BJA Education, 21(5): 187–193 (2021)

doi: 10.1016/j.bjae.2020.12.005
Advance Access Publication Date: 16 February 2021

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix
Matrix codes: 1H02, 2A07, 3A03

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Keywords: anaesthesia; cytoreduction surgical procedures; perioperative medicine

Learning objectives

By reading this article, you should be able to:

- Describe the operative aims of cytoreductive surgery and hyperthermic intraoperative chemotherapy.
- Discuss the importance of diligent selection of patients.
- Describe the anaesthetic management of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Key points

- The peritoneum is a common site of metastasis.
- Peritoneal metastases are associated with poor survival and quality of life.
- Cytoreductive surgery and hyperthermic intraoperative chemotherapy significantly increase survival in some cancers.
- Diligent selection of patients is key to reducing morbidity and mortality.
- Pertinent challenges faced by the anaesthetist include management of fluids, coagulopathy and complications specific to the hyperthermic intraperitoneal chemotherapy phase.

Each year, approximately 18 million people worldwide and 360,000 in the UK will develop some form of cancer.[1,2] Depending on the primary tumour type, between 5% and 46% will go on to develop peritoneal metastases.[3] After the liver, the peritoneum is the most common site of metastasis in gastrointestinal tract cancers.[3,4] Patients presenting with peritoneal metastases have a reduced survival rate and poorer quality of life secondary to bowel obstruction, ascites and pain, compared with those patients who have lung or liver metastases alone.[5]

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has long been an established treatment for patients with pseudomyxoma peritonei (PMP), a rare malignancy originating from the appendix.[6] In 2013, because of an increased survival time, NHS England commissioned CRS and HIPEC for patients with low- to medium-volume colorectal peritoneal metastases (CPM).[6,7] There is also accumulating evidence for the use of CRS and HIPEC in other cancer treatments, such as peritoneal mesothelioma and ovarian and gastric cancer.[7]

Cytoreductive surgery and HIPEC are a complex intervention independently associated with morbidity and mortality.[8,9] The experienced centres around the world recognise that there is a long learning curve for the multidisciplinary management of these patients. Evidence has shown that both morbidity and mortality decrease as the experience of the

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Accepted: 21 December 2020

team increases. Currently, there are two UK centres commissioned by NHS England for the management of PMP and CPM, and a further three that are commissioned solely for CPM. However, as the indications for CRS and HIPEC expand, it is likely both the number of procedures and the number of centres offering this type of surgery will increase.

What are CRS and HIPEC?

Whilst the use of extensive cytoreductive debulking procedures was first proposed in the 1930s for treatment of ovarian tumours, it was not until the 1970s that data began to be published supporting this approach. The 1970s also saw the development of intraperitoneal chemotherapy, and by the 1980s, the potential benefits of heating the intraperitoneal chemotherapy were being explored. The 1990s saw the advent of combined CRS and HIPEC therapy, popularised by Paul Sugarbaker at the Washington Cancer Institute in Washington, DC, USA.[10] It has since become well established as treatment for both PMP and CMP across the world. The aim of CRS is to eradicate all macroscopic tumours using a laparotomy approach. The surgical procedure involves removing all or part of any affected organs and the lining of the peritoneal cavity. In PMP, pathognomonic mucin is also removed. Cytoreductive surgery often includes, but is not limited to, the resection of:

(i) Right hemicolon, spleen, gall bladder, greater and lesser omenta and parts of the stomach
(ii) Stripping of the peritoneum, including pelvic and diaphragmatic
(iii) Stripping tumour from liver capsule or liver capsulectomy
(iv) Removal of ovaries and uterus in women.

Even with optimal macroscopic cytoreduction, microscopic tumour deposits will remain. This invisible residual disease is treated with on-table topical HIPEC.

Hyperthermic intraperitoneal chemotherapy

During HIPEC, the abdominal cavity is perfused with chemotherapy solution heated to between 40 and 43°C for 30–120 min. Intraperitoneal administration of chemotherapy during surgery allows the drug to be applied uniformly to all surfaces of the abdomen and pelvis. This topical approach removes the need for high systemic concentrations of chemotherapeutic agents and is not reliant on local blood supply to carry the cytotoxin to affected areas. The actual method of delivery of chemotherapy into the abdominal cavity varies between units from purpose-built pumps to modified bypass or Belmont pumps, and this method may be performed by a nurse, a perfusionist or an anaesthetist.

The penetration into peritoneal metastases of intraperitoneal chemotherapy is limited to a depth of between 2 and 5 mm, highlighting the importance of complete macroscopic cytoreduction before HIPEC administration.[11] Heat is known to potentiate the effects of chemotherapeutic agents and increase their penetration into tumour tissue, and it also appears to reduce mechanisms of tumour resistance to chemotherapy. The synergy between heat and drug cytotoxicity appears to require a minimum temperature of 39°C and starts to diminish above 43°C.[11] Temperatures above 44°C can result in apoptosis of normal cells. The majority of chemotherapeutic drugs used for HIPEC are 'cell cycle non-specific', acting in the cell resting phase, as opposed to more traditional chemotherapeutic agents that aim to act during a certain phase of the cell cycle, and hence delivered at intervals in several doses.

Another major advantage of HIPEC is regional dose intensity.[12] The peritoneal cavity is exposed to higher concentrations of the chemotherapy agent than the rest of the body. The concentration differential arises because peritoneal clearance of the chemoactive agent is relatively slow compared with clearance from the rest of the body. The rate of systemic absorption depends on lipophilicity, molecular weight and degree of ionisation. Low-molecular-weight and highly lipophilic drugs are better absorbed, and so the drugs chosen for HIPEC are the reverse.

There is ongoing debate about the advantages of the opencompared with the closed technique for HIPEC. The open abdomen (coliseum) technique, where the abdominal wall is elevated to create a funnel and the chemoperfusate flows between the inflow and outflow lines, which are attached to the pump and heating unit, ensures optimal distribution of both cytotoxic solution and heat because of the manual stirring performed by the surgeon. However, there is an increased risk of spillage of cytotoxic agents. Contrarily, the closed technique, in which the inflow and outflow of HIPEC are delivered through separate incisions, after the laparotomy incision has been closed, has been proposed to retain temperature more effectively and also reduce exposure risk to operating theatre staff by reducing local atmospheric contamination. However, homogeneous distribution of the fluid may not be achieved.

A variety of chemotherapeutic agents is currently in use and selection depends on the primary tumour type. Agents used commonly include mitomycin C, cisplatin, oxaliplatin and 5-fluorouracil. Dose calculations of chemotherapeutic agents are usually based on body surface area. However, there is currently no international consensus on dosage or duration of HIPEC administration. Although the low systemic uptake of these drugs appears to reduce the toxic effects, cisplatin is associated with an increased incidence of postoperative renal impairment (5%) and oxaliplatin is associated with a higher risk of postoperative bleeding.[13] Further studies are still required to ascertain exactly which chemotherapeutic agent should be used for a given cancer and the optimum drug dosage.

Controversy remains as to whether HIPEC is of benefit over optimal cytoreduction surgery alone. A recent multicentre trial comparing CRS with HIPEC with CRS alone for treatment of CPM found an increase in complications associated with combination therapy and no survival benefit.[14] This led some centres to cease the routine use of HIPEC for CPM.

Those continuing to use HIPEC in this patient population have questioned the dosage of chemotherapy used in the study and the inclusion of patients from smaller centres. However, in patients with PMP, 10 yrs survival was >60% in patients who had received complete/near-complete CRS and HIPEC compared with <10% survival in the group without HIPEC (Fig. 1).[15]

There is currently some interest in the use of bidirectional chemotherapy, which combines intraoperative i.v. chemotherapy with conventional HIPEC. Some centres also advocate the use of postoperative intraperitoneal chemotherapy *via* a port placed during surgery.

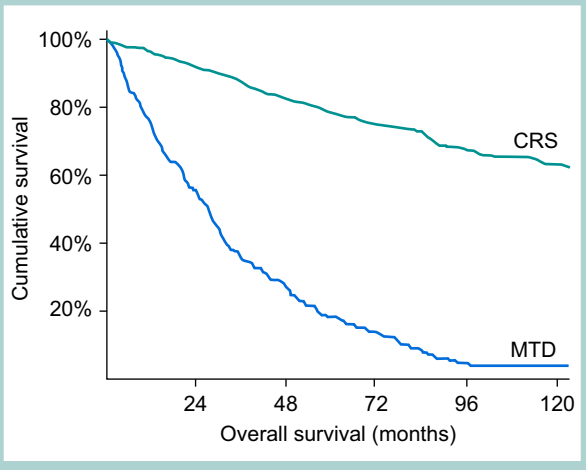

Fig 1 Ten-year survival in patients with PMP comparing patients with complete or near-complete CRS with HIPEC (CRS), and patients with incomplete resection and no or minimal chemotherapy (MTD).

Morbidity and mortality

Cytoreductive surgery and HIPEC therapy is associated with significant morbidity and mortality, although the reported rates vary widely. Mortality rates range between 0.5% and 5%, with major morbidity (Clavien–Dindo grade $\geq$3) rates reported at 16.6%.[16] Postoperative complications include bowel perforation, anastomotic leak, fistula formation, sepsis, acute kidney injury (AKI) and cardiorespiratory and thromboembolic events. To derive the maximal benefit of this treatment and avoid undesirable complications, careful patient selection and diligent perioperative care must be undertaken by an experienced multidisciplinary team.

Preoperative selection of patients

Selection for CRS and HIPEC is based on patients' surgical suitability, their current general health status and comorbidities. Patients with a recent positive smoking history, a poor subjective or objective physical performance status, previous extensive surgery or those who require extensive cytoreduction are all at risk of significant postoperative morbidity.[17] Anaesthetists should form an integral part of the team in selecting patients suitable for CRS and HIPEC. Although selection of patients varies between centres, the Peritoneal Surface Oncology Group International (PSOGI) has published recommendations of the clinical features linked to a favourable outcome and those where CRS and HIPEC should not be recommended (Table 1).[18] In addition, there is extensive multidisciplinary workup in these patients to maximise their fitness before surgery. Many of these patients are both cachectic and anaemic on presentation, and may require iron transfusions, physiotherapy or nutritional support before surgery.[19] However, the need for any intervention is balanced carefully against the urgency of surgery, as there is a risk of tumour progression and the tumour becoming inoperable if treatment is delayed. Emerging evidence may clarify the value of preoperative iron transfusions.

Peritoneal cancer index score

The peritoneal cancer index (PCI) score (Fig. 2) was developed by Sugarbaker in 1996 and is used to assess the extent of peritoneal cancer throughout the peritoneal cavity.[20] It divides the peritoneal cavity into 13 well-defined regions, with each region given a score from 0 to 3 depending on the extent of tumour present, with a maximum score of 39. The score is calculated during surgery, but can be estimated on imaging or at a staging laparoscopy. Because of the more aggressive nature of some tumour types, especially colorectal adenocarcinoma, surgery is only attempted if a 'complete cytoreduction' (removal of all visible/macroscopic tumour) is considered possible. Many institutions have a ceiling PCI score under which they would consider surgery an option. However, for patients with PMP and a high PCI, the prognosis is determined by the ability to radically remove the tumour rather than the PCI score.

Considerations for anaesthesia

Anaesthetising patients undergoing CRS and HIPEC can be extremely challenging. Fluid management, coagulopathy and complications specific to the HIPEC phase must all be taken into account as well, considering the optimal strategy for managing postoperative analgesia. The challenges are greater for patients with more extensive disease, especially if there is significant upper abdominal involvement.

Set-up

The set-up for patients undergoing CRS and HIPEC is similar to that for patients undergoing a major laparotomy. Baseline standards across most centres include tracheal intubation and mechanical ventilation; at least one wide-bore cannula for giving fluids, including blood products; an arterial cannula for intraoperative arterial pressure measurement and frequent blood sampling; and central venous access.[12]

Although rapid blood loss is rare during these procedures, significant intraoperative fluid shifts are commonplace and cardiac output monitoring is essential to guide perioperative fluid management.[19]

Thoracic epidurals are commonly sited before surgery for both intra- and postoperative pain relief as part of a multimodal approach to analgesia.[19] In addition, a temperature probe, a urinary catheter and a nasogastric tube are all placed as standard. Procedures can take anything from 5 to 15 h, and so careful positioning with protection of pressure areas is essential. There is active research into the type of anaesthesia used in cancer surgery to enhance tumour control, but currently, little evidence exists specific to CRS and HIPEC to definitively guide practice.

Fluids

Optimising organ perfusion and reducing morbidity through giving adequate volumes of fluids are significant challenges during CRS and HIPEC. Ascitic drainage, prolonged surgery and exposed raw visceral surfaces, combined with the cardiovascular effects of HIPEC, often lead to fluid requirements exceeding 12 ml kg^{-1} h^{-1}.[21] Articles on CRS and HIPEC often demonstrate large differences between minimum and

Table 1 PSOGI recommendations for selecting patients for CRS and HIPEC

Clinical features suggesting a favourable outcome from CRS and HIPEC:
• General medical condition compatible with survival and recovery from the procedure • Clinical information regarding the peritoneal metastases compatible with a complete or near-complete cytoreduction • Relative sparing of the small bowel and colon • Absence of disease outside the abdomen/pelvis • If hepatic metastases are present, they are limited and are compatible with wedge resection • Absence of disease within the porta hepatis • With a high-grade malignancy, a low or moderate peritoneal cancer index • Patients with symptoms
Clinical features suggesting CRS and HIPEC should not be recommended include:
• Poor physical performance status • Rapid progression of a high-grade disease process • Low likelihood of a response to perioperative chemotherapy • Prior abdominal or pelvic radiation therapy • Asymptomatic from peritoneal metastases

maximum rates of infusion (median: 9.8 [range: 5.3–24.3] ml kg^{-1} h^{-1}), illustrating the wide range of requirements for different patients in a given cohort.[22]

In colorectal surgery, prescriptive strategies for both liberal and restrictive fluid regimens have previously demonstrated an improved postoperative outcome. In CRS and HIPEC, there is huge variation in fluid shifts depending on tumour type, extent of disease and duration of surgery. Patients often develop a hyperdynamic circulatory state before HIPEC starts because of profound systemic inflammatory response syndrome secondary to extensive surgical injury.

As a guide, most centres suggest maintaining the MAP within 20% of the patient's preoperative baseline and maintaining the stroke volume variation below 10% with a combination of fluids and vasopressors. This should confer some degree of haemodynamic stability and optimise end-organ oxygen delivery. Although the data are scant in patients undergoing CRS and HIPEC, this type of 'goal-directed therapy' has been shown to reduce morbidity and hospital stay in a number of other surgical subspecialties. Given that morbidity after CRS is high, strategies to avoid perioperative hypovolaemia, or indeed fluid overload, are essential to minimise complications.[23] This suggests that the 'ideal' regimen is probably one tailored to each individual patient for that specific operation.

Perioperative fluid regimens usually comprise a mixture of crystalloids, albumin and blood products. Blood loss during CRS can be substantial, but is also often insidious. It is important to remain vigilant to help prevent intraoperative anaemia, acidosis and cardiovascular instability. Historically, in surgery for PMP, approximately 50% of patients required a blood transfusion.[24] Conversely, blood and fluid loss tend to be lower in patients with CPM, possibly as a result of them having less extensive disease. Preoptimisation, improved surgical techniques and enhanced intraoperative coagulation management have undoubtedly reduced the requirements for intraoperative blood transfusion in CRS.

Blood transfusion threshold Hb concentration is usually 70–80 g L^{-1}, in keeping with standard perioperative protocols. However, this may need to be varied for specific patients or situations.

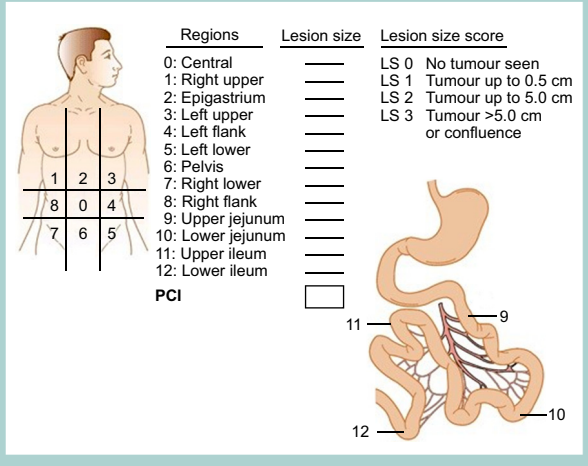

Fig 2 Peritoneal cancer index (PCI) score.

Management of coagulation

Patients undergoing extensive CRS and HIPEC will often develop a coagulopathy. Risk factors include tumour type, common with PMP and mesothelioma cases; specific procedures, such as liver capsulectomy or deep pelvic surgery; and the overall duration of surgery, possibly reflecting the extent of disease or the difficulty of the surgery.[12]

The exact cause of the coagulopathy in CRS and HIPEC is still poorly understood. However, it is probably a combination of consumption and dilution of coagulation factors.[12] Most centres are guided by standard laboratory testing, such as activated partial thromboplastin time, prothrombin time and international normalised ratio; some also use bedside thromboelastography (or rotational thromboelastometry). Centres using bedside viscoelastography have noted that an acquired fibrinogen deficiency is common, supporting the accumulating evidence for the critical role of

fibrinogen in haemostasis during haemorrhage. Regular doses of tranexamic acid are commonly given to prevent fibrinolysis.[12]

Intraoperative coagulopathy needs to be identified early to avoid significant intraoperative and ongoing postoperative blood loss. For cases involving very extensive disease, coagulation management must be proactive, often with transfusion of coagulation factors before any formal recognition of the development of coagulopathy.[12] Cryoprecipitate and fresh frozen plasma are the mainstays of treatment for the coagulopathy associated with this type of surgery. Giving platelets in isolation is rare and usually associated with a preoperative deficiency. However, thresholds for treatment and the specific blood products used to manage the intraoperative coagulopathy vary amongst the different centres. The median interval for coagulation testing is once every 2–4 h.[12]

Pain management

A combination of thoracic epidural anaesthesia and PCA is commonly used to control postoperative pain. Some centres use intrathecal opiates in preference to epidural analgesia. PCAs are typically opioid based and supplemented with regular simple analgesics, such as paracetamol, and other adjuncts, such as ketamine or lignocaine infusions.

Patients undergoing CRS and HIPEC commonly require analgesia to cover pain distributed from high thoracic dermatomes down to the sacral roots. Most have a large midline excision and have undergone surgical dissection in all quadrants of the abdomen. Extensive pelvic dissection or diaphragm stripping can be particularly painful. Despite the use of multimodal analgesia, achieving effective postoperative pain relief remains a challenge.

HIPEC phase

The HIPEC phase is associated with a number of potential complications.

Hyperthermia

During the HIPEC phase, patients become hyperthermic, as heat is absorbed from the abdomen from the warmed chemotherapy fluid (range: 36–41°C). Moderate hyperthermia is tolerated, but most centres aim to keep the patients' core temperatures below 39°C. Active cooling techniques include cooled i.v. fluids, ice packs and cooling mattresses. Very rarely, the HIPEC temperature needs to be reduced to control the core temperature.[12]

Haemodynamic instability

A hyperdynamic circulation often develops, which may require treatment with both fluids and vasopressors.

Electrolyte disturbances

Some chemotherapeutic agents are unstable in saline solutions, and historically, when used in HIPEC, required dextrose 5% as a carrier. The large volumes of dextrose solution given rapidly were associated with severe hyperglycaemia and an acute dilutional hyponatraemia. Patients subsequently experienced a significant osmotic diuresis compounded by a lactic acidosis common during HIPEC.[25] Oxaliplatin requires hypertonic dextrose solution, but where possible, most centres now use a balanced crystalloid solution or peritoneal dialysis fluids as carriers for their chemotherapeutic agents to reduce the possibility of hyponatraemia and subsequent risk of cerebral oedema.

Acute kidney injury

Cytoreductive surgery and HIPEC were historically associated with a moderate risk of an AKI, particularly when using platinum-based chemotherapy agents. However, by ensuring normovolaemia, either by using cardiac output monitoring or setting urine output targets has helped to preserve end-organ perfusion and limit the incidence of AKI. Sodium thiosulphate can also be given to confer some renal protection.[26]

Haemorrhage

Haemorrhage occurring at this time point can be detected by careful observation of the colour of the solution. Any possibility of active bleeding during this phase requires prompt treatment.

Environmental considerations

The chemotherapy solution poses a risk to operating theatre teams, and careful use of personal protective equipment should be undertaken (filtering face piece 3 [FFP3] mask, goggles, face shield, gloves and shoe covers). Adequate neuromuscular block is vital to avoid any accidental coughing or movement of the patient, leading to spillage of the chemotherapy solution. The cytotoxic agent may be present in body fluids for anything between 1 and 7 days, depending on what agent is used, and is important information to all staff caring for the patient. Some centres have specific protocols in place.

Postoperative management

All patients are transferred to the ICU after surgery to manage ongoing requirements for organ support and analgesia, even though patients are increasingly being allowed to wake and tracheal extubation performed at the end of surgery. The average length of stay in ICU is usually 2–3 days.[12,24] However, the length of recovery varies greatly from a couple of weeks in hospital to several months; operations can range from a relatively straightforward extended right hemicolectomy to a complex laparotomy, with multiple organ resections and multiple abdominal drains. If the diaphragm has been 'stripped' of disease, bilateral chest drains are often used to avoid the development of large pleural effusions. Multiple tubes and drains increase the postoperative analgesic requirements for patients undergoing CRS and HIPEC.

Staffing

Current estimates suggest the mean duration of surgery to be 8.8 h (range: 4–12 h), not including the time for anaesthesia, which may be considerable, especially when tracheal extubation in the operating theatre is attempted.[12] Lengthy procedures increase the likelihood of staff fatigue, human error and breaches in patient safety. Keeping the same teams working together regularly, access to guidelines and training, careful scheduling and meticulous planning along with appropriate fatigue management can all help to mitigate the risk of human error associated with long and complex cases. To achieve the best outcomes after CRS and HIPEC, it is essential to have a well-

established multidisciplinary team comprising surgeons, anaesthetists, intensivists, specialist nurses, oncologists, psychologists, dieticians and physiotherapists all working in collaboration.

Summary

Cytoreductive surgery is major multi-visceral surgery that leads to numerous challenges for the anaesthesia team. Patients with extensive PMP often provide the greatest challenge, and they are generally only undertaken in specialist centres. Increasing numbers of patients are likely to be considered for this type of surgery over the next few years.

Declaration of interests

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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