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# Postoperative complications and critical care management after cytoreduction surgery and hyperthermic intraperitoneal chemotherapy: A systematic review of the literature

Anjana S Wajekar, Sohan Lal Solanki, Vijaya P Patil

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## Abstract

### BACKGROUND

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment option performed for peritoneal surface malignancies. Postoperatively almost all patients are transferred to the intensive care unit electively.

### AIM

To describe the common and rare postoperative complications, postoperative mortality and their critical care management after CRS-HIPEC.

### METHODS

The authors assessed 54 articles for eligibility. Full text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion into the final review article.

### RESULTS

There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with the use of heated intraperitoneal chemotherapy with/out early postoperative intravenous chemotherapy. The expected postoperative course is further discussed. CRS-HIPEC is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%. Over the years, since its inception in the 1980s, postoperative morbidity and survival have significantly improved. The commonest postoperative surgical complications and systemic toxicity due to chemotherapy as reported in the last decade are discussed.

## CONCLUSION

CRS-HIPEC is associated with a varying rate of postoperative complications including postoperative deaths and needs early suspicion and intensive care monitoring.

**Key Words:** Intensive care units; Hyperthermic intraperitoneal chemotherapy; Morbidity; Peritoneal neoplasms; Postoperative period

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**Core Tip:** Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%. There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with use of heated intraperitoneal chemotherapy.

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## INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment option performed for peritoneal surface malignancies (PSM), both primary peritoneal cancers and peritoneal metastasis secondary to colorectal, appendiceal, ovarian, gastric and other malignancies. CRS comprises the surgical removal of visible tumour from peritoneal surfaces as well as abdomino-pelvic organs. CRS includes a wide spectrum which ranges from excision of a single peritoneal nodule to complete peritonectomy along with multi-visceral resections and up to 3-5 anastomoses. It is followed by HIPEC which involves pumping highly concentrated chemotherapy drugs heated to 41°C-43°C into the peritoneal cavity. HIPEC can be performed either with closed or open abdominal techniques. The advantages of a closed abdominal HIPEC are increased intraabdominal pressure leading to increased tissue penetration and prevention of heat loss whereas the advantage of open abdominal HIPEC is better distribution of the chemotherapeutic drugs. The primary disease and institutional protocol dictate the type of HIPEC treatment used in various institutes. The duration of surgery can vary from eight to fifteen hours, with longer duration being the norm rather than an exception.

CRSHIPEC is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%[1-4]. The postsurgical complications have been reported as late as 90 d after surgery[1,5]. Over the years since its introduction in 1980's, better patient selection, improvements in surgical techniques, surgical skills and perioperative management strategies, have further reduced the morbidity and improved the survival after CRS-HIPEC. Additionally, disease progression even after comprehensive treatment, necessitating a repeat CRS-HIPEC procedure has been reported to be useful in selected patients with recurrent peritoneal malignancies[6].

The present article reviews the early postoperative management and common complications after CRS-HIPEC, reported in the last decade.

## MATERIALS AND METHODS

### Literature search strategy

An electronic literature search was conducted using the databases of 'PubMed' and 'Google Scholar'. The 'Reference Citation Analysis', an artificial intelligence technology-based open citation analysis database was employed. The period of the search was from 2010 to 2021. The search terms included, "Peritoneal Cancer", "Hyperthermic", "Intraperitoneal", "HIPEC", "Critical Care, Intensive Care, Postoperative Care, Perioperative Care, Postoperative Complications and their synonyms in various combinations. The extracted articles were further reviewed in a step-wise manner for identification of relevant studies. The titles and abstracts were inspected independently by two authors.

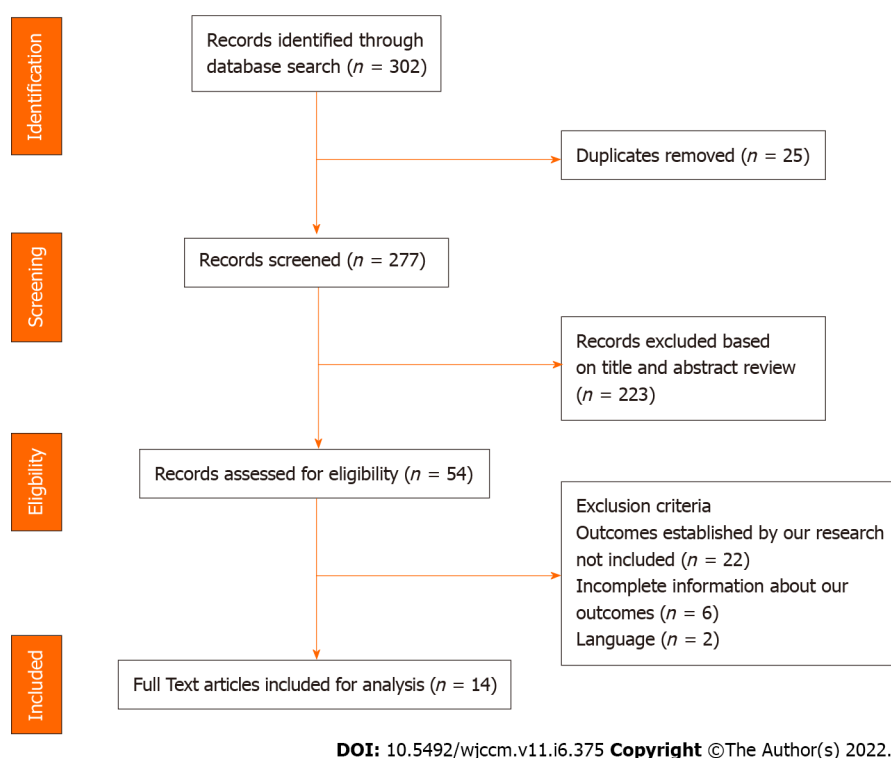


Figure 1 PRISMA flow diagram.

**Study selection criteria**

Only full text articles published in English were included for review. Only articles which reported postoperative critical care management and complications were included. Articles regarding only preoperative and intraoperative management were excluded. Only original research articles were included for analysis. Meta-analyses and review articles were excluded.

**RESULTS****Literature search results**

A total of 277 articles were identified after the initial literature search. Initial review included screening of article titles for relevance and identifying duplicates. A further screening of abstracts identified articles for full text review. Full text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion into the final review article (Table 1, Figure 1).

**DISCUSSION****Critical care management**

Postoperatively almost all the patients were transferred to the intensive care unit (ICU) electively. Only a few selected patients with limited CRS and short duration HIPEC may be amenable for high dependency unit (HDU) management. There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with use of heated intraperitoneal chemotherapy with/out early postoperative intravenous chemotherapy.

At the end of surgery, the decision to extubate or electively ventilate depends upon patient comorbidities, duration of surgery, degree of cytoreduction, haemodynamic instability, vasopressor use, blood loss and the need for massive blood transfusion, and metabolic derangement. Even in the ICU, it is quite common to extubate the patients to a high flow nasal cannula or non-invasive ventilation depending upon the extent of diaphragmatic peritonectomy, breathing efforts of the patients and site of gastrointestinal anastomosis. Preoperative malnutrition and anaemia, long duration of surgery, fluid overload, poorly controlled pain leading to diaphragmatic splinting, lithotomy with steep Trendelenburg positioning, preoperative pleural effusion, ascites or presence of preoperative compromised pulmonary functions predispose a patient to postoperative pulmonary complications. Adherence to enhanced recovery after surgery (ERAS) protocols including preoperative incentive

**Table 1** Demographic details and disease load

Ref.	Data duration	Type of Cohort/Study	No of Institutes (Country)	PSM	No of procedures	Age	PCI		
Cavaliere <i>et al</i> [35], 2011	1995-2007	Prospective	Five (Italy)	Colorectal	146	56 (19-76)	median (range)	< 11-48, 11-20-72, > 20-26	Range
Glehen <i>et al</i> [36], 2010	1989-2007	Retrospective	Twenty-five (Europe and Canada)	Non-ovarian	1154, 190(EPIC)	52 (12)	mean (SD)	13.1 (8.9)	mean (SD)
Cooksley <i>et al</i> [7], 2011	2009-2010	Retrospective	Single (England)	Mixed	69	53.3 (30-73)	mean (range)	10.5	Mean
Mizumoto <i>et al</i> [37], 2012	2007-2011	Retrospective	Single (Japan)	Mixed	284	57 (13) (23-88)	mean (SD) (range)	20 (13) (0-39)	mean (SD) (range)
Bakrin <i>et al</i> [1], 2012	1991-2008	Retrospective	Two (France)	Ovarian	246	57.5 (28.6-77.6)	Mean (range)	10.8 (1-31)	Mean (range)
Baratti <i>et al</i> [17], 2012	1995-2011	Prospective	Single (Italy)	Mixed	426	53.4 (12.7)	mean (SD)	18.7 (10.8)	mean (SD)
Bakrin <i>et al</i> [16], 2013	1991-2010	Retrospective	Thirteen (France)	Ovarian	566	57.89 (22-77)	Median (range)	8.5 (0-31)	Median (range)
Canda <i>et al</i> [27], 2013	2007-2012	Retrospective	Single (Turkey)	Mixed	118	53.4 (20-82)	Mean (range)	14.7 (3-28)	Mean (range)
Jafari <i>et al</i> [15], 2014	2005-2011	Retrospective	> 500 (USA)	Mixed	694	55 (10)	mean (SD)	NA	
Levine <i>et al</i> [30], 2014	1991-2013	Prospective	Single (USA)	Mixed	1000	52.9 (12.4)	mean (SD)	12	Mean
Cascales-Campos <i>et al</i> [24], 2016	2008-2014	Prospective	Single (Spain)	Mixed	156	57 (33-79)	Median (range)	8 (0-13)	Median (range)
Martin <i>et al</i> [25], 2016	1991-2014	Retrospective	Single (USA)	Mixed	302	54% (40-60)	Percent (range)	13 (6-18)	Median (IQR)
Elekonawo <i>et al</i> [38], 2019	2010-2015	Case matched RCT	Two centres in Netherlands	Colorectal	223	61.4(10.7)	mean (SD)	9.0 (0-24)	Median (range)
Kelly <i>et al</i> [39], 2018	2007-2014	Retrospective	Single (USA)	Mixed	226	53 (20-66)	Median (range)	14 (0-27)	Median (range)

RCT: Randomised controlled trial; PCI: Peritoneal carcinomatosis index; EPIC: Early postoperative intravenous chemotherapy; SD: Standard Deviation; PSM: Peritoneal surface malignancies; NA: Not available.

spirometry and respiratory muscle training and its continuation in the postoperative period have been proven to reduce pulmonary complications. Cooksley *et al* [7] extubated all their HIPEC patients at the end of surgery with the use of good epidural analgesia and goal-directed fluid therapy.

Massive fluid shifts, third spacing and blood loss are quite common in the CRS phase of the surgery whereas the HIPEC phase can lead to extensive vasodilatation necessitating use of vasopressors. The fluid losses, both external and internal (third space), continue in the immediate postoperative period. The abdominal drain losses can be as high as 40% of the total output, in the first 72 h after surgery [3,8]. Continuous monitoring and assessment of fluid status guided by various static and dynamic parameters such as cardiac output monitoring, central venous pressure, serum lactate, urine output, abdominal drain and nasogastric losses need to be conducted. Adequate and timely resuscitation with crystalloids, colloids, blood and blood products helps reduce postoperative morbidity and mortality. In view of the increased risk of postoperative sepsis, acute kidney injury and coagulopathy, it is advisable to avoid use of hydroxyethyl starches in the perioperative period. There is a significant protein loss secondary to the exudating ascitic fluid and extensive surgical dissection. Postoperative decline in albumin levels is common, which starts intraoperatively and continues postoperatively, with the need for exogenous replacement. The routine use of furosemide, mannitol or low doses of dopamine to prevent renal injury is no longer recommended.

Malfroy *et al* [8] found that abdominal drain output more than 1500 mL, postoperative fluid resuscitation > 70 mL/kg or the need for vasopressors in the first 24 h after surgery are predictors of increased 30-d morbidity and mortality. Earlier concerns regarding chemotherapy-induced nephropathy, replacement of large volume ascites and dehydration due to preoperative bowel preparations, led to liberal fluid replacement during the intraoperative period with resultant postoperative

fluid overload leading to tissue and bowel edema and increased abdominal, respiratory and cardiac complications. In CRS-HIPEC procedures, Colantonio *et al*[9] found that patients in the protocolised goal-directed therapy (GDT) group received significantly less fluids in the intraoperative period, had lower abdominal and other systemic morbidity and postoperative length of stay but with no significant difference in mortality. They reported that GDT with individualised therapeutic end points can be achieved using a combination of colloids, crystalloids and vasopressors.

Coagulopathy during the perioperative period is multifactorial which includes the length of surgery, extent of resection, both hypothermia and hyperthermia, blood loss and massive blood transfusion. There may be prolongation of prothrombin time, activated partial thromboplastin time and/or reduction in platelet count. Monitoring viscoelastic properties of clots with the use of thromboelastography both intra- and postoperatively can help with management. The coagulation profile generally normalises by the third to sixth postoperative day. Platelet transfusion is rarely required and should only be considered when platelet levels fall below 50000 with associated bleeding or additional surgical procedures become imminent.

Electrolyte abnormalities may be common due to perioperative massive fluid shifts. Sodium, chloride, potassium, calcium, magnesium and phosphate should be measured periodically and replacement should be done in the ICU.

Extensive CRS and HIPEC can cause wide fluctuations in temperature. The hyperdynamic alterations secondary to hyperthermia generally reverse once the temperature normalises. Hyperthermia can also cause coagulopathies, renal tubulopathy, liver dysfunction, neuropathies and seizures. Delta temperature (difference between lowest and highest temperatures) during CRS-HIPEC was found to be a significant predictor of ICU stay > 5 d[3]. This is highest in patients with a high peritoneal carcinomatosis index (PCI) necessitating longer, aggressive resection. Hypothermia during the CRS phase is associated with cardiac morbidity, decreased humoral and cell-mediated immunity and worsen metabolic acidosis and may be responsible for increased ICU stay. The lactate levels after HIPEC should be interpreted with caution and along with other markers of perfusion as the inflammatory state itself can be responsible for hyperlactatemia.

Perioperative fluid shifts and hypoperfusion combined with nephrotoxic chemotherapy especially cisplatin predisposes to acute kidney injury. The critical time for renal perfusion is generally the first 2 postoperative days. Transient severe hypophosphatemia may be observed on the first two-three postoperative days due to hyperthermia-related renal tubulopathy. It can lead to decreased diaphragm mobility leading to atelectasis and increased insulin requirements. Transaminitis (2 to 3 fold rise) is common during the first four postoperative days. Diarrhoea can occur in the first week due to digestive hypersecretion secondary to the hyper inflammatory status.

Initiation of enteral feed should depend on the extent of bowel resection, presence or absence of inflammation and haemodynamic stability. Parenteral nutrition should be initiated early and switched to enteral nutrition as soon as possible. The decisions regarding nutrition should consider patients baseline nutritional status, and surgical and medical concerns. Dieticians should be actively involved from the preoperative phase. Preoperative nutritional status may predict length of stay, risk of infectious complications and possibly long-term survival.

The anticipated postoperative course includes low grade fever up to 38°C, even in the absence of infection, during the first 7-10 postoperative days. Leukocyte counts and platelet counts progressively decrease in the first two weeks followed by a progressive increase. Inflammatory markers such as C reactive protein, interleukins and elastase increase during surgery and return to normal within 12-24 h. Hyperglycaemia can be a common finding due to surgical stress and hypercatabolic state, necessitating insulin infusions. The glycaemic targets are set at blood sugar levels between 140 to 180 mg/dL. Routine postsurgical antibiotic prophylaxis is recommended. An escalation after appropriate cultures may be required in the event of infections.

Moderate to severe pain is quite common. Use of thoracic epidural anaesthesia (TEA) is desirable in these patients for management of postoperative analgesia, prevention of respiratory complications and reduction in rates of paralytic ileus. Thoracic epidural analgesia with local anaesthetics and short acting opioids up to 72-96 h after surgery have been found to be useful. Owusu-Agyemang *et al*[10] in their study of 215 patients reported that intraoperative initiation of continuous epidural infusions pre-HIPEC was associated with significantly less blood loss and decreased intraoperative fluid requirements. Despite common postoperative coagulation abnormalities and an increased incidence of sepsis, no epidural hematomas or abscesses were reported in their study. A single centre retrospective analysis reported improved survival and reduced grade III/IV postoperative morbidity after HIPEC when TEA was used compared to patient-controlled opioid analgesia[11]. Along with thoracic epidural analgesia, adjuncts such as paracetamol as a component of multimodal analgesia are recommended. Opioid usage needs to be minimised. The use of truncal blocks such as transversus abdominis block or quadratus lumborum blocks in the absence of epidurals are encouraged.

Adherence to ERAS protocols in the perioperative period have helped to considerably decrease the grade III/IV complications and associated morbidity, length of ICU and hospital stays and improve the survival rates[3,12-14]. Mechanical and pharmacological deep vein thrombosis prophylaxis should be considered as appropriate during the entire perioperative period if not contraindicated. The first dose of low molecular weight heparin is generally given the previous night as part of ERAS and continued



postoperatively. Implementation of ERAS protocols in the postoperative period such as early extubation, early removal of drains and urinary catheter, and early mobilisation are recommended. Stress ulcer prophylaxis can be followed as per institutional protocols.

Compliance to ERAS protocols have been found to reduce the major postoperative complication rate from 33% to 21% due to early detection and reversal of the pathophysiological cascade after this major surgery, consequently reducing the length of stay from  $13.1 \pm 9.5$  d to  $8.6 \pm 4.9$  d[12]. A more recent National Surgical Quality Improvement Program review reported an average length of stay of 13 d[15].

### Complications in the postoperative period

The extent of peritoneal disease as scored by the PCI, the completeness of the cytoreduction (CC) score and dose of intraperitoneal platinum chemotherapy are important prognostic factors of both morbidity and survival[1,8,16]. PCI > 8-10 and CC-1/CC-2 have been found to have an increased incidence of postoperative grade III/IV complications. The risk of complications increased by 3.5% for every single point increase in PCI[17]. Additionally, initial indication of surgery, ECOG score, number of organ resections *etc* may help further prognostication[1,17]. Tao *et al*[18] in their meta-analysis, reported a similar incidence of anastomotic leaks and duration of hospital stay between younger (< 65 years) and elderly (> 65 years) patients but the morbidity outcomes and mortality were higher in elderly patients. Cooksley *et al*[7] found that the higher the vasopressor requirement intra- and postoperatively, the higher the risk of postoperative complications.

In recent years, a gamut of studies investigated the utility of inflammatory markers to predict the postoperative course as well as survival. Inflammation plays an important role not only in carcinogenesis but also during CRS-HIPEC surgery. Some inflammatory biomarkers have been found to have an increased association with postoperative infective complications. Kim *et al*[19] reported that higher values of preoperative neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV), platelet to lymphocyte ratio (PLR), and MPV on postoperative days 2, 3, and 5 were associated with decreased 1-year survival after CRS-HIPEC. C-reactive protein (CRP), an acute phase inflammation protein, is a highly sensitive but nonspecific biomarker of systemic inflammatory response. van Kooten *et al*[20] reported an increasing value of CRP after postoperative day (POD) 2 or CRP > 166 mg/L at POD3 or > 116 mg/L at POD4, had a predictive value for early detection of severe adverse events. Saeed *et al*[21] studied the dynamics of precalcitonin (PCT) pre and postoperative in CRS-HIPEC patients and compared them to CRP and white cell counts (WCC) in patients who developed infective complications postoperatively. They found a trend for faster rise in serum PCT on POD1 as compared to CRP and WCC, along with a faster PCT decline following appropriate therapy on POD3 and 6 when infected cases were clinically resolving while WCC and CRP continued to rise, particularly in non-splenectomised patients. Splenectomised patients had an increase in PCT postoperatively even in the absence of infection. Although all three, namely PCT, WCC and CRP showed an increase postoperatively consequent to systemic inflammatory response syndrome (SIRS) post CRS-HIPEC surgery, PCT had the highest negative predictive value to rule out bacterial infectious complications. Finally, they cautioned the interpretation of postoperative PCT in predicting infectious complications only in association with other clinical, biochemical, microbiological and radiological findings. Viyuela Garcia *et al*[22] reported that CRP on POD7 and 8 had best accuracy, with an optimal cut-off value of 88 mg/L and 130 mg/L, respectively, to predict postoperative infective complications in ovarian cancer patients who underwent CRS-HIPEC.

The complications are commonly graded on two main classification systems – Clavien Dindo classification and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE). Major surgical complications generally include those requiring interventional endoscopy or CT-scan/ultrasound-guided procedures (grade 3), return to the operating room or ICU (grade 4), and death (grade 5). It has been found that conventional 30-d mortality underestimates post-operative mortality by 50% in CRS-HIPEC patients[5]. In their study, Alyami *et al*[5] found that most major complications occurred within 30 d, but more than 50% of deaths related to postoperative complications occurred after 30 d. Various studies have suggested evaluating morbidity and mortality related to complex surgical procedures such as CRS-HIPEC, using a 90-d time period for its definition[5,17,23].

CRS-HIPEC, being a major abdominal surgery, is associated with a gamut of postoperative complications. Grade III/IV complications are most common in the first 2 wk after surgery (Table 2). Malfroy *et al*[8] reported a median time to complications post-surgery of 2.5 d.

### Gastrointestinal complications

CRS with HIPEC involves extensive abdominal surgery with major handling of small bowel, several visceral resections, anastomosis and peritonectomy. The major complications include anastomotic leaks, gastrointestinal perforations distant from the suture line, abdominal abscess, sepsis, haemorrhage, biliary, pancreatic or ureteral leakage, pancreatitis, paralytic ileus, diarrhoea *etc*. An important consideration is the timing of the anastomosis vis-à-vis HIPEC. There is no evidence in the literature to suggest an increased risk of anastomotic leaks or isolated disease recurrence on suture lines if anastomosis is performed at the completion of the cytoreduction and prior to HIPEC[6]. Some authors prefer bowel anastomoses to be performed before HIPEC in closed procedures to avoid reopening the patient but after HIPEC in cases of open procedure[16]. Malfroy *et al*[8] found that septic shock was the commonest

Table 2 Surgical complications

Ref.	N	Mortality (%)	Days	Morbidity (Grade III/IV), %	Complication classification	Commonest complications			Re-operations (%)
						First (%)	Second (%)	Third (%)	
Cavaliere <i>et al</i> [35], 2011	146	2.7	30	27.4	WHO	GI perforation/anastomotic leak (7.4)	Sepsis (4.1)	Pancreatitis/pancreatic fistula (1.4)	NA
Glehen <i>et al</i> [36], 2010	1154, 190 (EPIC)	4.1	30	33.6	NCICTCAE	GI perforation/anastomotic leak (9.7)	Pneumonia (9.1)	Intraabdominal bleeding (7.7)	14
Cooksley <i>et al</i> [7], 2011	69	0	30	5.79	NA	Pneumonia (2.9)	Central line infection (1.5)	Uncontrolled hypertension (1.5)	NA
Mizumoto <i>et al</i> [37], 2012	284	3.5	30	17	NCICTCAE	GI perforation/anastomotic leak (6.7)	Sepsis (4.6)	Intraabdominal bleeding (2.1)	11
Bakrin <i>et al</i> [1], 2012	246	0.37	30	11.6	NCICTCAE	GI perforation/anastomotic leak (4.9)	Intraabdominal bleeding (2.4)		4.9
Baratti <i>et al</i> [17], 2012	426	2.6	90	25.3	NCICTCAE	GI perforation/anastomotic leak (11.03)	Sepsis (3.76)	Intraabdominal bleeding (3.3)	10.7
Bakrin <i>et al</i> [16], 2013	566	0.8	30	31.3	NCICTCAE	Intraabdominal bleeding (8)	GI perforation/anastomotic leak (3)		8
Canda <i>et al</i> [27], 2013	118	7.6	30	31.35	NCICTCAE	Sepsis (7.6)	Pneumonia (2.5)	Ileus (2.5)	5.08
Jafari <i>et al</i> [15], 2014	694	2.3	30	32.9	NA	Intraabdominal bleeding (17)	Sepsis (15.9)	Pneumonia (4.8)	9.8
Levine <i>et al</i> [30], 2014	1000	3.8	30	42	NA	Sepsis	GI perforation/anastomotic leak	Pneumonia	NA
Cascales-Campos <i>et al</i> [24], 2016	156	0.6	30	11.5	NCICTCAE	Pleural effusion (4.49)	Sepsis (3.8)	GI perforation/anastomotic leak (1.9)	NA
Martin <i>et al</i> [25], 2016	302	3	30		NA	Pleural effusion (10.8)	Thrombosis (6.8)	Sepsis (5.4)	NA
Elekonawo <i>et al</i> [38], 2019	223	1.5	30	17.6	Clavien Dindo	Sepsis (14.7)	GI perforation/anastomotic leak		NA
Kelly <i>et al</i> [39], 2018	226		30	NA	NA	Ileus (31)	Sepsis (21)	Thrombosis (15)	16

EPIC: Early postoperative intravenous chemotherapy; GI: Gastrointestinal; NA: Not available; NCICTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE).

factor for postoperative ICU re-admission (28.1%) with gastrointestinal origin of sepsis to be the highest (64.3%). Paralytic ileus is the commonest morbidity observed postoperatively, classified as Grade I-III morbidity[24]. One meta-analysis showed an incidence of prolonged postoperative ileus of 10.2% following elective colonic surgery, with potential higher rates with added effects of the hyperthermic bath, chemotherapy and peritoneal carcinomatosis[14]. The use of thoracic epidural analgesia, postoperative use of prokinetics, laxatives and adjuncts such as coffee or chewing gum, and early mobilisation have all been recommended to hasten gut recovery after such major surgery. ICU readmissions occur in 11%-25% of patients and in one study, ileus/dehydration was responsible for one third of readmissions[14]. The rate of re-operations increases in patients with postoperative complications due to sepsis, anastomotic leaks, *etc.*

Sepsis both abdominal and unrelated to the surgical site is the commonest complication post-surgery. It is also the commonest cause of mortality. Infections with resistant organisms are also common[8].

Martin *et al*[25] reported 30- and 90-d readmission rates after CRS-HIPEC to be 14.9% ( $n = 32$ ), and 21.4% ( $n = 46$ ), respectively. The main factor implicated in re-admissions was the presence of enterocutaneous fistula. They did not find any association between factors such as age, sex, race, intraoperative

blood loss, pancreatic or hepatic resection at the index operation, and postoperative complications of surgical site infection, line infection, and thromboembolic events with higher re-admission rates.

### **Respiratory complications**

Common postoperative grade III/IV respiratory complications include pneumonia, pleural effusions, respiratory failure, and pulmonary embolism[8,23,26]. These can prolong the ICU stay or cause ICU re-admissions. Respiratory sepsis is the second most common cause of septic shock at 28.6%[8]. The massive fluid shifts during CRS-HIPEC are most commonly responsible for the increased incidence of unplanned intubations, prolonged ventilations and pulmonary interventions. Preti *et al*[26] reported an incidence of pulmonary adverse events of 10% which included 4.6% pleural effusions, 4.2% respiratory distress necessitating oxygen supplementation and intubations and 3.2% pneumonia. Martin *et al*[25] reported pleural effusions in 10.8% of patients postoperatively and mortality in two patients secondary to pulmonary embolism.

### **Cardiovascular complications**

Hypovolemic shock especially in the first 48 h post-surgery secondary to exuding peritoneal surfaces and systemic inflammatory response can lead to higher rates of grade III/IV complications. The incidence of acute myocardial infarction and arrhythmias is similar to any major gastrointestinal surgery. Jafari *et al*[15] reported a 0.3% incidence of postoperative myocardial infarction. Martin *et al*[25] reported a 4.4% incidence of cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and pulseless electrical activity) and attributed one patient's mortality to cardiac dysrhythmia.

### **Miscellaneous**

Sepsis (unrelated to abdominal complications), central line infections as well as urinary tract infection are common[6,17,25,27]. Some case reports have mentioned rare complications such as non-cirrhotic, non-total parenteral nutrition hyperammonia *etc*[28]. Prolonged postoperative acidosis has also been observed[8]. Multi-organ failure is common. The risk of pulmonary embolism, deep venous thrombosis and superior mesenteric vein thrombosis is in the range of 5%-10%[29]. The significant risk factors associated with the development of venous thromboembolism include advanced cancer stage at the time of diagnosis, prolonged immobilization, extensive surgical procedures, mucinous tumours of the gastrointestinal tract and the use of central venous catheters.

### **Systemic toxicity due to hyperthermic chemotherapy**

Depending on the cancer histology, high concentrations of different chemotherapeutic agents (20-1000 times greater than plasma levels) are delivered into the abdominal cavity. Drugs which have a synergistic effect with heat, namely, mitomycinC and the platinumbased drugs, cisplatin, carboplatin, and oxaliplatin are used for intraperitoneal (IP) administration. The less commonly used drugs are doxorubicin, 5fluorouracil, docetaxel, paclitaxel and irinotecan.

Intraperitoneal chemotherapy is sometimes combined with concomitant or early postoperative administration of intravenous chemotherapy, aiming to create a bidirectional diffusion gradient through the cancer cells.

Most of the PSM are platinum-sensitive, with cisplatin being the commonest chemotherapeutic agent used for HIPEC. Common toxicities include nephropathy and haematological toxicity (Table 3). A cisplatin dose more than 240 mg was demonstrated to increase both surgical morbidity and systemic toxicity[17]. Some centres have used sodium thiosulphate for the prevention of cisplatin-induced nephrotoxicity with promising results[3,14,30]. One of the considerations for patients with a second recurrence is platinum sensitivity. The progression-free interval since the most recent course of platinum chemotherapy may differentiate between platinum sensitive and platinum resistant disease [16]. Few studies have reported an increased rate of systemic complications with the combined use of cisplatin and mitomycin for IP chemotherapy[1,31]. Canda *et al*[27] found that patients with pre-operative renal dysfunction and previous chemotherapy may present with grade III/IV postoperative nephrotoxicity. Despite a 30% dose reduction in the chemotherapeutic agent doses during HIPEC in older patients (age > 70 years), patients with preoperative renal dysfunction or previous systemic/intraperitoneal chemotherapy, they found a high incidence of post-operative renal dysfunction with five patients requiring haemodialysis and two patients continuing with chronic haemodialysis[27]. Bakrin *et al*[16] suggested a 30% dose reduction in patients older than 70 years, with previous chemotherapy and/or extensive surgical cytoreduction as they found a higher incidence of postoperative renal dysfunction with 8% of patients ( $n = 51$ ) suffering from postoperative renal insufficiency, 2% of patients ( $n = 15$ ) chronic renal insufficiency and 1% of patients ( $n = 6$ ) requiring long-term dialysis.

Haematological complications secondary to chemotherapeutic agents are also commonly reported in various studies[1,7,32]. Leukopenia and neutropenia have been frequently reported. Mitomycin-C (MMC), when dosed by body surface area or weight, has been attributed to leukopenia to the tune of 20%-40%[32]. In a study by Feferman *et al*[32], the use of MMC-HIPEC produced an incidence of 7% severe leukopenia and 4.5% neutropenia, with some patients requiring therapeutic granulocyte colony

**Table 3 Systemic toxicities due to chemotherapy**

Ref.	HIPEC drugs	EPIC	Nephrotoxicity, %	Haematological toxicity, %
Glehen <i>et al</i> [36], 2010	MMC + CDDP/Ox + 5FU/leucovorin	MMC+5FU	1	13.3
Bakrin <i>et al</i> [1], 2012	CDDP + MMC/DX			3
Baratti <i>et al</i> [17], 2012	CDDP + MMC/DX		5.4	5.9
Bakrin <i>et al</i> [16], 2013	CDDP/MMC/DX		11	11
Canda <i>et al</i> [27], 2013	CDDP + /MMC		25.8	19.8
Jafari <i>et al</i> [15], 2014	NA		3.7	0

EPIC: Early postoperative chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy; MMC: Mitomycin-C; CDDP-Cisplatin, 5FU" % flurouracil; Ox: Oxaloplatin; Dx: Adriamycin.

stimulating factor (GCSF). They reported that the risk of myelosuppression was reduced with a fixed 40 mg dose of MMC in HIPEC and routine use of GCSF for prophylaxis is not indicated. Bakrin *et al*[16] reported an 11% incidence of grade III/IV leukopenia in their cohort of 566 epithelial ovarian cancer patients undergoing CRS-HIPEC.

### Limitations

The data provided in the included studies in this systematic review lacks standardisation in reporting of methodology, postoperative complications *etc*[33-37]. There is variance in the classification of complications, drugs used in HIPEC, *etc*. Although the first ERAS protocols for major abdominal surgery were developed in 2010, ERAS guidelines for CRS-HIPEC were recently published[14,38,39]. Hence the degree of adherence to ERAS in the studies included in our review and its effect on the rate of complications may vary in the future.

## CONCLUSION

CRS-HIPEC for PSM has advantageous survival outcomes, and has become a common surgery in oncological centres all over the world. Being a complex surgery, with proven postoperative systemic inflammatory response, the focus in recent years has shifted to understanding the immediate postoperative pathophysiology and its management, early detection of complications and the institution of appropriate treatment to reduce morbidity and improve survival. The implementation of ERAS guidelines specific to CRS-HIPEC should help to further reduce postoperative complications.

## ARTICLE HIGHLIGHTS

### Research background

CRS-HIPEC is an aggressive option for the comprehensive management of all peritoneal surface malignancies. It can result in some life-threatening complications in the immediate postoperative period and reported higher morbidity and mortality rates. Postoperative morbidity and survival have significantly improved. The commonest postoperative surgical complications and systemic toxicity due to chemotherapy as reported in the last decade are discussed.

### Research motivation

The number of patients undergoing CRS-HIPEC has increased in the last decade as have improvements in surgical techniques, surgical skills and perioperative management strategies. All these have led to improvements in post-surgical outcomes and survival rates. The present article reviews the early postoperative management and common complications after CRS-HIPEC, reported in the last decade.

### Research objectives

To review early postoperative management after CRS-HIPEC. To review common immediate post-surgical complications, namely gastrointestinal, respiratory, cardiovascular, miscellaneous and systemic toxicity secondary to chemotherapy, in these patients.



## Research methods

An electronic literature search was conducted using the databases of 'PubMed' and 'Google Scholar', during the period from 2010 to 2021. Postoperative complications and their synonyms in various combinations were searched. The extracted articles were further reviewed in a step-wise manner for the identification of relevant studies. The full-text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion in the final review article.

## Research results

This article reviewed the early postoperative critical care management of such patients and the immediate post-surgical complications as reported in the gamut of studies included in the final review.

## Research conclusions

CRS-HIPEC is a complex surgery, with a proven postoperative systemic inflammatory response. The focus in recent years has shifted to understanding the immediate postoperative pathophysiology and its management, early detection of complications and the institution of appropriate treatment to reduce morbidity and improve survival. The implementation of ERAS guidelines specific to CRS-HIPEC should help to further reduce postoperative complications.

## Research perspectives

There are two major avenues for research in this area. One is the early prediction of postoperative complications and early intervention to reduce morbidity and mortality. Although numerous inflammatory markers such as mean platelet volume, CRP, procalcitonin *etc* have been studied, no single test is foolproof and they should be utilized in association with the clinical scenario, microbiological and biochemical investigations. The second avenue is the implementation of ERAS guidelines for CRS-HIPEC and its impact on postoperative outcomes and survival.

## FOOTNOTES

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