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CONTROVERSIES IN GYNECOLOGICAL CANCERS

Standardization of Patient Selection and Hyperthermic Intraperitoneal Chemotherapy Protocol for Peritoneal Surface Malignancy in Indian Patients

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Abstract
Purpose Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) combined have been recognized as standard of care for treatment of patients with peritoneal carcinomatosis (PC). Different drug regimens have been employed over the years for HIPEC. Drug choice primarily depends on its known activity against the disease being treated and its suitability for intraoperative administration with hyperthermia. There is no standardized HIPEC dosimetry and methodology for intraperitoneal chemotherapy administration and varies amongst institutions in India. The quality of the HIPEC treatment should be constant and comparable between the different institutions, so that patients can receive high-quality treatment anywhere in India. The aim was to standardize the process of HIPEC by creating and implementing a protocol for Indian patients with PC.
Method We have performed CRS + HIPEC on 186 patients since February 2011 for various etiologies. This review will discuss the pharmacological principles of the various intraperitoneal chemotherapy techniques and the protocol being practised at our institution.
Results The treatment protocol was determined and implemented in 2011. Experience resulted in refining the patient selection and Manipal HIPEC protocol that has become the standard for our patients.
Conclusion It is a complex procedure that requires a high level of expertise of the institute and technical skills of the surgeons. The procedure comes with substantial morbidity and mortality risks when compared to other major procedures. The implementation of a standardized protocol could result in safe procedures and reduced complication rates.

Keywords Hyperthermic intraperitoneal chemotherapy (HIPEC) · Peritoneal carcinomatosis (PC) · Cytoreductive surgery (CRS) · Protocol · Peritoneal surface malignancies (PSM)

Introduction

Peritoneal carcinomatosis (PC), the presence of cancer cells on the surface of the peritoneum, can originate from the peritoneum membrane itself or more frequently is a direct extension of cancer originating from abdominal organs to the peritoneum (Fig. 1). The most common malignancies that can develop PC include (1) mucinous appendiceal neoplasms and appendix cancer, (2) colorectal cancer, (3) ovarian cancer and primary peritoneal carcinomas, (4) peritoneal mesothelioma, (5) gastric cancer, (6) small bowel cancer, (7) pancreatic cancer, and (8) sarcomas.

For a long time, PC was classified as an advanced stage of the cancer disease with frequent extension of the disease to multiple intra-abdominal organ and patients were sent for palliative care and eventually referred to hospice. The possibility of complete surgical debulking through a long complex surgery, involving resection of multiple abdominal organs, was traditionally aborted as per the high risk of

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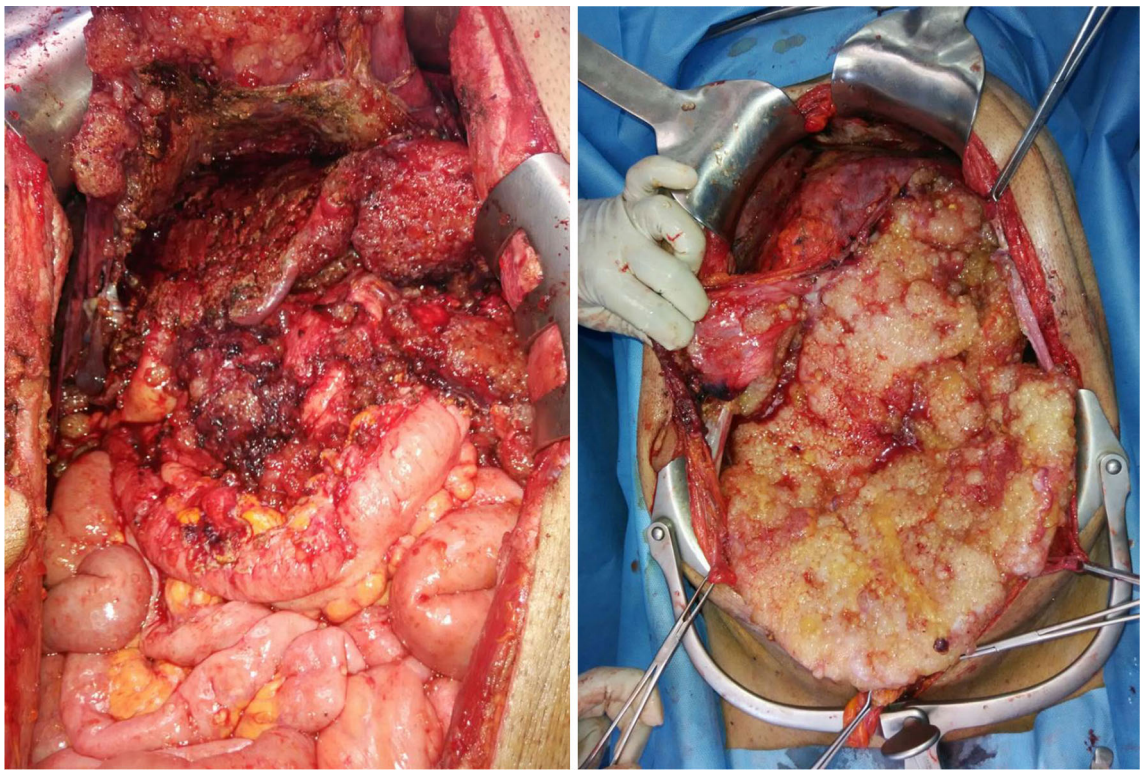

Fig. 1 Peritoneal carcinomatosis

such approach with limited benefits. Similarly, systemic intravenous chemotherapy had a little peritoneal penetration and effect on the peritoneal tumours, as the peritoneum membrane anatomically constitutes a compartment separate from the vascular compartment.

Background

Dr. John Spratt from the University of Louisville first reported in Cancer Research the combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in a patient with pseudomyxoma peritonei [1].

Over the last decade, there has been a paradigm shift in the treatment of PC. The development of CRS-HIPEC revolutionized the natural history of peritoneal tumours. The peritoneum is considered an intra-abdominal organ that is amenable to resection. The surgical approach changed from a debulking procedure to a more comprehensive surgery that involved stripping the peritoneal surfaces in addition to multiple visceral resections [2, 3].

Cytoreductive Surgery

The aggressiveness of surgery depends on the extent of peritoneal tumour dissemination that is determined by the intraoperative calculation of the Peritoneal Cancer Index (PCI) [4, 5].

The aim of CRS is to achieve complete cytoreduction. The completeness of cytoreduction was assessed using the completeness of cytoreduction score (CC score). The degree to which CRS is achieved has also been recognized as an important operative factor associated with prognosis. The CC score was developed in the early 2000s to theoretically predict likelihood of benefit from intraperitoneal therapy [6, 7]. Patients with no visible residual tumour after surgical debulking are given a score of CC-0, while those with largest residual tumour nodules < 2.5 mm are given CC-1 scores. A cut-off of 2.5 mm was designated as the largest nodule size thought to be affected by intraperitoneal chemotherapy, rendering that patient free of macroscopic disease at the end of treatment.

Ideally, surgery with therapeutic intent is aimed at achieving CC of 1 or less [8]. In a multicentre retrospective study of patients with colorectal carcinomatosis, Glehen et al. identified the CC score as the most significant independent prognostic factor associated with patient survival [9].

Hyperthermic Intraperitoneal Chemotherapy

After CRS and preparation for HIPEC, the abdominal and pelvic spaces are flooded with high-dose heated chemotherapy, resulting in a large exposure of tumour cells to high-dose chemotherapeutic agent. The development of the intraperitoneal route of heated chemotherapy administration allows for direct contact between the tumour cells and the chemotherapeutic agent to control all residual microscopic disease [10]. CRS with HIPEC represents a substantial improvement in outcomes compared to historical series and shows that meaningful long-term survival is possible for selected carcinomatosis patients. Multi-institutional cooperative trials are needed to further refine the utility of this procedure. This approach must be regarded as experimental at this point of time due to the lack of convincing level 1 data.

The aim of HIPEC is to obtain higher local concentrations of chemotherapeutic agents, combined with hyperthermia, to eradicate any microscopic residual disease [11]. It combines the pharmacokinetic advantage inherent to the intracavitary delivery of certain cytotoxic drugs, which results in regional dose intensification, with the direct cytotoxic effect of hyperthermia. HIPEC is performed with a continuous closed circuit of four drains (two inlet and two outlet) one heat exchanger and two roller pumps connected to the inlet and the outlet drains at intraperitoneal temperature of 42–43 °C for 30–90 min depending on the chemotherapy and pathology. To obtain a minimum of 42 °C in the out-drains, it is necessary to have between 44 and 45 °C in the inlet drains. During the procedure, temperature probes are placed at different sites of intraperitoneal cavity inflow and outflow drains, bladder, liver and mesentery (Fig. 2).

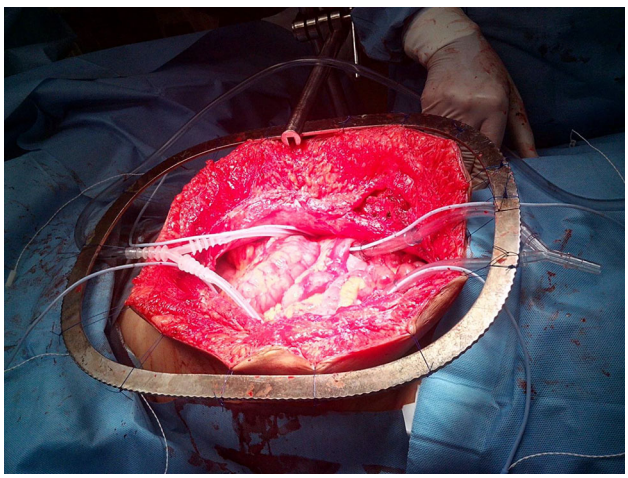

Fig. 2 "Coliseum technique" involves the skin edges of the abdominal incision being suspended from a Bookwalter retractor

Perioperative perfusion of the abdominal and pelvic spaces with high-dose heated chemotherapy allows for direct contact between the tumour cells and the chemotherapeutic agent to control all residual microscopic disease [12]. Hyperthermic temperatures around 42 °C immediately following maximal cytoreductive surgery enhance the antitumour effects of drugs, by augmenting cytotoxicity secondary to the loss of DNA repair activities [13]. The hypotheses offered to explain the better outcomes are (1) that the procedure capitalizes on the preferred timing of regional therapy immediately after tumour debulking and prior to the formation of post-operative adhesions that hinder drug distribution and efficacy, (2) that there is a synergistic antitumour effect of chemotherapy combined with hyperthermia, (3) that hyperthermia reverses platinum resistance, and (4) that hyperthermia enhances the penetration of drugs into tumours [14–18].

The peritoneal route of chemotherapy is based on the peritoneal plasma partition concept that allows a high concentration of the chemotherapy to be in direct contact with cancerous cells with minimal systemic absorption and side effects. The addition of heat to the chemotherapy potentiates the activity of some chemotherapeutic agents and increases diffusion of the chemotherapeutic agents between the cells [19–21]. Immediate application of intraperitoneal chemotherapy after the CRS controls the sub-millimetric disease and diffuses through two or three layers of cells before the formation of early physiologic post-operative adhesions where these cells can be trapped away from the reach of the chemotherapy. Moderate hyperthermia above 41 °C has a direct antitumour effect by augmenting the cytotoxicity of some chemotherapeutic agents and increasing the penetration depth of the chemotherapy into tumour nodules [22].

There are a variety of hyperthermic perfusion pumps available, and although it is not recommended, some hospitals deliver HIPEC via a modified cardiac bypass/perfusion machine and disposable cardiac lines. Commercially available automated pumps, specifically designed for intraoperative chemotherapy, are now being used internationally. We use HIPEC-specific RanD Biotech®, Italy, machines which are portable, temperature-regulated perfusion pumps that continually monitor the infusion process and all control systems (Fig. 3).

Anaesthetic Considerations in HIPEC

The role of the anaesthetist is crucial during CRS and HIPEC. Anaesthetic management in HIPEC is challenging due to potential complications associated with prolonged duration of surgery, haemodynamic instability due to major blood loss and fluid shifts, temperature variations including

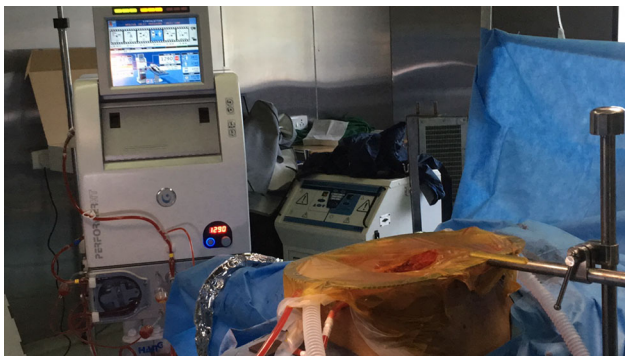

Fig. 3 RanD Biotech hyperthermic perfusion pump

heat loss during cytoreduction, rapid rise in temperature during HIPEC, arrhythmias due to exposure to heated chemotherapeutics, cisplatin-induced nephrotoxicity, electrolyte imbalance and acid–base changes. Fluid management is critical, keeping a balance between the use of crystalloids and colloids to achieve adequate central venous pressures and urine output without fluid overload. Arterial blood pressure, central venous pressure and PVI were used for continuous haemodynamic monitoring and as a guide for fluid management. Fluid overload is common after this surgery, causing acute pulmonary oedema or cerebral oedema. A minimal urine output of 100 cc (desirable 150 cc) every 15 min is mandatory to avoid renal toxicity, especially when cisplatin is used. The low-dose dopamine perfusion and furosemide are commonly used for better renal perfusion and improved output.

Central temperature is monitored by nasopharynx temperature probe. During cytoreduction, the body temperature is maintained at 35 °C by heating with forced hot air blanket, Hemotherm® and infusion of warm saline. One hour before the start of HIPEC, the heating devices are switched off. During HIPEC, the temperature may be expected to rise up to 39 °C or more; different cooling measures need to be implemented at this time to avoid sustained central hyperthermia. The ambient temperature is set at 18 °C. The patient is actively cooled to bring down the core body temperature to 34 °C. We prevent the core temperature from rising by intravenous administration of cold crystalloids, and Hemotherm® blanket is switched to cooling mode at 12 °C. In extreme cases, we use gastric lavage with cold saline and placement of ice packs around the groin, head and neck of the patient to cool the patient rapidly. To prevent the drop in temperature after HIPEC, the cooling process is stopped towards the end of HIPEC and warming devices were restarted.

Manipal HIPEC Protocol

A review of the literature also shows a wide range of HIPEC delivery, with many methodological variations including the technique, drug selection, dosage and the time of perfusion. At Manipal Hospital, Bangalore, we have performed CRS + HIPEC on 186 patients since February 2011 for various etiologies (Table 1). Clinical data on all patients are recorded in the HIPEC registry and maintained by a dedicated HIPEC unit. Since the start-up period of the treatment, at least two experienced oncological surgeons were trained to become specialized in CRS and HIPEC.

The medical oncology team was involved in all aspects of creating the HIPEC protocol, during drug selection, dose optimization and management of complications.

While the surgical technique is becoming fairly standard around the world as more evidence demonstrates the need of a complete CRS, there exists tremendous variation when it comes to application of HIPEC. It is characterized by six parameters: (1) drugs, (2) drugs dosage, (3) carrier solution and volume of perfusate, (4) duration of perfusion, (5) temperature of infusate and (6) perfusion method.

Drugs

The choice primarily depends on suitability for administration with hyperthermia, lack of severe direct local toxicity after intraperitoneal administration and its known activity against the disease being treated. Drugs that have to be metabolized systemically into their active form are inappropriate for intraperitoneal use. The chemotherapeutic agents employed in HIPEC have a cell cycle nonspecific mechanism of action (direct cytotoxic agent) with heat-synergistic cytotoxic effect [23]. Systemic exposure to intraperitoneally administered drugs inevitably occurs to a limited extent depending on tissue structure and drug properties, and is responsible for their toxicity [24].

The area under the concentration–time curve ratio (AUC ratio) of the drugs between the peritoneal cavity and the peripheral blood expresses the pharmacological advantage

Table 1 CRS and HIPEC performed at Manipal Hospital, Bangalore, since February 2013

Sl. no.	Pathology	No. of procedures ($n = 186$)
1	Ovarian carcinoma	103
2	Colorectal cancer	34
3	Pseudomyxoma peritonei	36
4	Gastric cancer	4
5	Mesothelioma	9

of intraperitoneal drug administration. The intraperitoneal to plasma drug AUC ratio is high of commonly used agents such as cisplatin, 5-FU, taxanes, irinotecan, adriamycin or mitomycin C who show this advantage. The penetration depth of drugs that are intraperitoneally delivered is estimated to be a maximum of 3 to 5 mm [25–27]. This is the reason why an adequate cytoreductive surgery should precede the intraperitoneal delivery of drugs and why 2.5 mm in largest diameter is considered the threshold for residual tumour nodule diameter if a cytoreduction is to be considered optimal complete cytoreduction.

Most centres have used mitomycin C (AUC ratio is 23.5) as the HIPEC drug of choice in patients with PC of colorectal and appendicular origin and in a subset of patients with mesothelioma. The most widely applied doses range from 12.5 to 35 mg/m2 over 90 min [28]. Cisplatin HIPEC has been used in mesothelioma, ovarian and gastric cancer with an AUC ratio of 7.8 [29]. Cisplatin HIPEC is associated with an increased incidence of nephrotoxicity, which is found in 5–15% of patients [30]. Saline diuresis and a urine output of greater than 1 mL/kg/hr are necessary to reduce the risk of nephrotoxicity. Oxaliplatin is used as HIPEC in PC from colorectal and appendix adenocarcinoma. Oxaliplatin with AUC ratio between 16 and 25 can only be administered in a 5% dextrose solution, and hyperglycaemia with hyponatremia is common during the perfusion [31].

In the last few years, bidirectional HIPEC regimens (concurrent administration of intraperitoneal and intravenous chemotherapy) have gained ground. In this two compartmental approaches, timing is critical to the success of the chemotherapy in relation to the surgical procedure to obtain a bidirectional fluid gradient in peritoneal tumour cells [28]. Elias first reported this therapy and suggested perioperative intravenous 5-FU and leucovorin in conjunction with oxaliplatin-based HIPEC for colorectal cancer. By acting synergistically, this study showed that bidirectional chemotherapy is pharmacokinetically beneficial and that after the intravenous administration of 5-FU in a patient under general anaesthesia in an intraperitoneal hyperthermic environment, the drug unexpectedly accumulates in the peritoneal cavity, a true heat-targeting phenomenon [32].

Drugs Dosage

In order to make exposure and the subsequent toxicity predictable, standardized dosing by body surface area of both the drug and the volume of the carrier solution to be employed are recommended. Body surface area (BSA) is an accurate predictor of drug metabolism and is useful to estimate systemic drug toxicity [28]. Most researchers calculate both drug dose and carrier solution volume based on body surface area (mg/m^2).

HIPEC regimens using fixed doses (same dose for any patient) and drug dosing by the litre of perfusate or by body weight are more prone to find untoward events secondary to unnoticed overdosing of the cytotoxic drug employed. A dose reduction by 33% is recommended for patients over the age of 60, previously exposed to multiple lines of systemic chemotherapy, who needed GM-CSF rescue for febrile neutropenia while on systemic chemotherapy or who have received radiation therapy to bone marrow-bearing regions.

Carrier Solution and Volume of Perfusate

The carrier solution also plays an important role in the distribution of the drug and efficacy of the treatment by impacting clearance of the drug from the peritoneal cavity to plasma. The factors like chemical aspect of the carrier, concentration and volume impact the pharmacokinetics and penetration ability [33]. The ideal carrier solution should provide enhanced exposure of the peritoneal surface, prolonged high intraperitoneal volume, slow clearance from the peritoneal cavity and the absence of adverse effects to peritoneal membranes. Common perfusate volumes are 1.5 or 2 L/m^2 [34, 35]. The total volume of intraperitoneal chemotherapy can vary widely between individuals. Females have a 10% larger peritoneal surface in proportion to body size than males [28]. Regulation of both the drug dose and carrier solution volume based on the patient's body surface area and HIPEC delivery technique (open or closed) is necessary [36]. The carrier solution of 1.5% dextrose isotonic peritoneal dialysis solution is the most widely used; however, some groups use normal saline or 5% dextrose depending on the type of chemotherapy agent [37].

Duration of Perfusion

The cytotoxic effect is also relative to the duration of exposure. In most reported studies, intraperitoneal drug half-life is 90 min or less. Intraperitoneal treatment length should be dependent on systemic exposure and bone marrow toxicity. There are clinical data demonstrating safety with different schemes established on an empirical basis which includes a temperature of 41 °C during 90 min and 43 °C for 30 to 40 min [38].

Temperature of Infusate

The basis for the use of hyperthermia in the treatment of peritoneal malignancy is multifactorial. Synergism between various cytotoxic drugs and hyperthermia starts at

Table 2 HIPEC protocol at Manipal Hospital

Organ	Surgery (CC 0–1)	Drugs	Dosage	Perfusate fluid and total volume	Circulation rate (mL/min)	Duration (min)	Intraperitoneal temperature (°C)	Special instructions
Ovary cancer	Primary setting	Cisplatin	100 mg/m^2 (standard surgery) or 75 mg/m^2 (extensive surgery)	Peritoneal dialysis fluid (2 litres/m^2)	1000	90	42	Good hydration to prevent nephrotoxicity. Maintain 100 mL of urine output every 15 min for the duration of HIPEC. Monitor magnesium levels
	Recurrent setting 1. All platinum-sensitive disease 2. Platinum-resistant disease with single-site recurrence	Adriamycin and cisplatin	15 mg/m^2 and 75 mg/m^2	Peritoneal dialysis fluid; (2 litres/m^2)	1000	90	42	
Colorectal cancer	Standard surgery	Intraperitoneal: Oxaliplatin Intravenous: 5-FU + leucovorin	360–460 mg/m^2 450 (IV 5-FU) mg/m^2 20 (IV Leucovorin) mg/m^2	5% Dextrose (2 litres/m^2)	1000	30	42	Bidirectional chemotherapy: intravenous 5-FU + leucovorin 60 min prior to start of HIPEC
	Allergy to oxaliplatin or extensive surgery or risk of bleeding	Mitomycin C (MMC)	20–35 mg/m^2	Peritoneal dialysis fluid; (2 litres/m^2)	1000	90	42	Two-thirds of MMC is added at 0 min and rest given at 45th min
Pseudomyxoma peritonei	Standard surgery	Mitomycin C (MMC)	20–35 mg/m^2	Peritoneal dialysis fluid; (2 litres/m^2)	1000	90	42	Two-thirds of MMC is added at 0 min and rest given at 45th min
Stomach	Standard surgery	Mitomycin C (MMC)	20–35 mg/m^2	Peritoneal dialysis fluid; (2 litres/m^2)	1000	90	42	Two-thirds of MMC is added at 0 min and rest given at 45th minute
Mesothelioma	Standard surgery	Cisplatin	100 mg/m^2	Peritoneal dialysis fluid (2 litres/m^2)	1000	90	42	Good hydration to prevent nephrotoxicity. Maintain 100 mL of urine output every 15 min for the duration of HIPEC. Monitor magnesium levels

a temperature of 39 °C, but at temperatures of 45 °C, it is limited by clinical tolerance [33]. Moderate hyperthermia level of 41 to 43 °C is optimal and selectively induces cytotoxicity of malignant cells due to impaired DNA repair, protein denaturation and inhibition of oxidative metabolism in the microenvironment of malignant cells, which leads to an increased acidity, lysosomal activation and an increased apoptotic cell death and inhibition of angiogenesis [28].

Perfusion Method

The chemoperfusion can be performed in an open or closed abdominal technique, or even via the laparoscopic route using a roller pump and a heat exchanger. There is no consensus for a superior method as there are advantages and disadvantages to each.

A major advantage of the closed technique is the ability to rapidly achieve and maintain hyperthermia as there is minimal heat loss. In addition, it increases intraperitoneal pressure, which is reported to enhance the penetrative ability of the chemotherapy. There is minimal contact or aerosolized exposure of the operating room staff to the chemotherapy. The main disadvantages are the lack of uniform distribution of the chemotherapy and lack of thermal homogeneity. Heterogeneous distribution inside the closed abdomen may increase the rate of intra-abdominal complications.

We follow the open method of performing HIPEC. This method, or "Coliseum technique", involves the skin edges of the abdominal incision being suspended from a Thompson or Bookwalter retractor by a running suture to create an open space in the abdominal cavity. A plastic sheet is incorporated into this suture with a small opening in the centre to allow for the surgeon's hand to access the abdomen and pelvis for manipulation during chemotherapy. Temperature probes are placed near the inflow catheters. Smoke evacuators are placed to guard against any potential cytotoxic aerosol contamination. The main benefit of the Coliseum technique is that heated chemotherapy is adequately distributed throughout the abdominal cavity and there is no pooling of temperature or chemotherapy. Disadvantage of the open technique is heat loss that makes it more difficult to initially achieve a hyperthermic state, drug leakage and an increased exposure of operating room personnel to chemotherapy [39]. Excessive heating of normal tissue that can exacerbate post-operative ileus and increase the incidence of post-operative perforation or gastrointestinal fistula formation may be avoided when using the open technique [40].

Experience with CRS and HIPEC in a tertiary hospital resulted in a development of a treatment protocol that has become the standard for our patients. HIPEC is performed only in patients who have achieved CC score of 0–1. Outcome of CRS and HIPEC was reviewed in all our patients, and the differences between the initial pioneer phase and the subsequent period were analysed. Based on the observations, changes were made and the modified protocol was clinically implemented. Table 2 shows the Manipal protocol for CRS and HIPEC.

Patient Selection

Obviously, this treatment modality has changed a lot since the pioneer phase, and the most forthcoming is patient selection. The patients were discussed at the multidisciplinary tumour board consisting of medical oncologists, surgical oncologists and radiologists, and the final decision was made by consensus, taking into consideration the patient-related variables as well as parameter which could represent contraindications. As we became more familiar with this procedure and understood the role of HIPEC, the selection criteria expanded (Table 3). Clinical data of patients who underwent CRS and HIPEC since the past 5 years at our institution and analysis of the same helped us in standardizing the selection criteria for optimal treatment [41, 42].

Table 3 Inclusion criteria to perform HIPEC

Sl. no.	Criteria
1	ECOG 0/1
2	< 70 years age
3	With multiple comorbidities age < 65 years
4	Pre-operative serum albumin > 3 g/d
5	Intraoperative anastomosis < 3
6	Gastric cancer: PCI < 6
7	Colorectal cancer: PCI < 15
8	Ovarian cancer: primary and recurrent (all platinum-sensitive disease + platinum-resistant disease with single-site recurrence)

Conclusion

The combination of CRS and HIPEC provides the only chance for long-term survival for selected patients diagnosed with PC. It is a complex procedure that requires a high level of expertise of the institute and technical skills of the surgeons. The procedure comes with substantial morbidity and mortality risks when compared to other major procedures. The implementation of a standardized protocol could result in safe procedures and reduced complication rates.

It is a complex procedure that requires not only a high level of expertise of the institute and the surgeons, but also the entire team including a very vital role of medical oncologist, considering critical assessment of drug selection, doses optimization and management of complications. This approach must be regarded as not a standard of care, irrespective of opinion about the efficacy of HIPEC procedure as the randomized trials are not available or unreliable. Despite the many accomplishments to date, continued clinical research into CRS and HIPEC is mandatory.

Compliance with Ethical Standard

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.For this type of study, formal consent is not required.

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