REVISTA DE INVESTIGACIÓN CLÍNICA

Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

PERMANYER

Rev Invest Clin. 2015;67:39-45 ORIGINAL ARTICLE

Morbidity and Mortality Following Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy at a Tertiary Care Center: Initial Experience

Uriel Clemente-Gutiérrez, Adrián Garza-Gangemi, Gabriela Trejo-Gómez and Heriberto Medina-Franco*

Department of Surgery, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, D.F., Mexico

ABSTRACT

Background: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy increases progression-free and overall survival in patients with peritoneal carcinomatosis of appendicular or colorectal origin. The morbidity associated with this procedure is significant (30-52%). This modality is also routinely used in other peritoneal diseases with improvement of outcome. The aim of this study was to analyze the morbidity and mortality associated with this procedure. **Material & Methods**: Thirteen patients had cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a period from May 2011 to March 2013 and were followed up prospectively. Demographic, pathologic, and surgical variables were recorded. The Clavien-Dindo classification was used to assess surgical complications. The main outcome variable was 30-day morbidity and mortality. Descriptive statics were used. **Results**: The mean patient age was 52.4 ± 11.1 years. The most common diagnosis was epithelial ovarian cancer (46.2%). Most patients had an adequate preoperative functional status (77% with ECOG 0). Mean hospital stay was 13.5 ± 11.2 days and 2.7 ± 4.2 days in the intensive care unit. Major morbidity (Clavien-Dindo III or IV) observed in this series was 23%, with 0% mortality. **Conclusion**: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a feasible option with acceptable morbidity and mortality for selected patients with peritoneal carcinomatosis in Mexico. (REV INVEST CLIN. 2015;67:39-45)
Corresponding author: Heriberto Medina-Franco, herimd@hotmail.com

Key words: Cytoreductive surgery. Hyperthermic intraperitoneal chemotherapy. Peritoneal carcinomatosis.

Corresponding author:
*Heriberto Medina-Franco
Department of Surgery
Instituto Nacional de Ciencias Médicas y Nutrición
Salvador Zubirán
Vasco de Quiroga 15, Colonia Sección XVI
Tlalpan C.P. 14000, México D.F.
E-mail: herimd@hotmail.com

Received for publication: 27-09-2013
Accepted for publication: 16-10-2014

INTRODUCTION

Tumors that occur in the abdominal cavity can spread by three different routes: lymphatic, hematogenous and transcoelomic. Peritoneal carcinomatosis is a manifestation of the progression of these tumors when they spread through the transcoelomic route, which is characterized by the presence of multiple nodules composed of cancer cells scattered all across the peritoneal cavity; these nodules coalesce to form plaques, masses or clusters that cover the entire peritoneal surface[1].

Peritoneal carcinomatosis was associated with advanced disease and a poor prognosis in patients. Treatment for this condition was basically limited to supportive and palliative care. Surgery did not play an important role in its treatment other than to relieve the symptoms arising from large tumor masses or bowel obstruction secondary to these intraperitoneal adhesions. It was not until 1995, when P. Sugarbaker described the first peritonectomy procedures in an attempt to eradicate all traces of peritoneal carcinomatosis, that surgery began to take on an important role in this disease[1,2].

Before therapeutic approaches for the local control of peritoneal carcinomatosis were developed, the overall survival rate of patients was limited. Survival depends on the location of the primary tumor and stage of peritoneal carcinomatosis. Median survival for patients with tumors of gastric origin was 3.1 months and for those with colorectal tumors it was 5.2 months[3].

New surgical techniques for the local control of peritoneal carcinomatosis have been developed recently. This approach consists of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC), which aims to completely eradicate macroscopic peritoneal disease with CRS and microscopic disease with HIPEC[4-6]. The rationale for administering chemotherapy through the intraperitoneal route is the safety of this route; it has also been observed that it allows drug penetration between 0.5 to 1 mm deep, absorption of the chemotherapeutic agent through the peritoneal, and tumor vasculature is greater and reaches high local and systemic concentrations in addition to the direct impact that hyperthermia has on cancer cells[7].

This multimodal approach has been used to treat a variety of diseases that involve peritoneal carcinomatosis such as ovarian, gastric, and colorectal cancers, pseudomyxoma peritonei, and malignant peritoneal mesothelioma[8].

The results of this treatment are encouraging; studies on the survival of patients with peritoneal carcinomatosis secondary to various cancers who were treated with CRS and HIPEC have been conducted. In ovarian cancer, survival has improved to 30.4 months[9], and in malignant peritoneal mesothelioma, survival is reported to be 53 months[4,7,10]. It is important to mention the study by Verwaal et al. that compared survival in patients with peritoneal carcinomatosis of colorectal cancer origin who received standard treatment with that of patients who received CRS and HIPEC. It was found that mean survival was 12.6 months in the standard therapy group and 22.3 months in the group of patients who received CRS and HIPEC[11].

Although there are high expectations for improvement in the overall survival rate of patients with peritoneal carcinomatosis, special attention must be paid to morbidity and mortality associated with CRS and HIPEC. Cytoreductive surgery itself is a procedure with substantial morbidity and mortality as it involves all four abdominal quadrants. Of all the complications that can occur, bleeding has been reported as one of the most frequent and significant. In addition to the complications associated with CRS, those related to the direct exposure of a hyperthermic solution to the peritoneal cavity and the toxicity of the chemotherapy drugs used in the process should be taken into account. Among the complications associated with the toxicity of the chemotherapeutic drugs that have been reported are the hematologic toxicities of oxaliplatin and mitomycin C[12-15].

There have been studies reporting on the morbidity and mortality associated with CRS and HIPEC. Reports on morbidity and mortality from specialized centers show morbidity ranging from 12 to 52%. Factors associated with increased morbidity were the extension of the carcinomatosis, duration of surgery, number of previous peritonectomy procedures, number of anastomoses performed, and the chemotherapy doses used. The perioperative mortality rates reported went from 0 to 17% at high-volume centers and from 0.9 to 5.8% for institutions with a lower volume of patients[12,13,16].

The combination of CRS and HIPEC is a treatment that has been in use since 2011 at the Instituto

Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) in Mexico City. The aim of this paper is to analyze morbidity and mortality in this institution's initial experience with this form of treatment.

MATERIAL AND METHODS

Patient selection

All of the cases were discussed during multidisciplinary meetings attended by staff members from the departments of medical oncology, radiology, and other specialties involved in the treatment of the patients. The selection criteria were as follows:

– Having a clinical, radiological and pathological diagnosis of peritoneal carcinomatosis (All patients had to have at least one CT scan with oral and intravenous contrast in the preoperative evaluation and histological confirmation of the disease)

– Eastern Cooperative Oncology Group (ECOG) performance status of 0-2;

– Absence of metastatic visceral disease (liver parenchyma or extra-abdominal metastases e.g. lung);

– High potential for complete resection of the tumor (e.g. without involving the celiac trunk and other major arteries; this criterion was left up to the surgeon who was to perform the cytoreductive surgery).

Cytoreductive surgery

The goal of CRS was to remove all visible disease in every case. The surgery consisted of the removal of all gross tumors and involved organs, peritoneum, or tissue deemed technically feasible and safe for the patient. Following standard procedure, a supra/infra umbilical midline incision was made, from the xiphoid process to the symphysis pubis to access the abdominal cavity. The first step in all the surgeries was to perform adhesiolysis in order to determine the distribution of all of the gross disease. We then proceeded to evaluate the peritoneal carcinomatosis using the Peritoneal Cancer Index (PCI)[17]. Supramesocolic omentectomy was performed in all cases where it had not been previously done. Peritonectomy was performed only in those areas where there was visible disease. Status following CRS was classified according to the following criteria: R0: complete removal of all visible tumor; R1: minimal residual tumor, nodule(s) measuring 0.5 cm or less; and R2: gross residual tumor, nodule(s) greater than 0.5 cm.

Hyperthermic intraperitoneal chemotherapy

In every case the patient's core temperature was monitored continuously (esophageal thermometer). After CRS was complete, perfusion was performed with 24 French Silastic® catheters joined with a Y-connector, with in lines at the bottom of the surgical wound with tips inserted in both hemidiaphragms for the inflow catheters and exit through dual ports at the top of the surgical wound to catheters placed along both pelvic and paracolic gutters for outflow. Temperature probes were placed at both ends to monitor the inflow and outflow temperatures. The skin incision was closed temporarily with a running 0 Prolene® suture to prevent leakage of the perfusate fluid. A perfusion circuit was established with about 3 liters of crystalloid solution (usually Hartmann's solution) maintaining a flow rate of about 1 l/min with a roller pump used for extracorporeal circulation by the perfusionist during cardiac surgery (GTG). The circuit was established using a roller pump, a heat exchanger, and the patient. After the circuit was established and the outflow had reached a temperature higher than 39°C, chemotherapy drugs were added to the perfusate fluid. A maximum inflow temperature of 43°C was set, with a target outflow temperature of 40°C. The abdomen was gently massaged to improve the chemotherapy drug distribution to all peritoneal surfaces. The perfusion time after the addition of chemotherapy was 90 minutes. Mitomycin C (40 mg) was used for tumors of gastrointestinal origin and carboplatin (1000 mg/m^2) for tumors of ovarian origin. At the end of the perfusion, laparotomy was performed again to drain the fluid, the area was washed thoroughly with saline (at least 5 liters) at room temperature, the required anastomoses were performed, hemostasis verified, and the abdominal wall closed in a conventional manner.

Monitoring of the patients

As part of the protocol, all of the patients were transferred to the intensive care unit (ICU) after the cytoreductive surgery and HIPEC. Complications were

Table 1. Description of the indication for cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy, with clinical stage, organs resected during cytoreduction, Peritoneal Cancer Index score at the time of cytoreduction, the neutrophil-lymphocyte ratio, progression-free survival (*in months*), overall survival (in months) and the current status of the patients

ID	Age	Indication	PCI	NLR	IC	Resected organs	PFS	OS	Status
1	63	Ovarian (IIIC)	9	1.2	Bladder injury	BSOH, right diaphragm peritonectomy, omentectomy	10	15	NED
2	60	Ovarian (IIIC)	24	0.9	NC	Cytoreduction for recurrence + HIPEC	5	47	AWD
3	50	Ovarian (IIIC)	6	0.7	NC	SOB, HHD, Appendectomy, omentectomy	15	17	NED
4	63	Appendiceal	10	0.7	NC	Omentectomy, right hemicolectomy, right diaphragm peritonectomy	14	20	NED
5	46	Colon (IV)	16	3.8	NC	Omentectomy, splenectomy, wedge resection of the liver	8	19	DOD
6	47	Ovarian (IIIC)	6	4.0	NC	Cytoreduction for recurrence + HIPEC	3	26	AWD
7	34	Appendiceal	11	2.5	NC	Hemicolectomy + BSOH + splenectomy	9	11	NED
8	55	Gastric (IV)	2	12.4	NC	Partial gastrectomy + duodenectomy + Cholecystectomy (2nd time with HIPEC)	1	10	AWD
9	62	Appendiceal	20	4.6	Gastric perforation	Partial colectomy + splenectomy + distal pancreatectomy + Omentectomy	3	3	NED
10	59	Peritoneal	1	0.3	NC	BSOH + appendectomy + omentum	4	ND	AWD
11	41	Appendiceal	3	3.7	NC	Right hemicolectomy	3	7	NED
12	31	Ovarian (IIIC)	12	1.0	NC	BSOH	3	11	NED
13	60	Ovarian (IV)	14	1.8	NC	BSOH, appendectomy, omentectomy, peritonectomy	11	42	AWD

NLR: neutrophil-lymphocyte ratio; HIPEC: hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal Cancer Index; IC: intraoperative complications; PFS: progression-free survival in months from the date of CRS and HIPEC; OS: overall survival; ND: not determined; NED: no evidence of disease; AWD: alive with disease; DOD: dead of disease; BSOH: bilateral salpingo-oophorectomy and total hysterectomy; HHD: hypertensive heart disease; SOB: shortness of breath; NC: no complications.

prospectively recorded on a daily basis throughout the patient's hospital stay. After discharge, the patients went for check-ups every three months at the INCMNSZ out-patient clinic, where they were evaluated clinically, radiologically (CT scan), and through laboratory tests (tumor markers and general tests). Here status of their disease was evaluated and they were classified into four groups: no evidence of disease, alive with disease, dead from disease, or dead from other causes.

Statistical analysis

Analyses were performed using Stata 12.1 software. For continuous variables, means and medians and measures of dispersion in accordance with their distribution were calculated. For categorical variables, frequencies were calculated and expressed as percentages.

RESULTS

Thirteen patients were included, three men (23%) and 10 women (77%) with a mean age of 52.4 ± 11.1 years, in the period from May 2011 to March 2013. The main indications were for: epithelial ovarian carcinoma in six patients (46%), mucinous adenocarcinoma of the appendix in four patients (31%), colon cancer in one patient (8%) and gastric cancer in one patient (8%). Ten (77%) of the 13 patients had previously received systemic chemotherapy. Comorbidity was assessed using the Charlson Comorbidity Index and 77% (10 patients) had a score of 8 while scores of 9, 10, and 12 were seen in the rest of the individuals. Most of the patients (10) had an adequate presurgical ECOG performance status of 0 (77%), average albumin of 3.67 ± 0.72 mg/dl and preoperative hemoglobin levels averaged 11.51 ± 1.38 mg/dl. The average score on the Peritoneal Cancer Index (PCI) was 10.3 ± 6.9 (range 1-24). The main characteristics of each patient are summarized in table 1, in which progression-free survival times are measured in months from the date of CRS and HIPEC. In the case of the patient with stage IV colorectal cancer on whom omentectomy, splenectomy, and wedge resection of the liver were performed, we have to explain that the wedge resection was performed because there were multiple tumor implants in Glisson's capsule without involvement into the liver parenchyma.

Table 2. The Clavien-Dindo classification of surgical complications.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics, and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention.
III a	Intervention not under general anesthesia.
III b	Intervention under general anesthesia.
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
IV a	Single organ dysfunction (including dialysis)
IV b	Multiorgan dysfunction

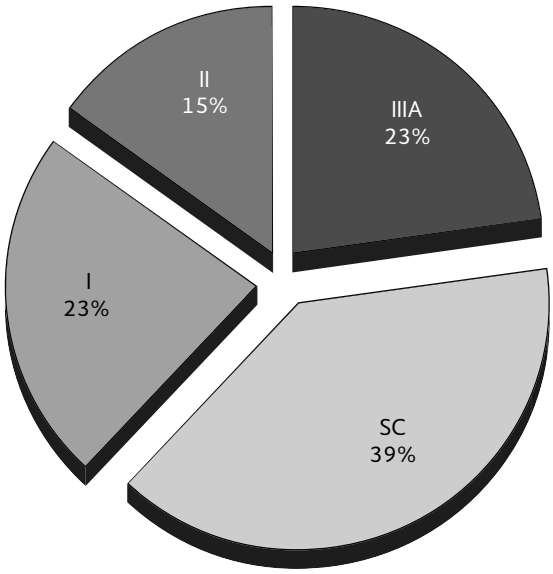
*Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, transient ischemic attack not included.
CNS: central nervous system; ICU: intensive care unit.
Adapted from Dindo, et al.[17].

Operative variables

Operative time was on average 150.1 ± 369 minutes (range 180-690 minutes). The average blood loss was 645.8 ± 443.9 ml, eight of the 13 patients did not required transfusions, while one patient required 33 bags of packed red blood cells and four packs of fresh frozen plasmas (the patient who had multiple organ resection bled 1,300 ml with an operative time of 610 min).

There was no mortality at 30 days. The only two intraoperative complications observed were a bladder lesion and a gastric perforation that were repaired intraoperatively. The Clavien-Dindo classification[18] was used to evaluate surgical complications (Table 2); the complications are shown in figure 1. The average length of hospital stay was 13.5 ± 11.2 days and the average length of stay in the ICU was 2.7 ± 4.2 days (range 0-16 days). Most of the patients went from the operating room to the ICU where length of stay was variable depending on their clinical course.

Figure 1. The pattern of complications observed in accordance with the Clavien-Dindo classification[17].



DISCUSSION

Peritoneal carcinomatosis is a public health problem in Mexico. In recent decades we have studied strategies to combat this illness. Three multicenter, randomized, phase III studies have already shown that intraperitoneal chemotherapy is superior to standard intravenous chemotherapy for the management of advanced ovarian cancer[19]. It has been observed that the intraperitoneal administration of cisplatin as primary chemotherapeutic agent after cytoreductive surgery increases progression-free and overall survival by 20-30%[20]. This is relevant because most patients with this disease present at an advanced stage (stage III or IV)[20]. Likewise, it has been observed that this approach gives good results in patients with advanced colorectal cancer, gastric cancer, peritoneal mesothelioma, and cancer of the appendix[21].

The number of cases of patients with peritoneal carcinomatosis at the INCMNSZ has allowed us to use this combination of therapies in selected patients. In the cases we report here, the Clavien-Dindo classification[18] was used to assess postoperative complications. In every case, CRS and HIPEC were performed successfully. There were no complications in 39% of cases. Grade I complications were recorded in 23% of cases and classified in this way, mainly because of

Table 3. Morbidity related to cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy compared to other institutions

Main author	Major morbidity	Reoperation	Sepsis	Fistula	Abscess	Anastomotic leaks
Elias, et al.[23]	52%	23%	NR	23%	8%	0%
Van Leeuwen, et al.[24]	43%	18%	8%	5%	9%	4%
Rufian, et al.[25]	36%	6%	0%	0%	0%	0%
Gusani, et al.[26]	30%	NR	4%	2%	4%	7%
Present series	23%	0%	0%	0%	7.7%	0%

NR: not reported.
Adapted from Chua, et al.[20].

Table 4. Perioperative factors and mortality related to cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy compared to other institutions

Main author	Average length of hospital stay	Stay in ICU	Deaths related to the procedure	Mortality	Causes
Glehen, et al.[27]	11.8	NR	7	3.2	*Septic shock, peritonitis, PTE, multiorgan failure, aplastic anemia, acute renal failure*
Elias, et al.[23]	24	NR	4	4	*Aspiration pneumonia, ischemic bowel necrosis*
Van Leeuwen, et al.[24]	15	1	1	1	*Cerebral infarction*
Rufían, et al.[25]	11	NR	0	0	-
Gusani, et al.[26]	12	3	2	1.6	*Dead of disease, unknown*
Sugarbaker, et al.[28]	21	NR	7	2	*Systemic inflammatory response, fistula, PTE, neutropenia*
Present series	13.5	2.7	0	0	*Abdominal sepsis*

ICU: intensive care unit: NR: not reported; PTE: pulmonary thromboendarterectomy.
Adapted from Chua, et al.[20].

persistent nausea, vomiting, and difficult to control abdominal pain. Grade II complications accounted for 15% of those observed, in which a case with hemodynamic instability requiring vasopressor therapy and blood transfusions was reported. Grade III complications made up 23% of cases; we observed a patient with bowel obstruction that resolved with conservative management and a patient with a PCI score of 20 who required multiple organ resection, which was complicated by a gastric perforation that was repaired intraoperatively. The patient developed an intra-abdominal collection, requiring intravenous antibiotic therapy and interventional radiology drainage (which is why it was classified as Clavien), with a total hospital length of stay of 38 days.

It is important to note that grade I complications (23%) are expected in surgery of this magnitude and may be considered to be part of the normal postoperative course for this procedure, i.e. excluding grade I and II complications, the greatest morbidity in this series was 23% with 0% mortality.

The morbidity and mortality rates reported at high-volume centers make up 12-52 and 0.9-5.2%, respectively, of outcomes[21]. The main factors associated with increased morbidity include the patient's prior functional status, comorbidities, the extent of the surgical cytoreductive procedure, the number of anastomoses, and dose of chemotherapy[21]. The morbidity and mortality rates we observed in our institution are comparable to those of high-volume centers (Table 3).

The main predictors of morbidity at our institution were a higher score on the peritoneal carcinomatosis index and the actual extent of surgery. Table 4 provides a comparison of the perioperative factors that we observed at our institution and those at institutions with more experience in this procedure. The complications associated with this procedure are similar to those of most gastrointestinal surgery, such as pancreaticoduodenectomy (Whipple surgery) and colon procedures[21].

Another factor that has proved of great importance to reduce the morbidity and mortality of this procedure is the learning curve for surgeons at the hospitals where it is performed. The recommendations of some reports focus on the importance of direct supervision by an experienced surgeon at the beginning of the learning process, and that there subsequently be at least two trained surgeons on the surgical team performing the procedure[13,22].

To conclude, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is a procedure that can be performed with low morbidity and mortality outcomes at our Institute.

ACKNOWLEDGEMENT

The authors want to recognize Héctor Martínez-Said, M.D., surgical oncologist at the National Cancer Institute in Mexico City for his valuable support to began the HIPEC program at our Institution.

REFERENCES

1. Sugarbaker PH. Overview of Peritoneal Carcinomatosis. Cancerologia. 2008;3:119-24.
2. Sugarbaker PH. Peritonectomy Procedures. Ann Surg. 1995; 221:29-42.
3. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;1:358-63.
4. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: Multi-institutional experience. J Clin Oncol. 2009;27:6237-42.
5. Sugarbaker PH. Carcinomatosis--Is Cure an Option? J Clin Oncol. 2003;21:762-4.
6. Roviello F, Pinto E, Corso G, et al. Safety and potential benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal carcinomatosis from primary or recurrent ovarian cancer. J Surg Oncol. 2010;102:663-70.
7. Rao G, Crispens M, Rothenberg ML. Intraperitoneal chemotherapy for ovarian cancer: Overview and perspective. J Clin Oncol. 2007;25:2867-72.
8. Golse N, Bakrin N, Passot G, et al. Iterative procedures combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal recurrence: Postoperative and long-term results. J Surg Oncol. 2012;106:197-203.
9. Di Giorgio A, Biacchi D, Sibio S, et al. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer. 2008;113:315-25.
10. Reichman TW, Cracchiolo B, Sama J. Cytoreductive surgery and intraoperative hyperthermic chemoperfusion for advanced ovarian carcinoma. J Surg Oncol. 2005;90:51-6.
11. Verwaal Vic, van Ruth S, de Bree Eelco. et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737-43.
12. López-Basave HN, Morales-Vásquez F, Ruiz Molina JM, et al. Morbidity and mortality of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: national cancer institute, Mexico city, Mexico. ISRN oncology. 2011;2011:526384.
13. Mohamed F, Moran BJ. Morbidity and mortality with cytoreductive surgery and intraperitoneal chemotherapy. Cancer J. 2009; 15:196-9.
14. Kusamura S, Dominique E, Baratti D, et al. Drugs, carrier solutions and temperature in hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2008;98:247-52.
15. Feldman AL, Libutti SK, Pingpank JF, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol. 2003;21:4560-7.
16. Younan R, Kusamura S, Baratti D, et al. Morbidity, toxicity, and mortality classification systems in the local regional treatment of peritoneal surface malignancy. J Surg Oncol. 2008;98:253-7.
17. González-Moreno S, Ortega-Pérez G, González-Bayón L. Indications and patient selection for cytoreductive surgery and perioperative intraperitoneal chemotherapy. J Surg Oncol. 2009;100:287-92.
18. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
19. Markman M. Intraperitoneal chemotherapy of ovarian cancer: A review, with a focus on practical aspects of treatment. J Clin Oncol. 2006;24:988-94.
20. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet. 2009;374:1371-82.
21. Chua TC, Yan TD, Saxena A, et al. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? Ann Surg. 2009;249:900-7.
22. Kusamura S, Baratti D, Virzi S, Bonomi S. Learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies: analysis of two centres. J Surg Oncol. 2013;107:312-19.
23. Elias D, Goere D, Blot F, et al. Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43 degrees C after compete cytoreductive surgery: mortality and morbidity in 106 consecutive patients. Ann Surg Oncol. 2007;14:1818-24.
24. Van Leeuwen BL, Graf W, Pahlman L, et al. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. Ann Surg Oncol. 2008;15:745-53.
25. Rufian S, Muñoz-Casares F, Briceño J, et al. Radical surgery-peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. Ann Surg Oncol. 2006;94:316-24.
26. Gusani NJ, Cho SW, Colovos C, et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol. 2008;15:754-63.
27. Glehen O, Osinsky D, Cotte E, et al. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: Morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol. 2003;10:863-9.
28. Sugarbaker PH, Alderman R, Edwards G, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol. 2006;13:635-44.