Preoperative Management of Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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Introduction

The combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has become the standard of care for treating selected patients with peritoneal metastases (PM). [1] CRS and HIPEC comprises of complex gastrointestinal surgery and is associated with major morbidity. [2] The prolonged duration and extensive nature of the CRS and the use of hyperthermia during HIPEC especially with the closed abdomen technique produce characteristic pathophysiological changes like fluid, blood and protein losses, increased intra-abdominal pressure, systemic hyperthermia and increased metabolic rate in the perioperative period which require appropriate management by the anesthesiology and the critical care teams. [3–5] Patient selection plays an important role in reducing the morbidity of the procedure and avoiding surgery in those who are unlikely to derive a benefit in survival and/or quality of life. Quantitative prognostic indicators like disease extent as determined by imaging and predicted PCI, histopathology and tumor grade and primary site have been defined for selecting patients who will gain maximal benefit out of this procedure. [6] While these indicators are important from the disease perspective, the patient should be in good physical and mental health to undergo the procedure. Along with the complexity of

the surgical procedure, the factors known to influence the outcomes of major gastrointestinal surgery are the age and co morbidities as well as the perioperative management. [7] This manuscript reviews the criteria for patient selection from the point of view of physical and mental preparedness for the procedure as well as the pre-operative optimization required for the procedure.

Preoperative Management

History and Clinical Examination

A detailed medical history and a thorough clinical assessment of the patient's physical and psychological condition are important. Some of the common problems with patients scheduled for CRS and HIPEC are a compromised pulmonary function due to ascites, debilitation and malnutrition and these need to be identified and optimized prior to the procedure. These patients may also have undergone one or more surgical procedures the details of which should be recorded. The prior surgical score (PSS, Table 1) is used to categorize patients according to the extent of the surgery they have undergone and should be recorded. [8] Similarly prior chemotherapy treatments administered and the associated toxicity should be known since they influence the doses and choice of drugs used intraperitoneally. Though patients who progress on chemotherapy may not be the ideal candidates for the procedure, certain tumors are unresponsive to chemotherapy and definitive surgery should be performed as soon as possible for these patients. In a study by Chua et al. of patients with appendiceal tumors with PM treated with CRS and HIPEC, PSS influenced the disease free survival ($P < .001$) whereas prior chemotherapy influenced the disease free survival ($P < .001$) and

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overall survival both. (hazard ratio [HR], 1.91; $P < .001$) [9] PSS has not been found useful for colorectal PM.

Routine Diagnostic Tests

The routine preoperative diagnostic tests include a complete blood count, renal and liver function tests, serum electrolytes, international normalized ratio, activated partial prothrombin time, chest radiography, electrocardiography and echocardiography. The cut off values for CRS and HIPEC are as follows

- Hematology: ANC $\geq 1500/\mu\text{L}$; Platelets $>100,000/\mu\text{L}$.
- Adequate Renal function Creatinine $<1.5 \times$ the upper limit of normal (ULN) or calculated creatinine clearance of $\geq 50 \text{ ml/min}$.
- Adequate Hepatic function: Bilirubin less than 1.5 mg/dL ; Hepatic enzymes <3 times the upper limit of normal

A significant impairment in cardiac, pulmonary, hepatic, or renal function should be a contraindication to surgery. ASA score of ≥ 3 is associated with a significant increase in the morbidity and mortality. [10].

Cardiac Status

Major gastrointestinal surgery is associated with a medium cardiac risk. [11, 12] An electrocardiogram and echocardiogram should be performed in all patients irrespective of their age. Further investigations like a stress test may be needed in patients with a reduced cardiac reserve, those with a history of heart failure or chemotherapy induced cardiotoxicity. Close cooperation with the anesthesiologist and cardiologist is needed in selecting patients and those with decompensated cardiac conditions are poor candidates for the procedure. Cardiac insufficiency is associated with a greater risk as compared to ischemic heart disease. [13].

Respiratory Function

Gross ascites with or without pleural effusion and hypoalbuminemia is common in patients undergoing CRS and HIPEC and often results in basal atelectasis developing overtime thus

putting these patients at risk of hypoxia postoperatively. [14] In most patients a precise medical history and evaluation with a chest radiogram/computed tomogram usually suffices. Whenever indicated, preoperative arterial blood gas (ABG) analysis and pulmonary function tests would help to evaluate and optimize the patients, especially those with reactive airways. The extensive nature and prolonged duration of the procedure increase the risk of pulmonary complications in these patients. [15] Patients undergoing subphrenic peritonectomies have a higher incidence of pleural effusions and chest tube placements though the morbidity is not significantly different from those that do not have these procedures. [16] Specifically, patients who require a full thickness diaphragm resection have a greater incidence of postoperative respiratory failure and mortality as compared to those who do not. [17] Intensive spirometry done in the preoperative period can reduce the incidence of pulmonary complications. [18] Patients need to be educated and counselled about the same.

Nutritional Status

While there are no data available on the prevalence of malnutrition in patients with PM, malnutrition is observed in up to 67 % of patients with ovarian cancer [19] and up to 34–54 % of patients with advanced colorectal cancer, the two most common cancers associated with the development of PM, but it is seen in only 3 % of the patients with pseudomyxoma peritonei. [20, 21] There is enough evidence in the literature documenting the association of malnutrition with longer hospital stay, increased complications, increased cost and mortality in surgical patients. [20] Routine nutritional assessment is recommended for all patients undergoing CRS and HIPEC and a more indepth analysis for malnourished patients. There is no single test that can accurately assess the risk. Some of the clinical indicators are recent weight loss, reduced dietary intake and a low Body Mass Index (BMI). [21] Malnutrition is considered in patients with weight loss of $>5 \%$ in 3 months, BMI of $<18.5 \text{ kg/M}^2$, and a dietary intake $<50 \%$ of the normal requirement. [22] Further assessment is done using biochemical indicators like serum levels of total protein, albumin, prealbumin, transferrin, cholinesterase and lymphocytes. An albumin level of $<30 \text{ g/L}$ is considered to be an indicator of potential morbidity. [23] Subjective Global Assessment (SGA) is a clinical technique that combines data from subjective and objective aspects of medical history (weight change, dietary intake change, gastrointestinal symptoms, and changes in functional capacity) and physical examination (loss of subcutaneous fat, muscle wasting, ankle or sacral edema and ascites) and could be used for assessing the nutritional status. After evaluation, patients are categorized into three distinct classes of nutritional status; well nourished (SGA-A), moderately malnourished (SGA-B) and severely malnourished (SGA-C) [24]. The SGA has been

Table 1 Prior Surgical Score (PSS)

Prior surgical score	Extent of surgery
0	No prior surgery or only a biopsy
1	Prior surgery with only 1 region dissected
2	Prior surgery with 2–5 regions dissected
3	Prior surgery with >5 regions dissected

validated in a number of diverse patient populations, including cancer patients [25]. The evidence supporting the use of any kind of artificial nutrition in the preoperative period in patients undergoing CRS and HIPEC is limited and guidelines that are used for other surgical patients should be employed. [26, 27] For malnourished patients, prior to surgery, enteral nutrition is preferred when oral intake is possible and parenteral nutrition is recommended only when enteral nutrition is not feasible. [22, 28].

Performance Status

Many scores are available to categorize patients according to their level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.) Commonly used scores are the Eastern Cooperative Oncology group (ECOG) performance score, also known as the WHO or Zubrod score and the Karnofsky performance score. [29, 30] Patients with an ECOG score of 0/1 are eligible for CRS and HIPEC. Similarly, a Karnofsky score of at least 80 is needed for patients undergoing the procedure. [31, 32].

Obesity

Patients with a BMI of 25–30 kg/M² are categorized as overweight and those with a BMI of >40 kg/M² are considered to be obese. Obesity is known to increase the rate of perioperative complications following major gastrointestinal surgery. [33, 34] Few studies have evaluated the morbidity and mortality in obese patients undergoing CRS and HIPEC for peritoneal metastases from various primary tumors and not found a difference in the mortality or the long term oncological outcomes. [35–37] Obesity may limit the physical evaluation but obese patients do not present later than those with a normal BMI nor do they have more advanced disease. [37] Though there is an increased risk of renal and pulmonary complications, the application of CRS and HIPEC can lead to meaningful prolongation of life. [36].

Age

Candidates for CRS and HIPEC are often older than 65 years of age. While some regard those aged 65 and above as elderly, others use 70 years as a cut-off. It has been previously shown that elderly patients are at increased risk for postoperative morbidity. [38] The life expectancy at 70 years does not negate the survival benefit that could be offered by CRS and HIPEC in appropriately selected patients and hence age alone should not be a contraindication for the procedure. In a study of 81 patients over the age of 70, Votanopoulos et al. found a significant increase in the morbidity and mortality as compared to younger patients (30-day mortality of 13.6 %, 90-day mortality of 27.4 % and the combined grade III and IV

morbidity of 38 %). [39] Splitting the data at the midpoint of surgical experience, there was a drop in 1- and 3-month mortality over time to 9.5 and 19.3 %, respectively, while the median survival increased from 11.2 ($N = 39$) to 46.9 months ($N = 42$). (Fig. 1) The authors concluded that HIPEC in the elderly is associated with a steep learning curve and institutional experience and stringent patient selection are important for attaining prolonged survival. Despite the considerable morbidity and mortality, age alone should not be a contraindication for the procedure. [39] In another study of 124 patients aged 65 and above, Huang et al. found no statistically significant difference in terms of the mean hospital stay, intensive care unit stay and complications rates when compared to 487 patients under 65 years of age. The postoperative mortality was 2 % and 3 % in the 2 groups respectively and there was no difference in the overall survival as well. [40] Three other retrospective studies with smaller number of patients have concluded the same. [41–43] The above evidence strongly suggests that age alone can not be a contraindication for the procedure.

Patient Motivation and Informed Consent

CRS and HIPEC has a protracted recovery period with a significant impairment in the quality of life though temporary. Symptoms like nausea and vomiting, pain, anorexia and weight loss tend to return to baseline by 3 months. [44–49] However, physical and functional well-being may take up to a year to return to normal with persistence of gastrointestinal symptoms, fatigue, sleep disturbances and depression which is reported in as high as 50 % of the patients. [37, 50] There are asymptomatic patients who have to be prepared for a deterioration in their quality of life for a few months after the

Fig. 1 Survival curves at the midpoint of the institutional experience ($p = 0.009$) (Reproduced from Ref 39 with permission)

Fig. 2 Selected SF-36 scales at 4 time points (Reproduced from Ref 22 with permission)

procedure as well as those who are symptomatic and can expect an improvement in their symptoms and quality of life. It is important that the patient is well informed and motivated to undergo the procedure and this goes beyond the signing of an ‘informed consent’. [51] It could require one or more counseling sessions with the surgeon and the rest of the team. Adequate patient motivation does not come without adequate, good-quality information that includes not only details about the procedure but also the realistic outcomes to be expected. [51] Thus, there could be a patient who is fit for the procedure in all aspects, but fears being permanently disabled by it or another who is a borderline candidate but highly motivated to undergo the treatment. [51] Performing these complex procedures in patients without an adequate motivation should be by all means avoided. [51] Interaction with former patients and survivors and patient support groups could of help in building up the confidence of the patient. Figure 2 shows a diagrammatic representation of the return of some important functions to the baseline levels over a period of 1 year. These parameters are taken from short-form 36 (SF-36). Such diagrams could be used to counsel patients prior to the procedure. [22].

Prognostic Indicators

Quantitative prognostic indicators have been defined to measure the outcomes of CRS and HIPEC and are used in selecting patients for the procedure. [52] These indicators are histopathology, imaging findings, peritoneal cancer index (PCI) and the completeness of cytoreduction score (CCR). [52, 53] These are dependent on the extent and biology of the disease and are discussed in detail elsewhere in this issue. In addition, the peritoneal surface disease severity score (PSDSS) proposed by Esquivel takes into account 3 important prognostic indicators; clinical symptoms, the peritoneal cancer index

(PCI) and tumor histopathology each is given a score depending on the severity of the factor. A summation of the scores of each category gives a final score according to which patients are staged; PSDSS Stage I < 4; PSDSS Stage II = 4–7; PSDSS Stage III = 8–10; PSDSS Stage IV > 10. [54] Several studies have retrospectively evaluated the usefulness of this score in selecting patients with colorectal and appendiceal primaries for CRS and HIPEC and found it to be an accurate predictor of resectability and survival. [55–57] Further validation could be done in randomized controlled trials.

Final Decision Making: Multidisciplinary Meeting

All cases being considered for CRS and HIPEC should be discussed in a multidisciplinary meeting comprising of surgical and medical oncologists, radiologists, pathologists, anesthesiologists, nutritionists and other specialists as required. A brief summary of the various factors to be considered while selecting patients is listed in Table 2.

Table 2 Patient selection for CRS and HIPEC

Patient related factors

Age
Comorbidities/ASA score
Nutritional status
Performance status
Mental preparedness for the procedure

Disease related factors

Primary site and grade, response to chemotherapy
Extent of the disease/Peritoneal Cancer Index
Imaging/sites of disease spread
Completeness of Cytoreduction score (CC-score)

Preparation of the Patients before Surgery

Mechanical Bowel Preparation

Several randomized controlled trials have shown that patients who undergo mechanical bowel preparation before colorectal surgery have similar outcomes as those who do not. [58, 59] However, this is not true for rectal cancer surgery, there is a higher incidence of infectious complications and morbidity in patients not undergoing mechanical bowel preparation before elective rectal cancer surgery. [60] Hence, mechanical bowel preparation is mandatory in patients undergoing CRS as a large proportion undergo rectal resection.

Hydration with Intravenous Fluids

Maintaining adequate hydration before the procedure helps in reducing or fluid electrolyte imbalance during the procedure itself and is useful when high doses of cisplatin or oxaliplatin are to be used for HIPEC. In patients with an inadequate oral intake, intravenous supplementation Patients could have reduced intake due to the ascites, bowel obstruction, or mechanical bowel preparation itself that could cause diarrhea or vomiting. [61].

Antibiotic Prophylaxis

Routine antibiotic prophylaxis is used 1 h prior to the procedure and repeated every 6 h. A third generation cephalosporin or extended spectrum penicillin that provides gram negative coverage is generally used. For anaerobic coverage, metronidazole is preferred. [62, 63].

Conclusions

CRS and HIPEC requires stringent patient selection to attain optimal results in terms of survival and quality of life. Quantitative prognostic indicators like histopathology, PCI, imaging findings and completeness of cytoreduction score are based on the disease extent and tumor biology, patient related factors like age, comorbidities, performance status, nutritional status and motivation and willingness for the procedure should be taken into consideration while selecting patients. All patients should be evaluated by a multidisciplinary team.

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