functions and major cardiac or non-cardiac comorbidities should be individualised		No
6	Fluid therapy in postoperative period should be based on	Fluid therapy guided by mean arterial pressure, heart rate and urine output	Consensus
		Fluid therapy guided by arterial lactate concentration	Consensus
7	Starting early enteral nutrition or parenteral nutrition in patient who cannot tolerate enteral nutrition		Yes

such as electrocardiogram, noninvasive blood pressure, pulse oximetry, end-tidal CO2 monitoring and core-body temperature monitoring [8]. In patients with significant disease burden (PCI >15) cardiac output monitoring can additionally be used. Goal-directed therapy (GDT) in CRS-HIPEC had shown to decrease morbidity and thereby shorten postoperative hospital stay. Additionally, there was no difference in mortality.

Throughout the surgery at regular intervals arterial blood gas monitoring is often needed to assess gas exchange, electrolyte, glucose and lactate levels [8]. Serum magnesium level monitoring is preferred both before initiating HIPEC phase and also in the postoperative period. This is because hypomagnesaemia can occur after fluid infusion (dilution) and following platinum-based chemotherapy perfusion [9]. Ionized calcium should also be monitored and corrected if there is massive transfusion of blood and blood products.

39.3.2 Goal for Intraoperative Urine Output

Following CRS-HIPEC, acute kidney injury (AKI) can be witnessed in 21–48% of patients [10]. Some of the predictors of development of AKI are higher age, BMI, pregabalin use (preoperatively), platinum-based chemotherapy, massive blood loss, high blood pressure and low intraoperative diuresis. Factors associated with development of AKI were low intraoperative urine output, angiotensin II receptor antagonist use and raised blood pressure [9]. Urine output is used as a surrogate marker for intraoperative measurement of renal perfusion. The target urine output during various phases are 0.5 mL/kg/h during CRS phase, 2–4 mL/kg/h during the HIPEC and 1–2 mL/kg/h after HIPEC across various studies [11]. However fluid therapy should also be individualized from patient to patient.

There are also controversies about hydration and higher diuresis during HIPEC. Firstly, chemotherapy is administered intraperitoneally rather than usual intravenous route. Secondly, with variation in surface area the degree of absorption and serum concentration may vary. Thirdly, clearance of a drug depends on the renal blood flow rather than urine output. Finally, the etiology of renal failure can be often multifactorial instead of attributing only to platinum. Thus, maintaining euvolaemia by individualising fluid therapy seems essential.

39.3.3 Coagulation Monitoring

The etiology of coagulopathy is multifactorial and depends on various factors like the duration of surgery, PCI, resection extent, blood loss and hemodilution. This in turn depends on the volume of replacement fluids (crystalloids and colloids), packed red cells transfusion and temperature attained (hypothermia). Postoperatively, coagulopathy peaks at 24 h and can remain up to 72 h [12]. Intraoperative monitoring of coagulation parameters periodically is advisable. Most centres use prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalised ratio (INR) for monitoring in preoperative and postoperative period [13]. Thromboelastography (TEG or ROTEM) is used additionally in some centres [13, 14].

39.3.4 Fluid Management

An important aspect of haemodynamics in patients undergoing CRS-HIPEC is sustaining an optimal fluid balance. Intraoperative fluid loses may reach as high as 12 mL/kg during CRS phase [15]. To ensure optimal haemodynamic goals without causing volume overload adequate perioperative crystalloids and colloids are needed. Hydroxyethyl starch (HES) was found to have a adverse impact on the renal function in patients undergoing HIPEC. HES causes increased perioperative bleeding compared with crystalloids and albumin and increased reduction in maximum amplitude on TEG. Isotonic normal saline has high chloride content which can

induce hyperchloremia and metabolic acidosis. Ringer's lactate and acetate-based solutions, have an electrolyte composition nearly similar to plasma and are generally preferred.

Increased fluid administration can be dangerous as it could lead to overload and tissue oedema thereby causing abdominal, cardiac or pulmonary complications. An increase in morbidity has been associated with fluid overload. Restrictive fluid regimens have demonstrated decreased perioperative mortality in other major surgical procedures. However, restricted fluid therapy can cause suboptimal tissue and renal perfusion in the face of extreme haemodynamic changes that occur during the phases of CRS-HIPEC. Secondary to surgical dissection, an extensive loss of protein in the ascitic fluid was observed. Hence, albumin replacement was found to be beneficial in patients requiring extensive debulking and large-volume ascitic fluid drainage.

39.3.5 Temperature Management

In the perioperative period among patients undergoing CRS-HIPEC, maintaining a normothermic status is a challenging goal. Wide variations in temperature can be caused by extensive CRS and HIPEC [16]. During the HIPEC phase hyperthermia raises metabolic rate, consequentially resulting in increased heart rate, demand for oxygen, end-tidal carbon dioxide, lactatemia and metabolic acidosis [16]. These peak of the hyperthermia usually reaches a peak level by 60 min after starting infusion. Once the temperature normalizes these hyperdynamic alterations reverse. Hyperthermia can lead to coagulopathies, renal and liver dysfunction, neuropathies and seizures. High body temperatures can be prevented by using forced air warmers at ambient temperature, using cold intravenous fluids (<6 °C), cooling mattress and ice packs placed in the axilla and head and neck area before initiating HIPEC. Cooling (active or passive) the patient before starting the HIPEC phase can also be done. During the CRS phase, a lower body temperature (hypothermia) can be associated with cardiac morbidity, decreased humoral and cell-mediated immunity and acid–base abnormalities [14]. Hence, body temperature should be kept at normothermic levels forced air warming with blankets and blood/fluid warmers.

39.4 ICU Management

39.4.1 Coagulation and Blood Products

Substantial blood loss may occur during cytoreductive surgery, and transfusion may be necessary. A hemoglobin transfusion threshold of 8 g/dL is considered by many centers.

Commonly used drugs include antifibrinolytic group i.e., tranexamic acid and epsilon aminocaproic acid. These are used routinely for high blood loss during various surgeries (e.g., cardiac surgery, orthopedic and spine surgery). Little literature exists for the use of tranexamic acid during CRS with HIPEC.

Abnormal coagulation can also be caused by hyperthermia but that in practical this is less likely at usual core body temperatures during HIPEC [16]. Most institutions consider sending blood studies for hemoglobin, platelets, fibrinogen, and coagulation parameters as necessary based on blood loss, and correct abnormalities. Thromboelastography can be useful tool to help diagnose coagulopathy.

The timing of removal of the epidural catheter can be affected by alteration in coagulation parameters and platelet counts following CRS and HIPEC. The reasons for coagulopathy can be multifactorial, including dilution related to blood loss, chemotherapy effects, and other factors. Most patients return to normal by postoperative day 6.

39.4.2 Fluid Therapy

39.4.2.1 Restrictive Fluid Therapy

Restrictive or goal directed fluid therapy is suggested rather than a liberal administration, to decrease complications related to fluid overload. Some of the useful points are highlighted below:

- A Crystalloid solution is used for maintenance IV fluid therapy at 4 mL/kg/h.
- Aim for urine output between 0.5 and 1 mL/kg/h during cytoreduction and 4 mL/kg/h during HIPEC.
- If the patient remains hypotensive and SVV and urine output thresholds have been reached, start a vasopressor.
- Ongoing bleeding as a source of hypotension should be investigated, and laboratory studies used to determine whether blood product transfusions are needed.
- Continue goal directed therapy in the postoperative period, adding vasopressors as necessary to maintain hemodynamic stability. Aim for urine output of >0.5 mL/h.

39.4.2.2 Restrictive Versus Goal Directed Versus Liberal Fluid Therapy

Early advocates for CRS with HIPEC included liberal fluid administration, particularly during HIPEC phase. But, practice has gradually shifted towards more restrictive fluid therapy for all major abdominal procedures, including CRS with HIPEC. Many institutional protocols now-a days include restrictive or goal directed fluid therapy. This practice change has resulted in low complication rates, morbidity and mortality [17]. Liberal fluid administration during CRS with HIPEC has also been associated with increased perioperative pulmonary and cardiac morbidity. For instance, in a randomized trial of goal directed versus standard fluid therapy for 80 patients (CRS with HIPEC), the incidence of major abdominal complications has decreased significantly (10.5 versus 38%). Additionally, the length of hospital stay also decreased (19 versus 29 days) in the group who received goal directed therapy (GDT). In a retrospective review of 169 CRS with HIPEC cases before and after an institutional change from liberal to restrictive fluid therapy, restrictive fluid therapy

was associated with decreased 60-day complications and reduced hospital length of stay. Renal failure and peak creatinine rates were similar between groups [18].

39.4.3 Electrolytes

It is prudent to check blood gases and electrolytes every 30 min during HIPEC and during the two hours after infusion of HIPEC is complete. Abnormalities in electrolytes occur commonly as chemotherapy is infused during HIPEC [19]. The metabolic acidosis is multifactorial including:

(i) Massive fluids shifts and electrolyte disturbances due to hyperthermia generated in the peritoneal cavity.
(ii) Hyperthermia induced vasodilation and systemic hypotension lead to increased lactic acid production.
(iii) Lysis of tumor cells releasing organic acids.

As intra-abdominal pressure increases, respiratory acidosis occurs during the HIPEC phase, due to increased airway pressure and decreased functional residual capacity. Dextrose infusions containing carrier solutions can cause hyperglycemia and hyponatremia. Intravenous insulin infusion is usually required to correct hyperglycemia. Other electrolyte disturbances can also be encountered including hypomagnesemia, hypokalemia, and hypocalcemia .Postoperative electrolyte disturbances are very common as large intraoperative fluid shifts can occur following intravenous fluids administration and absorption of carrier solutions used during HIPEC.

39.4.4 Transfusion of Blood and Blood Products

CRS and HIPEC procedures are among the most extensive abdominal surgeries in terms of duration, multi-visceral resections and stripping of parietal peritoneum over large surface area resulting in significant blood loss. As per an Australian study 77% of patients undergoing CRS & HIPEC require intraoperative blood transfusion. High tumor burden (i.e. PCI > 15), extensive surgery (operative length more than 9 h or more than three peritonectomy procedures), preoperative anemia and impaired coagulation profile (INR > 1.2) are risk factors for massive blood transfusion (MBT) [20].

The deleterious effects of blood transfusion in colorectal surgeries are well known. It is associated with increased postoperative morbidity and inferior long-term outcomes [21, 22]. In patients undergoing CRS and HIPEC, a dose-dependent relationship between amount of packed red blood cell (PRBC) transfusion and oncological outcomes has been established [23]. Also, in a single centre experience of 936 patients, it was found that MBT (5 or more units) was associated with an increase in peri-operative grade III/IV morbidity and mortality. MBT was also

associated with a significant compromise in long term survival among patients of colorectal carcinoma and pseudomyxoma peritonei. This is because allogenic blood transfusion aggravates systemic inflammation and transfusion-related immunomodulation [24].

Therefore, it is suggested that strategies to reduce incidence of MBT be implemented to achieve better perioperative and oncological outcomes. This can be achieved by increasing the threshold of blood transfusion, reduction of intraoperative blood losses and preoperative correction of anemia.

Restrictive approach (trigger of hemoglobin <7 g/dL in asymptomatic patients without significant cardiac comorbidity) and liberal approach ('10/30' approach: transfusion for hemoglobin <10 g/dL or hematocrit <30%) are the two approaches to blood transfusion. Upon meta-analysis, restrictive strategy was equivalent to liberal strategy in terms of peri-operative morbidity and mortality [25]. A Cochrane review of 31 trials across multiple specialities provides a good evidence that transfusion threshold of 7–8 g/dL with allogenic PRBCs is adequate for most patients [26]. Therefore, it would be prudent to adopt a restrictive approach to transfusion in patients undergoing CRS and HIPEC, so as to reduce the incidence of MBT.

Intraoperative blood losses can be minimized by improved surgical techniques and maintaining a prothrombotic state intra-operatively. Surgically, losses can be minimized by effective sealing of vessels using energy devices and double ligation, packing and compression of the operative field with dry gauzes after excision and by application of hemostatic materials. A balanced pro-thrombotic state can be achieved intraoperatively by appropriate transfusion of fibrinogen, prothrombin and calcium during peritonectomy. Sargant et al. [27] described a protocol to maintain a higher average fibrinogen levels intraoperatively and postoperatively. As per the protocol, Tranexemic acid is administered at the beginning of surgery and repeated at 4 h into the surgery. Throughout the surgery, the goal is to maintain the patient's fibrinogen level at 2 g/dL.

Alleviation of anemia preoperatively can significantly reduce requirement of peri-operative transfusion. In a Greek study, patients of gastro-intestinal tract cancer-induced anemia were randomised in a double-blind fashion to receive preoperative iron and recombinant erythropoietin (rEPO) or else placebo and iron. The patients who received rEPO received significantly fewer transfusions intraoperatively and postoperatively. Also, these patients experienced lower post-operative morbidity and improved 1-year survival [28].

39.4.5 Analgesia Modalities and Advantages

Pain after CRS and HIPEC is caused both due to inflammation caused by surgical injuries and chemotherapy agents which result in stimulation of peripheral as well as central nociceptors.

The optimal analgesic regimen for a major surgery should provide good pain relief, facilitate early mobilisation, early return of gut function and to prevent respiratory complications [29]. There are no randomised trials providing evidence for

superior analgesic regimen in CRS & HIPEC. Multimodal analgesia (regional analgesia and local anesthesia), in order to reduce doses of parenteral opioids, remains the cornerstone of analgesia management.

Thoracic epidural anesthesia (TEA) containing short acting opiates and local anesthetics should be administered for at least 72 h after surgery [30]. TEA aids in recovery of gut function, improves the stability of anastomosis by aiding early recovery of gut function and reduces pulmonary complications [31–33]. Epidural block should be administered before incision and should include segments T5 to T11 [34]. An improved survival was noted when TEA was used for a minimum of 48 h postoperatively, among colorectal cancer and ovarian cancer patients undergoing HIPEC, upon retrospective analysis.

Combination of short-acting opioids and local anesthetics is considered the best for TEA, as this combination reduces the risk of hypotension and motor block due to sympathetic blockade [35]. In comparison to conventional continuous epidural infusion, patient controlled epidural analgesia is gaining popularity [36]. TEA should be removed 48–72 h postoperatively. Breakthrough pain, hypotension and neurological side effects of TEA should be treated as per local policy [34].

As HIPEC can potentially affect hemostasis and cause thrombocytopenia, administration of TEA is potentially unsafe. Korakiantis et al., in a prospective study, demonstrated that TEA is a safe option in patients undergoing CRS & HIPEC [37]. In a retrospective study evaluating 4277 patients who underwent CRS & HIPEC, none of the patient had postoperative epidural hematoma [38].

Transversus abdominal plane (TAP) block was found to be non-inferior to TEA in a study evaluating the postoperative analgesic effects of the two modalities in open colorectal surgery. TAP block produces analgesic effects on anterior abdominal wall skin, muscle and parietal peritoneum by acting on lower thoracic nerves (T7 to T12) and the anterior branch of first lumbar nerve (L1). Requirement of parenteral opioids can be effectively reduced by TAP block [39].

Paracetamol is a vital part of multimodal analgesia. NSAIDs can be given but careful consideration should be made in patients with renal dysfunction. Use of alternative analgesic drugs such as lidocaine, ketamine or gabapentin are presently not recommended, awaiting further studies.

39.4.6 Extubation Planning

Among patients undergoing CRS & HIPEC, the rate of extubation varies from 62 to 100%, depending upon institutional policy [40–42]. Most patients undergoing CRS & HIPEC can be extubated after surgery. A few patients, who are clinically unstable, require ionotropic support, had diaphragmatic resection or multiple comorbidities, remain intubated and are shifted to ICU for postoperative ventilation.

Criteria for extubation in CRS & HIPEC patients have not been defined and differ with institutional practices and anesthesiologist's comfort and experience. In a retrospective study by Balakrishnan et al. [42], higher PCI, longer duration of surgery, higher delta temperature, increased estimated blood loss, high intraoperative

fluid requirement, lower mean arterial pressure and higher blood product requirement were associated with prolonged post-operative ventilation (>24 h) and longer ICU stay.

The advantages of early extubation include early ambulation and shorter duration of sedation, resulting in earlier return of bowel function and shorter duration of hospitalisation. Opioid requirement in perioperative period is reduced upon use of TEA and local anesthetic infusion, thereby facilitating early extubation.

ERAS guidelines for perioperative care in CRS & HIPEC recommend early extubation to be performed routinely in absence of contra-indications [43].

39.4.7 Thromboprophylaxis

Stasis, hypercoagulability and endothelial injury are the classic risk factors associated with venous thromboembolism (VTE) and are usually present in patients after CRS & HIPEC. Western data suggest that without thromboprophylaxis, 30–50% of patients of peritoneal malignancy undergoing surgery may experience VTE [44]. It is the most common cause of death in perioperative period [45].

Risk factors for VTE include disease burden, blood transfusion and extent of surgery, PCI, blood loss, operative time, length of hospital and ICU stay and lack of administration of anticoagulant on discharge [46]. Standard guidelines for thromboprophylaxis among patients undergoing major cancer surgery can be extrapolated to patients undergoing CRS & HIPEC.

It is observed that 2/3rd of cases of VTE occur in patients 'after' discharge. Extended thromboprophylaxis reduce the 60 day VTE rate from 10 to 5% and post discharge VTE rate from 8 to 2%. ERAS guidelines for CRS & HIPEC strongly recommend use of peri-operative mechanical and pharmacological thromboprophylaxis and also recommend extended pharmacological thromboprophylaxis [30].

39.4.8 Immediate Postoperative Complications

Review of literature reports 18–52% major morbidity in patients undergoing CRS & HIPEC during the post-operative period [47]. Majority of complications are related to surgical procedures and can be handled as per standard guidelines. In this section, we will be focussing on immediate systemic complications caused by HIPEC.

Risk of postoperative renal dysfunction is significant and multifactorial. Nephrotoxicity is the main dose-limiting side effect of cisplatin, especially at doses greater than 240 mg [48]. Sodium thiosulfate can be used to reduce the risk of renal failure [49]. Mitomycin C (MMC) can also less commonly lead to nephrotoxicity. Goal directed fluid resuscitation and optimising oxygen delivery by hemodynamic monitoring is perhaps the most suitable method to prevent and/or

treat nephrotoxicity [50]. Use of other nephrotoxic agents in these patients should be avoided. Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP 7) have been approved by USFDA as biomarkers for risk stratification of acute kidney injury (AKI) in critically ill patients and can be extrapolated for use among patients undergoing HIPEC [51].

Respiratory complications are important source of morbidity after CRS & HIPEC and should therefore be prevented by prophylactic usage of non-invasive ventilation (NIV) or HFNC and routine implementation of thoracic epidural analgesia.

Septic shock and multisystem organ failure is the leading cause of mortality in patients undergoing CRS & HIPEC and causative factors include extensive nature of procedure, immunosuppression due to previous chemotherapy, surgical complications as well as extensive peritoneal inflammation and inflammatory response.

Hematological toxicity is a recognised complication of HIPEC and has been reported in up to 10–28% of patients in postoperative period [52]. It appears to be primarily related to the type of chemotherapy agent used for HIPEC. Using a dose of MMC 35 mg/m^2 over 90 min of HIPEC can result in postoperative neutropenia/leukopenia in as many as 27% of patients. Routine prophylactic granulocyte colony-stimulating factor (G-CSF) does not alter neutropenia rates but may be used to avoid or prevent profound aplasia when white cell counts are decreasing [53].

Major surgical complications are anastomotic leaks (0–9%), intraabdominal abscesses (0–37%), intestinal perforation/peritonitis (0–10%), fistulas (0–23%) and prolonged ileus (0–86%). Intra abdominal bleeding, bile leaks, pancreatitis, major wound infections, acalculous cholecystitis, mesenteric ischemia, mechanical intestinal obstruction are other surgical complications that can be encountered after CRS and HIPEC

39.5 Conclusion

Peri-operative management and critical care are extremely important determinants of outcomes following CRS and HIPEC. Dedicated multi-disciplinary teams including Anesthesiologists, and critical care experts play a significant role in the management of these patients. Protocol based management approach and establishment of standard operating procedures is critical for optimal outcomes. Important domains need to be focussed include fluid, blood and protein losses, increased intra-abdominal pressure, systemic hypo-/hyperthermia and increased metabolic rate in patients undergoing HIPEC. TAE and NIV are recommended to ensure adequate pain relief and early post-operative extubation. Postoperatively, volume status optimization, early nutrition support, sufficient anti-coagulation and point of care coagulation management are essential. Systemic toxicities need to be identified early and optimally managed.

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