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CASE REPORT

A Modified Low-Cost Technique of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Two Patients: a Solution for Pseudomyxoma Peritonei in the Indian Scenario?

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Abbreviations

HIPEC	Hyperthermic intraperitoneal chemotherapy
CRS	Cytoreductive surgery
PCI	Peritoneal cancer index
CC	Completeness of cytoreduction
DPAM	Disseminated peritoneal adenomucinosis
PMP	Pseudomyxoma peritonei

Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have emerged as feasible treatment modalities for peritoneal dissemination (pseudomyxoma peritonei—PMP) in selected malignancies of the ovaries, appendix, colorectum, stomach, and even urinary bladder [1–3]. The time period after 2010 has seen a noticeable boost in the number of centers adopting this technique [3]. It has been shown that removing all macroscopic tumor tissue from the peritoneal surface (residual < 2.5 mm) facilitates destruction of the residual cells by local chemotherapy, heated to 40–45 °C for maximum penetration. This approach has shown better survival and less complication rates than systemic chemotherapy administered pre-or postoperatively in the same subset of patients. Better results have been demonstrated in certain pathological subtypes of PMP like metastatic colorectal carcinoma and disseminated peritoneal adenomucinosis (DPAM) [4, 5].

Since the procedure is time-consuming and tedious, and the condition of the patient is suboptimal, the treatment is challenging. The therapy is available only at the most advanced centers, due to constraints of resources and expertise. Due to this, experience from India is less than 500 cases, mostly at centers with adequate resources [6, 7]. However, the large population visiting public hospitals warrants widespread development of this technique and personnel, that too, at affordable costs. We have performed two cases of CRS/HIPEC with an indigenous low-cost perfusion technique with satisfactory results; this is probably the second such attempt in literature.

Case 1

A 30-year-old woman presented to the gynecology department with a 3-month history of lower abdominal pain, massive distension, and weight loss. Examination revealed pallor, massive ascites, and multiple firm intraabdominal lumps (Fig. 1). Routine laboratory tests were unremarkable, except for microcytic anemia (Hb = 7.8 g/dL). CT abdomen revealed bilateral large multilobulated septated abdominopelvic masses with omental deposits and gross ascites (*Peritoneal Cancer Index—PCI = 20*). CT chest was normal. Serum CA-125 was 88 U/mL, serum CA 19.9 was 0.6 U/mL, and, serum CEA was 234 mcg/L.

A staging laparotomy was performed in the gynecology department; bilateral enlarged cystic ovaries exuding mucin were found with disseminated peritoneal mucinous deposits. Multiple peritoneal and omental biopsies were performed, and the procedure was abandoned due to disseminated disease. Biopsy of the tumor and peritoneal deposits revealed

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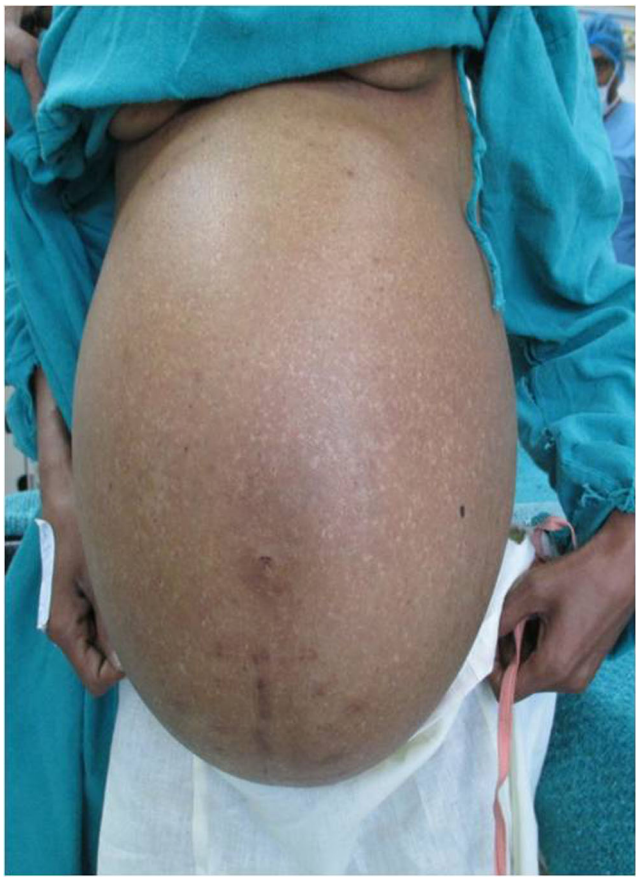

Fig. 1 Hugely distended abdomen in pseudomyxoma peritonei (PMP)—patient 1 presented with massive ascites and minimal other symptoms. This picture is typical of PMP

fibroconnective stroma with pools of mucin on the surface, inside dilated mucinous glands and in acellular lakes. No nuclear atypia or mitosis was identified; cells were positive for CK 20 and negative for CK 7. A diagnosis of disseminated peritoneal adenomucinosis (DPAM) was suggested, with possible primary in the ovaries or appendix (Fig. 2).

The patient was re-explored through the previous midline laparotomy scar 4 weeks later; we found 5–6 L of thick, greenish mucinous jelly filling the entire abdominal cavity. The entire peritoneal surface was studded with gelatinous nodules, especially over the greater and lesser omentum, appendices epiploicae of sigmoid colon, umbilical fissure, and transverse mesocolon. Both of the ovaries were replaced by very large (right—30 × 25 cm, left—15 × 10 cm) cystic masses partially ruptured and exuding mucin. There was no evidence of small bowel serosal involvement or solid organ metastases. The cytoreductive surgery (CRS) performed included a total hysterectomy with bilateral salpingo-oophorectomy, distal gastrectomy, right hemicolectomy, cholecystectomy, splenectomy, and total peritonectomy (completeness of cytoreduction—CC score = 0; Figs. 3 and 4). Bowel continuity was restored after HIPEC (vide infra). The entire procedure (including HIPEC) lasted 16 h.

Postoperatively, the patient developed acute renal failure and myelosuppression; the total leucocyte count dropped to less than 50/mm^3. After 2 weeks of treatment with hemodialysis and parenteral filgrastim (granulocyte colony-stimulating factor—G-CSF), the counts stabilized. She was discharged 1 month after the procedure and was well at follow-up of 6 months.

Case 2

A 52-year-old woman presented to the surgery clinic with a 1-year history of recurrent mild abdominal pain; there were records of an emergency appendectomy performed 2 years back for acute appendicitis at another center. On examination, the patient was obese with no specific clinical findings. Suspecting adhesive partial bowel obstruction, contrast-enhanced CT abdomen was done, which revealed diffuse peritoneal and omental soft tissue densities, apart from a 3.6 × 4.6 cm, high-density well-defined lesion in the right iliac fossa (*Peritoneal Cancer Index—PCI = 14*; Fig. 5); CT-guided fine needle biopsy from this revealed peritoneal adenomucinosis. A review of the slides of the previous appendicectomy revealed mucinous cystadenoma; with a final diagnosis of PMP, a plan for cytoreductive surgery was made. Serum tumor markers were in the normal range; other laboratory tests were unremarkable. On exploration through a large midline incision, we found 2 to 5 cm jelly-like tumor nodules over the greater and lesser omentum, the right diaphragmatic peritoneum, the umbilical fissure, and the broad ligament. However, there were no ascites or solid organ metastases. The cytoreductive surgery performed included a total hysterectomy with bilateral salpingo-oophorectomy, right hemicolectomy, cholecystectomy, splenectomy, and peritonectomy of the involved surfaces including the area close to the caudate lobe of liver (completeness of cytoreduction—CC score = 0; Fig. 6). HIPEC was administered as below. The duration of the procedure was 10 h. Postoperatively, the patient recovered uneventfully and was well 6 months later.

Hyperthermic Intraperitoneal Mitomycin-C in Both Patients

After copious saline wash, we perfused HIPEC using mitomycin-C 26 mg and 30 mg (15 mg/m^2 × 1.76 m^2/1.96 m^2) in case 1 and case 2, respectively, dissolved in 3 L normal saline heated to 41–42 °C, using the "open coliseum" technique for a contact time of 90 min. Here, the edges of the abdominal wound were sutured to the oval blades of the *Bookwalter* retractor system™. A sterile plastic drape with a flap was useful in both augmenting the temperature with more heated solution and preventing heat loss (Fig. 7). The

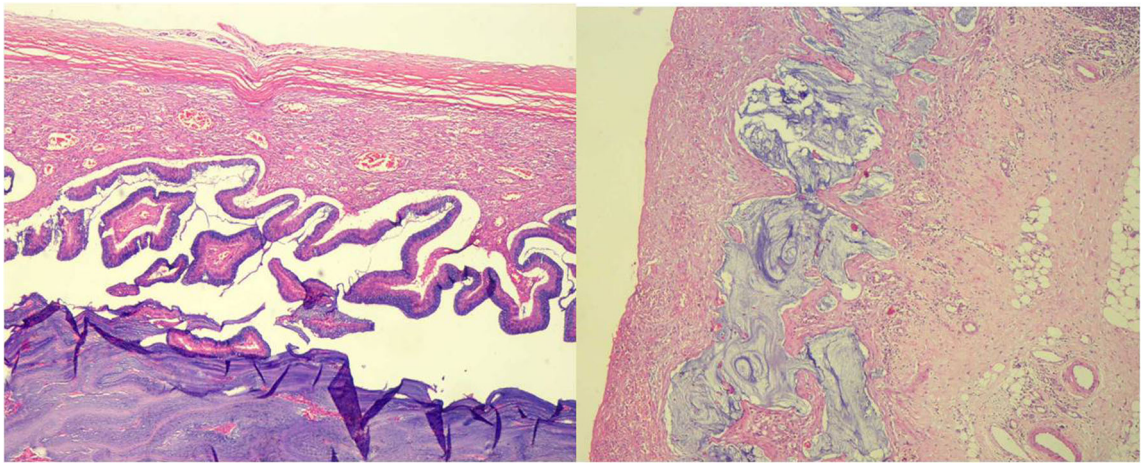

Fig. 2 Pathology of PMP (H&E × 10)—ovarian (*left*) and peritoneal (*right*) biopsy in patient 1 reveals preserved architecture with acellular mucin lakes; there is no nuclear atypia or mitosis suggestive of disseminated peritoneal adenomucinosis (DPAM)

temperature was maintained by a real-time temperature probe inserted deep inside the right paracolic gutter (oropharyngeal temperature probe with monitor). Manual manipulation ensured thorough circulation of the chemotherapy into all peritoneal crevices. Another oropharyngeal temperature probe provided an indirect assessment of the core temperature to avoid overheating. A hot water bath at 60 °C served as the "heat reservoir" and was kept at a height higher than the operating table, using a video monitor trolley.

The drug was instilled into the six saline bottles (3 L) preheated to 41–42 °C in a saline-heating water bath, using sterile syringes with the needle inserted through the air port provided in the bottles. These were then emptied into the peritoneal cavity, and their temperature was monitored. When the temperature was close to 40 °C, sterile steel containers were used to manually shift about 300 mL fluid at a time into two sterile plastic saline funnels. These were immersed in a water bath at 60 °C and connected to sterile tubings to re-infuse the abdominal cavity. This continuous circulation was able to keep the tight temperature control required. The manual transfer of fluid was done with gloved hands, and spillage was avoided carefully.

Discussion

The Indian experience with CRS and HIPEC is evolving and not well-documented; apart from the obvious constraints of training and resource deficit, several other problems are evident from our experience. Proper selection of cases is possible

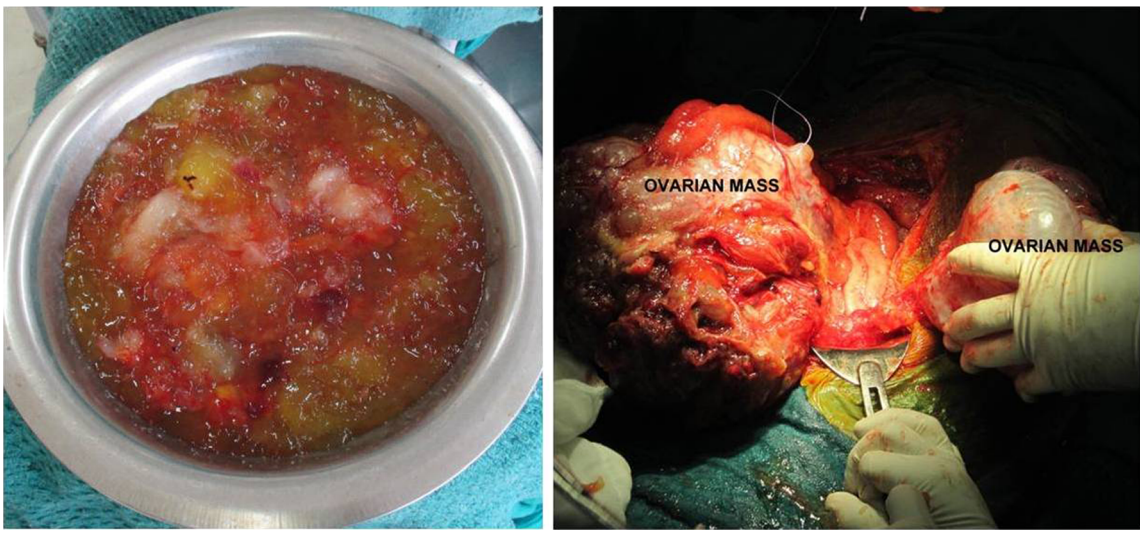

Fig. 3 "Jelly belly"—copious amounts of mucin was drained from patient 1 (*left*). The peritoneal cancer index was 20. Large (> 20 cm) ovarian masses (*right*) were also removed

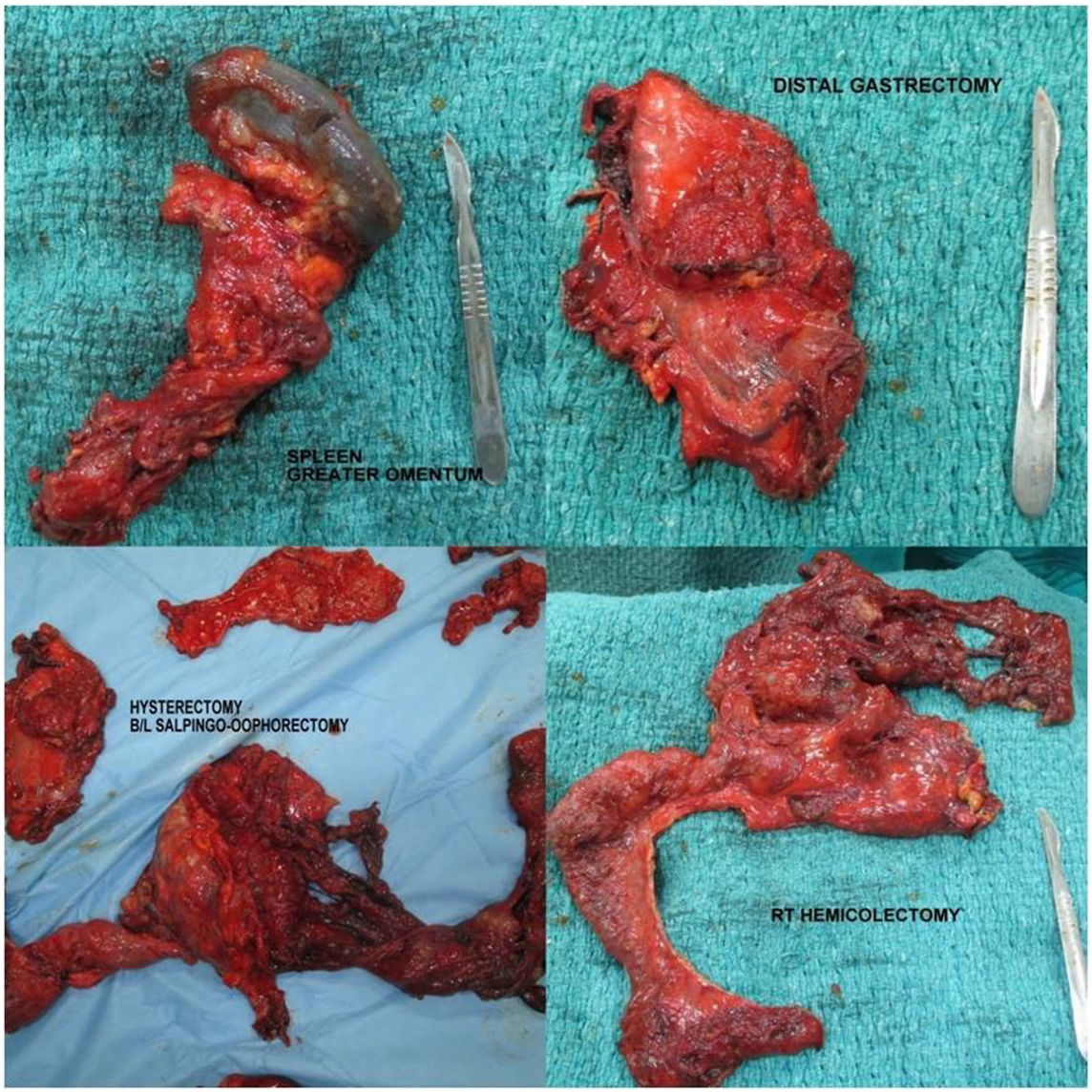

Fig. 4 Cytoreductive surgery patient 1—all visible disease was resected and completeness of cytoreduction (CC) score was "0"

when the index of suspicion is high *not only* with respect to clinical, *but also* radiological and histopathological findings. Typical radiological findings which should alert one to the possibility of PMP are generalized peritoneal or omental thickening/nodules, liver "scalloping," and nodules/thickening of the liver ligaments and right colon, especially in the background of a well-preserved patient [1]. In the Indian scenario with a *very high* incidence of abdominal tuberculosis, these findings of PMP may be reported as tuberculosis and not easily appreciated. Many patients of PMP have a history of surgery for ovarian or appendiceal pathology; during the first intervention, the clinical or pathological findings may be missed due to inexperience or poor follow-up and referral facilities. In our second patient, despite the reported mucinous cystadenoma of the appendix, specialized treatment was not sought or advised until very late. Most Indian centers have used cardiovascular pumps with thermostats to deliver HIPEC [6–8]; this is affordable, but many hospitals may not have cardiac operation rooms. Nevertheless, the results from most Indian studies are encouraging, with acceptable perioperative mortality (< 8%) [6].

Mitomycin-C (MMC) is a favored drug for CRS and HIPEC, especially when the origin is appendiceal or colonic; its synergistic cytotoxic action with hyperthermia, high molecular weight which limits systemic absorption, and tissue penetration of 5 mm are the perceived advantages. However, there have been reports of systemic toxicity with MMC, especially neutropenia and renal failure [2, 9, 10]. Lambert et al. reviewed 123 patients who underwent HIPEC with MMC; 39% developed neutropenia, defined as absolute neutrophil counts < 1000/mm^3. The authors concluded that female gender and dose were independent risk factors for neutropenia,

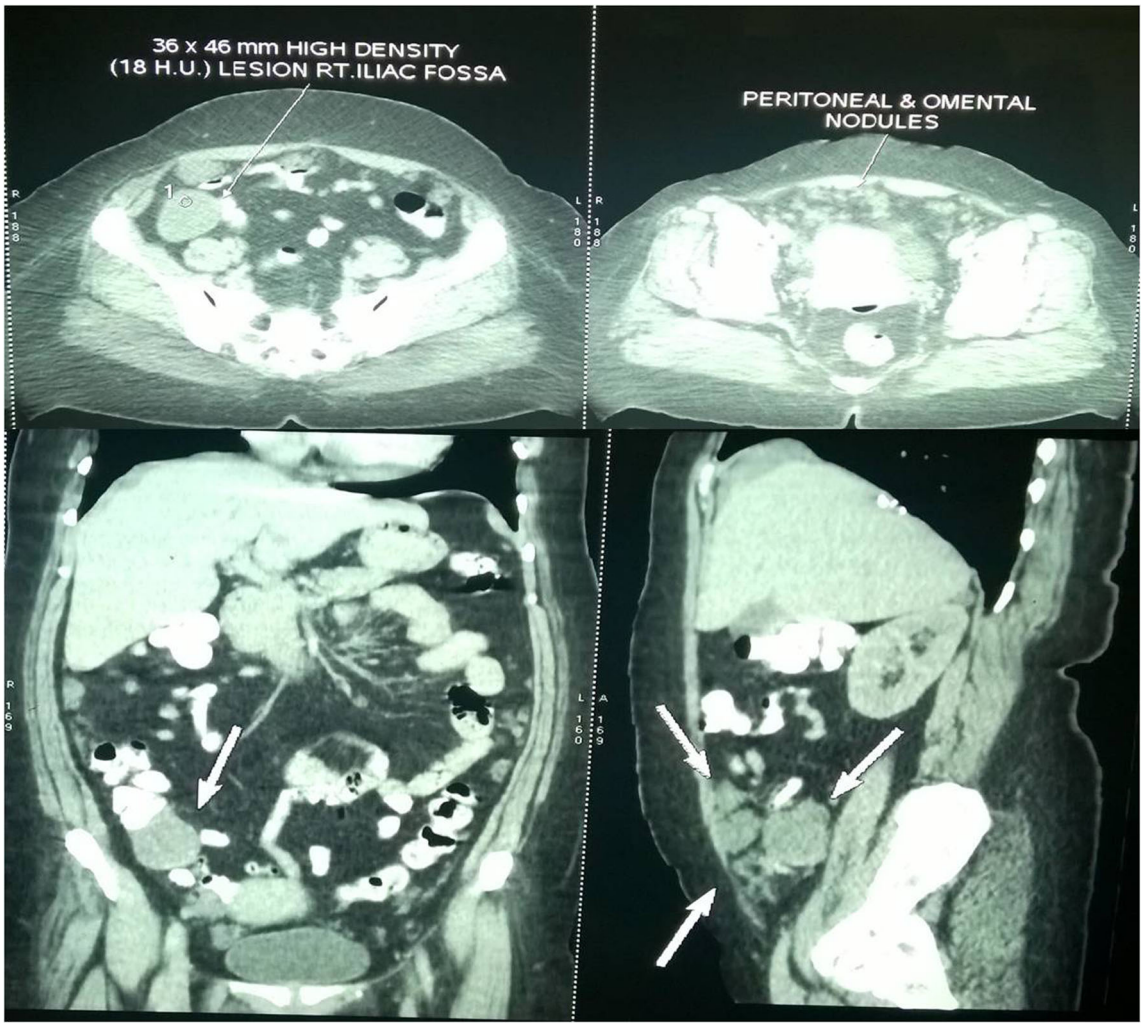

Fig. 5 Contrast CT abdomen patient 2—*clockwise from upper left*—two cross-sectional images depicting a large lower right quadrant nodule (18 HU) and multiple peritoneal nodules, respectively, then sagittal and coronal images depicting the same large lower right nodule with thick arrows

probably due to the relatively larger peritoneal surface in females for the same body weight; thus, caution should be exercised in deciding the appropriate dose [10]. In our first patient, despite using a lower dose (15 mg/m^2), there was severe myelosuppression, probably as she was chronically malnourished with a high PCI of 20 and a low lean body mass. The ideal dose of intraperitoneal MMC is yet to be determined, with current practices ranging from 15 mg/mm^2 to 35 mg/mm^2 [2].

Issues of Cost

Apart from the scientific feasibility of initiating CRS and HIPEC at a new center, there are also significant considerations of resources and cost. The equipment used to deliver HIPEC is expensive and not readily available in our country. Additionally, these issues have not been dealt adequately in literature. In a retrospective review of 36 patients undergoing CRS/HIPEC, Hinkle et al. calculated the average direct cost per patient to be around $26,000, of which about 65% were operating room and pharmacy costs [11]. Squires et al. analyzed clinicopathologic variables, hospital costs, and reimbursement for all patients undergoing CRS/HIPEC at a single institution from 2009 to 2013; they found total hospital costs to be upwards of $50,000 [12]. The authors also calculated that the costs increased by about 10% when there were significant complications; the costs were not uniformly covered by insurance. These studies illustrate that this therapy is resource-intensive even in developed countries; the difficulties faced by Indian centers, even private ones, are hardly fathomable.

On probing literature, we could find only one attempt to devise a low-cost modification for HIPEC in humans. Cravioto-Villanueva and colleagues from Mexico [13] treated

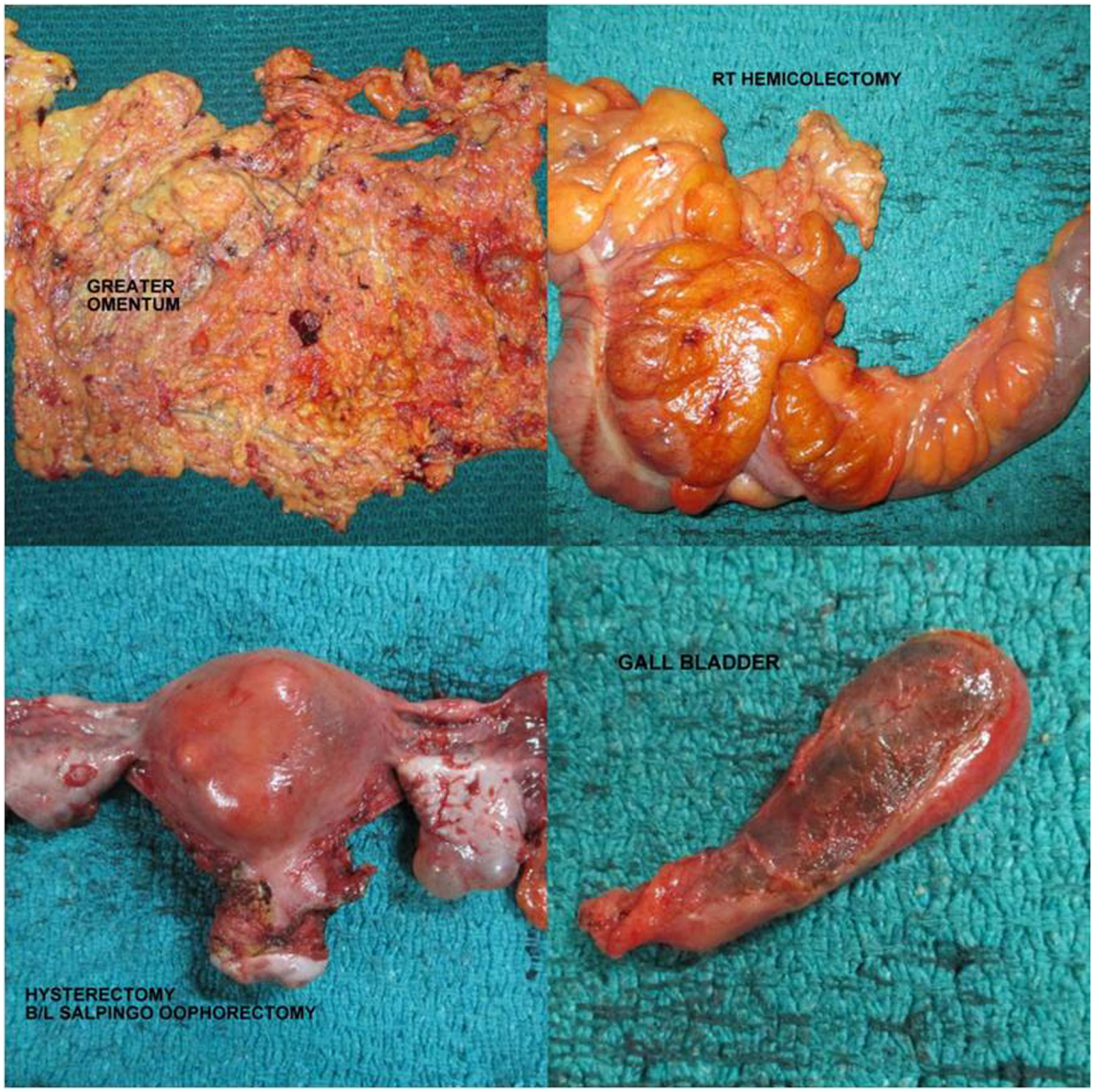

Fig. 6 Cytoreductive surgery patient 2—all visible disease was resected and completeness of cytoreduction (CC) score was "0"

10 patients of PMP with a modified perfusion system; they used two cardiovascular pumps, a chemotherapy reservoir, a filter, and some inflow and outflow tubes to fashion the circuit. The circuit was put to use after testing adequately with saline; it was demonstrated that a target intraoperative intraperitoneal temperature of 40.1–41.69 °C was achieved for a contact time of 90 min in all 10 patients using this apparatus. No patient suffered hyperthermia of thermal injuries. The only drawback was the need for manual monitoring of the reservoir temperature. Ortega-Deballon et al. have also used a simple inexpensive technique for heating intraabdominal solution in a pig model [14]. Here, too, a separate person was required to manually circulate the fluid within the abdominal cavities. Our technique is similar to both the above low-cost models; however, we did not use cardiovascular pumps, bringing the costs down further. We used the temperature probes readily available in the operating rooms with the cardiac monitors; we also used the Bookwalter retractor system™ and simple plastic sheets to fashion our "coliseum." At no point of time was the core body temperature allowed to cross 38–39 °C, while the intraperitoneal temperature was maintained between 41 and 42 °C for 90 min. As with the abovementioned studies, our effort was labor-intensive with 2–3 personnel required for running the circuit; however, we did not perceive this as a disadvantage as the operating team for such a major case is sufficiently large. To the best of our knowledge, this is the second reported low-cost modification for CRS/HIPEC and the first from the country. The feasibility and success of this apparatus will provide encouragement to many new centers to initiate this treatment for suitable candidates.

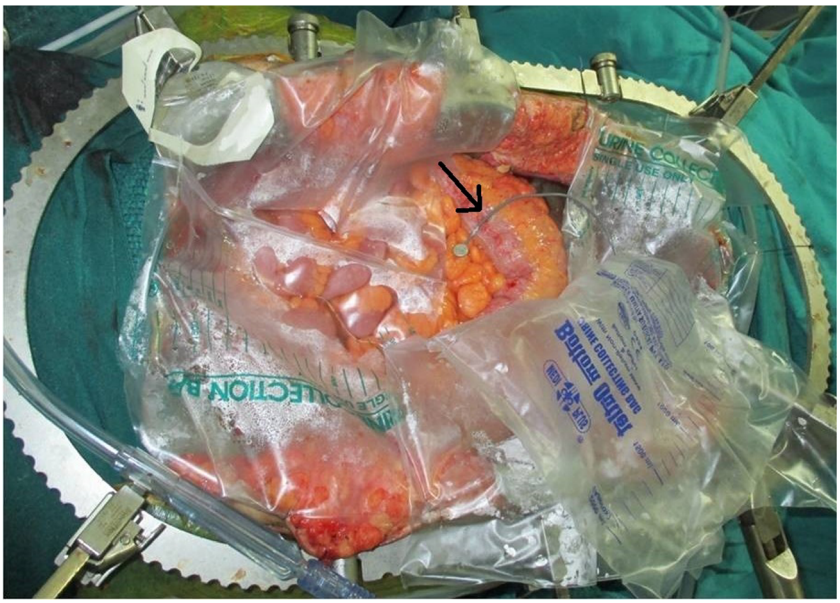

Fig. 7 Modified "open coliseum"—*see text*. A *Bookwalter* retractor system™ was used to convert abdomen into a deep cavity so that all the viscera and parieties bereft of peritoneum were immersed. Two large flaps of *Urobag*™ were sutured to the two edges of the abdominal wall with considerable overlap, covered by multiple layers of dry sponges to prevent heat dissipation. The temperature probe is marked with a black arrow

Authors' Contributions Rana AKS: idea, clinical contribution, editing
Agarwal N: idea, clinical contribution, writing of manuscript, and editing
Dutta S: writing of manuscript and editing
Dokania MK: writing of manuscript and editing
Goyal H: writing of manuscript and editing.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate Informed consent was taken from the patient; the study is case report which conforms to the standards of the institutional ethics committee.

Consent for Publication Informed consent was taken from the patient.

Availability of Data and Material Not applicable.

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

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