

# Preoperative Preparation and Patient Selection for Cytoreductive Surgery and HIPEC

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Received: 8 October 2015 / Accepted: 16 February 2016 / Published online: 27 February 2016  
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**Abstract** Peritoneal dissemination is a significant variable affecting long term survival of abdominal cancer patients. A generally accepted clinical point of view is that peritoneal dissemination is tantamount to distant organ metastases. This implies it to be a terminal condition. Current practice dictates that if peritoneal dissemination is observed intraoperatively, the curative therapeutic options are deferred and comprehensive systemic chemotherapy remains the only option with a dismal prognosis. The past few years have generated lot of interest in management of peritoneal carcinomatosis. Prof Paul Sugarbaker has researched, validated and fine-tuned the concept of cytoreductive surgery with peritonectomy procedure (Sugarbaker technique) and perioperative chemotherapy as HIPEC & EPIC. Recognition of a HIPEC centre is based on an infrastructure equipped with basic knowledge of the tumor biology, oncosurgical techniques, technical knowhow for HIPEC administration, intensive care unit etc. There are some aspects which need to be accorded special consideration. Comprehensive therapy of Cytoreduction surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is initiated with exploration and cytoreductive surgery and includes visceral resections and peritonectomy procedure when achieved optimally results in complete, visible resection of all cancer within the abdomen and pelvis. Subsequent to CRS, HIPEC forms an integral part of the surgical procedure. This approach involves conceptual

changes in both the route and timing of chemotherapy administration. Patient selection is of utmost importance. The greatest impediment to lasting benefits from intraperitoneal chemotherapy remains an improper patient selection. Currently, there are four important clinical assessments of peritoneal metastasis that need to be used to select patients ie; histopathological type of tumour, radiological distribution of disease, peritoneal cancer index and completeness of cytoreduction. Patients undergoing HIPEC surgery face the usual physiological insults of a major surgery in addition to the thermal stress secondary to intraperitoneal administration of heated chemotherapy agent. A team approach of everyone involved in care of these patients is known to improve patient outcomes. It has also been observed that with the necessary preoperative & perioperative steps, the morbidity and mortality for this treatment can be brought down as comparable to any other major abdominal surgeries.

**Keywords** Peritoneal carcinomatosis · Preoperative management · Cytoreductive surgery & HIPEC · Patient selection

Peritoneal dissemination is a significant variable affecting long term survival of abdominal cancer patients. A generally accepted clinical point of view is that peritoneal dissemination is tantamount to distant organ metastases. This implies it to be a terminal condition. Current practice dictates that if peritoneal dissemination is observed intraoperatively, the curative therapeutic options are deferred and comprehensive systemic chemotherapy remains the only option with a dismal prognosis. Peritoneal carcinomatosis in colorectal cancer confers a dismal prognosis and traditional treatment involving systemic chemotherapy, with or without palliative surgery (typically

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reserved for acute complications such as intestinal obstruction) is associated with a median survival of 5–7 months.

According to the multicenter EVOCAPE I study, the median survival in patients with peritoneal metastases was 5.2 months for those with advanced colorectal cancer ( $n = 118$ ) and 3.1 months for those with advanced gastric cancer ( $n = 125$ ). Despite significant advances in the development of more efficacious systemic chemotherapy for many GI cancers, most notably colorectal cancer; systemic treatment is associated with potentially severe toxicity in many patients and median survival is still less than two years (Table 1).

The past few years have generated lot of interest in management of peritoneal carcinomatosis. The boost in this field of peritoneal surface malignancy was given by the pioneering work done by Prof Paul Sugarbaker. He has researched, validated and fine-tuned the concept of cytoreductive surgery with peritonectomy procedure (Sugarbaker technique) and perioperative chemotherapy as HIPEC & EPIC.

As a foreword to Prof Sugarbaker's textbook on cytoreductive surgery & perioperative chemotherapy for peritoneal surface malignancy, Prof Xinyu Qin from china, has subtly enumerated the major obstacles faced by clinicians in therapy of peritoneal carcinomatosis; i.e. acceptance by medical community, criteria for patient selection and development of specialized centers [1].

With newer insights and generation of prospective data, more centers have evolved an interest in HIPEC. It remains difficult to replicate high volume centers uniformly and hence comes the necessity to evolve from them with reference to protocols and optimizing results. Recognition of a HIPEC centre is based on an infrastructure equipped with basic knowledge of the tumor biology, oncosurgical techniques, technical knowhow for HIPEC administration, intensive care unit etc. There are some aspects which need to be accorded special consideration.

This comprehensive therapy of Cytoreduction surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is initiated with exploration and cytoreductive surgery, which includes visceral resections and peritonectomy procedure, when achieved optimally results in complete, visible resection of all cancer within the abdomen and pelvis. As validated by Prof. Sugarbaker, this includes total parietal peritonectomy, left upper quadrant peritonectomy, greater

omentectomy plus splenectomy, right upper quadrant peritonectomy, pelvic peritonectomy plus rectosigmoid colon resection and cholecystectomy plus lesser omentectomy with peritonectomy of the omental bursa. In addition, right colon resection or total abdominal colectomy may be required concurrently [1].

Subsequent to CRS, HIPEC forms an integral part of the surgical procedure. This approach involves conceptual changes in both the route and timing of chemotherapy administration.

## Rationale for Perioperative Chemotherapy

Abdominal malignancies spread through haematogenous, lymphatic and peritoneal space route. In a significant subgroup this spread will be isolated to peritoneal surfaces or the primary resection site only, which suggests that effective therapy for these relapses, may impact patient survival. Retrospective data suggests that perioperative chemotherapy with some technical modifications could be an effective approach for dealing with peritoneal carcinomatosis. Initially an intraperitoneal route for chemotherapy is essential as it allows for uniform distribution of a high concentration of anticancer therapy at the malignancy site. This is followed by chemotherapy administration so that all peritoneal metastasis, except for microscopic residual disease, would be removed prior to the chemotherapy treatments so that limited penetration of chemotherapy into tissues of 1–2 mm will be adequate to eradicate tumor cells fully. Intraoperative intraperitoneal chemo administration will ensure absence of adhesions or scar tissue which would otherwise prevent contact of chemotherapy to affected surfaces. HIPEC combines the pharmacokinetic advantage inherent to the intracavitary delivery of cytotoxic drugs leading to regional dose intensification, with direct cytotoxic effect of hyperthermia as well [2].

## Rationale for the Use of a Heated Intraoperative Intraperitoneal Chemotherapy Solution

- Heat increases tissue penetration for the drug.
- Heat increases the cytotoxicity of selected chemotherapy agents.

**Table 1** Survival in patients with peritoneal dissemination secondary to various cancers based on variability in tumor biology

Histology in order of decreasing biological aggressiveness	Estimated median survival (months)
Pancreatic adenocarcinoma	~6
Gastric adenocarcinoma	~6–12
High-grade appendiceal adenocarcinoma	12–36
Colorectal adenocarcinoma	18–48
Peritoneal mesothelioma	36–60
Low grade appendiceal neoplasms	>60

- Heat has an anti-tumour effect by itself per se.
- Intraoperative chemotherapy allows manual distribution of drug and heat uniformly to all surfaces of the abdomen and pelvis

### Patient Selection

Patient selection is of utmost importance. The greatest impediment to lasting benefits from intraperitoneal chemotherapy remains an improper patient selection. Earlier, many patients with advanced intra-abdominal disease have been treated with minimal benefits. The patient subsets most likely to benefit from HIPEC have minimal/resectable peritoneal surface disease with an absence of systemic metastasis.

Currently, there are four important clinical assessments of peritoneal metastasis that need to be used to select patients who are most likely to benefit from treatment protocols [1]:

1. Histopathology to assess the invasive character of the malignancy,
2. A preoperative CT scan of thorax, abdomen & pelvis,
3. The peritoneal cancer index (PCI), and
4. The completeness of cytoreduction (CC) score

Pretreatment records need to be checked carefully with histological confirmation by an experienced histopathologist. Pathology review and an assessment of the invasive or non-aggressive nature of a malignancy are essential for planning treatment. Protocols for CRS & HIPEC may have curative influence in patients with a large mass of widely disseminated pseudomyxoma peritonei and well differentiated peritoneal mesothelioma [3, 4].

Imaging studies need to be thorough to rule out extra-abdominal disease. The CT scan would be of help in locating and quantitating mucinous adenocarcinoma within the peritoneal cavity [5]. Two distinctive radiologic criteria are found to be useful to assess patients with a high likelihood of complete cytoreduction and to prevent patients who are unlikely to benefit from undergoing cytoreductive surgical procedures:

- Segmental obstruction of small bowel,
- Presence of tumour nodules greater than 5 cm on small bowel mesentery or small bowel serosal surfaces

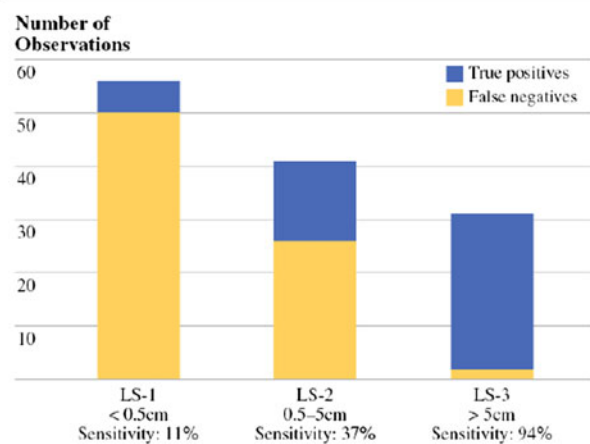
For peritoneal mesothelioma, criteria found to be useful includes, extensive tumor in epigastrium and generalized involvement of small bowel. An interpretative CT-classification has been defined to assess small bowel involvement. Characteristic interpretative CT findings of the small bowel and its mesentery are categorized into four classes. Class 0 CT showed no ascites in the region of the small bowel. The jejunal and ileal vessels appeared as round and curvilinear densities within the mesenteric fat. Class

I CT scans showed free intraperitoneal fluid only. The mesentery was stranded and stratified as the fluid accumulation outlined the small bowel mesentery. The small bowel vessels are easily identified within the mesenteric fat. Class II CT showed tumor involvement of the small bowel and/or its mesentery. The peritoneal surface was thickened and enhanced due to the presence of nodules (usually half-spherical bodies) or plaques (flat implants whose diameter was greater than thickness). There may be an increased amount of ascitic fluid and the mesentery may appear to be stellate or pleated. The small bowel mesenteric vessels were still identifiable. Class III CT showed increased solid tumor involvement and adjacent small bowel loops are matted together in some cuts. The configuration of the small bowel and its mesentery was distorted and thickened. Segmental small bowel obstruction may be present and intraperitoneal fluid may be loculated. The small bowel mesenteric vessels may be difficult to define on some cuts due to obliteration of mesenteric fat.

In predicting likelihood of adequate cytoreduction in peritoneal mesothelioma interpretative CT classification of the small bowel has been shown useful. A second criterion by which to predict adequate cytoreduction is large volume tumor involvement of the epigastric regions. If there is extensive disease infiltrating the lesser omentum, adequate cytoreduction is not usually possible [6, 7].

In peritoneal carcinomatosis, screening peritoneal nodules with CT scan is inaccurate many a times. The sensitivity of detecting peritoneal nodules depends on their sizes [8].

CT Colorectal Peritoneal Carcinomatosis

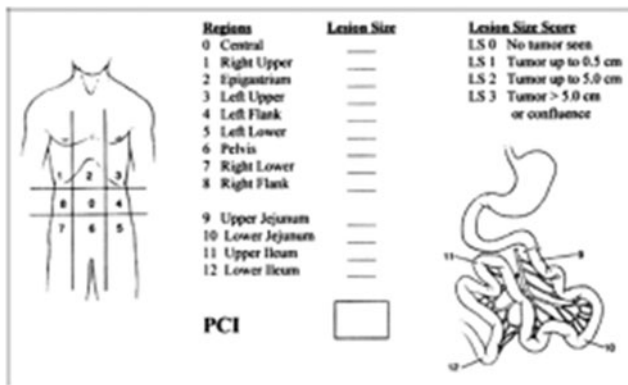


#### Impact of lesion size on sensitivity of CT-scan

If diagnosed to have peritoneal carcinomatosis from any of the favorable malignancies then he/she may be a candidate for cytoreductive surgery with perioperative chemotherapy.

### Assessment of PCI

The Peritoneal cancer index (PCI), is a clinical integration of peritoneal implant size and distribution of nodules on the



**Fig. 1** The Peritoneal Cancer Index [11]. The abdomen & pelvis are divided into 9 regions and 4 more regions of intestines as upper jejunum, lower jejunum, proximal ileum, distal ileum. Scoring of each region is done as per lesion size and it is then summated to get PCI which ranges from 1 to 39

peritoneal surface. To calculate the score size of intraperitoneal nodules must be assessed. The number of nodules is not scored, and only the size of the largest nodule is considered. The summation of the LS score in each of 13 abdominopelvic regions is the PCI for that patient. A maximal score is 39. This has been adequately validated in literature (Fig.1) [5, 9, 10].

### Completeness of Cytoreduction Score

The most definitive assessment used to predict prognosis with peritoneal surface malignancy is the CC- score. In both non-invasive and invasive peritoneal surface malignancy, the CC-score is the major prognostic indicator and has been shown to be accurate in pseudomyxoma peritonei, peritoneal carcinomatosis from colon cancer, sarcomatosis, peritoneal mesothelioma, and ovarian cancer. CC-0 score indicates that no visible tumor exists after cytoreduction; CC-1 score indicates that tumor nodules persisting after cytoreduction are <2.5 mm; a CC-2 score indicates tumor nodules between 2.5 mm and 2.5 cm; and a CC-3 score indicates tumor nodules >2.5 cm or a confluence of unresectable tumor nodules at any site.

### Approach towards Patient

Patient and relatives should be counselled initially regarding therapy, expected response with same, prognosis and expected cost of treatment. Risks involved and quality of life issues need to be discussed. Need for systemic chemotherapy if required is to be explained beforehand.

Prehabilitation is a significant part of patient's surgical preparation. It includes nutritional assessment and support; abstinence from smoking/alcohol and other addictions. Discontinuation of NSAIDs and anticoagulants should be discussed. Systemic chemotherapy, if going on concurrently, should be stopped, at least 6 weeks prior to surgery.

Each patient should undergo individual assessment by the CRS/HIPEC team including validation of weight and height, calculation of body surface area and careful examination of: [12]

- Prior chemo regimens delivered with special attention to response & toxicity
- Renal, liver & cardiac function that may necessitate dose modifications
- Evaluation of disease free interval
- Dose adjustments should be made for age and comorbid conditions

Nutritional planning should take into account: recent weight loss as percentage of current body weight; body mass Index, serum albumin, which unless very low, is not of much significance. Total parenteral nutrition supplementation should be given only if albumin is very low or else in the postoperative setting when oral diet could not be initiated early. Preoperative (subjective global assessment) SGA predicts length of stay and overall survival in patients undergoing HIPEC [13].

Stoma counseling & marking is a preoperative exercise and should be done in upright position.

### Surgical & Preanaesthetic Preparation

Patients undergoing HIPEC surgery face the usual physiological insults of a major surgery in addition to the thermal stress secondary to intraperitoneal administration of heated chemotherapy agent. A team approach of everyone involved in care of these patients is known to improve patient outcomes [14, 15].

#### Preoperative Evaluation

Preanaesthetic check up should, as for any other major surgery, include operative risk assessment using ASA classification. Patient's co-morbidities need to be assessed. [16].

In addition to usual preanesthetic check-up, the patient should be subjected for a thorough assessment of airway as these subsets usually have abdominal distension leading to decreased function residual capacity predisposing patient to higher chances of desaturation and aspiration. Hence, rapid induction remains a preferred modality for inducing these patients and availability of a videolaryngoscope offers an added advantage intraoperatively. Patient positioning and padding sites prone for pressure sores should be a part of surgical preparation [17]. Broad spectrum antibiotic prophylaxis covering gram positive & gram negative bacteria is to be given as per institutional guidelines. DVT prophylaxis should be prescribed as per the protocol.

## Cardiac Risks

Patients with cardiac pathology such as coronary artery disease, left ventricular failure and a poor left ventricular function are at a higher risk of decompensation and poorly tolerate high intraoperative volumes of fluids during the procedure [18, 19].

## Hemodynamic Monitoring

Routine placement of central venous lines/PA catheters is not indicated owing to inaccuracies in preload responsiveness assessment for the above. A radial arterial line for monitoring invasive blood pressure and ABG sampling should be placed additionally. Positive pressure ventilation induced changes in stroke volume on a rhythmic basis can be useful to predict fluid responsive subgroups.

While the chemotherapy agent is infused there is an initial hyperdynamic, vasodilated circulatory state during the heated chemotherapy phase which returns to baseline after temperature recedes to normal and chemotherapy lavage is completed.

## Fluid Management during HIPEC

Goal directed fluid therapy vis-à-vis liberal fluid administration has been documented to have better perioperative results as volume overload can lead to postoperative complications.

Both human derived and synthetic colloids are known to provide a 1:1 effect for a fluid responsive patient. Voluven was used earlier and favored over first generation hydroxyl ethyl starches. However, it comes with its own risks of nephrotoxicity and coagulopathy and in a changed scenario whether Plasmalyte-A will perform better in these patients remains to be seen. Patients who have large volume ascites/require extensive surgical debulking would benefit more with albumin as opposed to hydroxyl ethyl starches [20].

## Urine Output

As certain chemotherapeutic agents are nephrotoxic, urine output measurements become a significant monitoring parameter. However, in absence of any set guidelines/defined therapeutic end points the targets remain empirical. The goals vary from 50 to 100 ml every fifteen minutes depending upon the patient subsets. Euvolemia should be ensured. A diuretic challenge can be attempted once euvolemia and optimal renal perfusion have been achieved [21].

## Temperature Variations

Infusion of the heated chemotherapy agent leads to an increase in core temperature and this can be controlled by a combination of cooling and warming regimens which may be institution specific.

## Electrolyte Management

Dyselectrolytemias have been widely reported in HIPEC surgery and tend to vary depending on the agent used for chemotherapy. While Cisplatin leads to hypomagnesemia and cardiac arrhythmias secondary to the same Oxaliplatin causes lactic acidosis, hyperglycaemia and hyponatremia. ABGs, Hemoglobin and biochemistry should be done 15 min prior to surgery and most of these patients require calcium, magnesium and potassium replacement.

“The sugarbaker procedure “, needs a well-developed surgical team, supported by intensive staff, medical oncology team and the hardware.

## The Technology

The centre needs an external device/system to heat the chemotherapy solution (perfusate) and circulate it into and from the peritoneal cavity [22]. The principal components of this device (now also commercially available) includes-

- Circuit-tubing with a reservoir to contain the perfusate
- A heat source and heat exchanger
- Roller pump with a suction system for circulation of perfusate
- Temperature probes and monitors

HIPEC administration is performed with open ‘collosum’ technique or closed abdomen technique. Both the methods have their own advantages & disadvantages.

## Safety Concerns

The staff involved with HIPEC surgery must be educated thoroughly regarding the hazards associated with the same. The educational program should cover the surgical technique, details on intraperitoneal therapy and drugs used, effects of hyperthermia and the finer details on indications, rationale and expected outcomes of the procedure. This would include effects of exposure to drug and handling spills [23].

## Smoke Exposure

HIPEC surgery involves use of high voltage electro surgery and amount of smoke generated during the procedure exceeds that produced by other surgical procedures and when we add the duration of surgery to above it results in substantial cumulative exposure. This can lead to poor visualization of surgical field, headache, nausea, ocular and nasal irritation.

Smoke related issues in OR can be decreased by keeping OR well ventilated/keeping a smoke evacuator. Air conditioner should be in continuous operation with a higher pressure inside the OR relative to surroundings with filters able to

remove high efficiency particulate air and regular surveillance for fungal infection. Hermetic door closure should be achieved intraoperatively for the OR. Working of the smoke evacuator with electrosurgical generator should be synchronous. Air suction with device in situ is practiced (esp. during coliseum technique). Use of high power filtration masks in OT remains a debatable practice till date. Eye protection equipment should be used [24].

### Exposure to Chemotherapy

The drugs used for chemotherapy include mitomycin C, Cisplatin, Doxorubicin and oxaliplatin and although acute toxicity effects are known long term effects of prolonged exposures remain unknown. The common routes of exposure include direct contact and inhalation of aerosols and vapours.

The following subgroups should be excluded from a HIPEC team

1. Pregnant/nursing women.
2. History of abortions/congenital malformations.
3. Individuals planning a pregnancy (men/women).
4. Hematologic/teratogenic history.
5. Prior chemotherapy/radiotherapy treatment.
6. Radiographers/people working with radiotherapy.
7. Patients on immunosuppressive therapy.
8. History of allergic reactions to cytotoxic drugs/latex.
9. Severe dermatologic disease.

Regular health checks should be done every 6–12 months along with haematology and biochemistry work up and documenting the frequency of exposure and any new symptoms.

### Conclusion

Cytoreductive surgery with perioperative chemotherapy forms the most evolving modality of treatment for peritoneal carcinomatosis from various abdominal malignancies. With the recent data, interest in this treatment is blooming and newer centres are developing. For getting optimum results, we need to extrapolate the experience of high volume centres in our practice. Proper patient selection after evaluating radiological findings and correlating it with histopathological diagnosis helps in optimizing the procedure to achieve optimum outcome. Understanding the physiology of haemodynamic, electrolyte and fluid shifts, makes it easier to manage these potentially high risk patients. It has also been observed that with the necessary preoperative & perioperative steps, the morbidity and mortality for this treatment can be brought down as comparable to any other major abdominal surgeries.

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