Journal of BUON **14:** 259-264, 2009

ORIGINAL ARTICLE

Morbidity and mortality of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal carcinomatosis

J. Spiliotis[1], A. Rogdakis[1], A. Vaxevanidou[2], A. Datsis[1], G. Zacharis[1], A. Christopoulou[3]

[1]Department of Surgery and [2]Department of Anesthesiology, Mesolongi General Hospital, Mesolongi; [3]Department of Medical Oncology, St. Andrew General Hospital, Patras, Greece

Summary

Purpose: *Peritoneal carcinomatosis (PC), which has been regarded as a lethal condition, may now be treated, achieving a long-term disease-free survival with cytoreductive surgery by treating macroscopic tumor seeding and hyperthermic intraperitoneal chemotherapy (HIPEC) by treating residual microscopic disease. The purpose of this study was to analyse the morbidity and mortality of this procedure.*

Methods: *A total of 39 consecutive patients were included in this retrospective study. After complete resection of the PC, HIPEC was performed via the coliseum technique. The chemotherapeutic agents used depended on the tumors' histology.*

Results: *Postoperative mortality and morbidity rates were 5.1% (2/39) and 43.5% (17/39), respectively. The most frequent complications were pulmonary complications (31%), gastrointestinal fistulas (20%), hematologic toxicity (16%) and postoperative bleeding (11%). Statistical correlations were evidenced between morbidity and PC index ($p<0.004$), duration of surgery ($p<0.001$) and blood loss ($p<0.001$).*

Conclusion: *This approach has resulted in a relatively high but acceptable percent of adverse events considering the expected advantage for survival.*

Key words: cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal carcinomatosis

Introduction

PC is a common way of spread of cancers of gastrointestinal origin, gynecologic tumors and occasionally of cancers from other primary sites. PC is a major cause of decline in functional status and the quality of life, presenting as pain, ascites and bowel obstruction and is a major cause of treatment failure and death in these patients [1].

On the other hand, efforts to optimize PC outcomes with combination of surgery (treatment of macroscopic disease) and HIPEC (treatment of microscopic disease) have shown a prolonged survival in selected patients [2,3].

This study presents the preliminary results from 39 patients with PC, treated with cytoreductive surgery and HIPEC, in terms of morbidity and mortality in an experienced peritoneal carcinomatosis national treatment center.

Patients and methods

This retrospective study included 39 cancer patients treated for PC from July 2005 to July 2008.

Inclusion criteria: age ≤80 years; peritoneal cancer index (PCI) ≤ 20; primary malignancy from ovary, colon, stomach, appendix (pseudomyxoma peritonei); and American Society of Anesthesiologists (ASA) physical status score P1-P2.

Exclusion criteria: age >80 years; PCI >21; primary cancer other than the previously reported; ASA physical status score ≥P3; and metastases outside the peritoneal surfaces (extra-abdominal, parenchymal or bulky retroperitoneal disease).

ASA physical status score includes the following categories: P1: a normal patient, P2: a patient with mild systemic disease, P3: a patient with severe systemic disease, P4: a patient with severe systemic disease that is a constant threat to life, P5: a moribund patient who

Correspondence to: John D. Spiliotis, MD, PhD. Papadiamanti 2, Ag. Vasileios, 26504 Rion, Patras, Greece. Tel: +30 2610 995 982, E-mail: jspil@in.gr
Received 31-07-2008; Accepted 25-10-2008

is not expected to survive without the operation, P6: a declared brain-dead patient whose organs are being removed for donor purposes.

PCI is determined at the time of surgical exploration of the abdomen and pelvis. PCI quantitatively combines the distribution of tumor throughout 13 abdominopelvic regions with a lesion size score. Two transverse and two sagittal planes divide the abdomen into 9 regions. The upper transverse plane is located at the lowest aspect of the costal margin, and the lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into 3 equal sectors. The lines define 9 regions, which are numbered in a clockwise direction with 0 at the umbilicus and 1 defining the space beneath the right hemidiaphragm. Regions 9 through 12 divide the small bowel into upper and lower jejunum and upper and lower ileum. To make the PCI tool more quantitative and reproducible, each region is not only defined by the surface landmarks as previously described, but can also be defined by the anatomic structures found in each region. The lesion size (LS) score is determined after complete lysis of all adhesions and complete inspection of all parietal and visceral peritoneal surfaces within the abdominopelvic regions. LS-0 indicates no implants seen. LS-1 indicates implants less than 0.25 cm. LS-2 indicates implants between 0.25 and 2.5 cm. LS-3 indicates implants greater than 2.5 cm. It refers to the greatest diameter of tumor implants that are distributed on the peritoneal surfaces. Primary tumors or localized recurrences at the primary site that can be removed definitively are excluded from the assessment. If there is a confluence of disease matting abdominal or pelvic structures together, this is automatically scored as LS-3 even if it is a thin layer of cancerous implants.

The lesion sizes are then summated for all abdominopelvic regions. The extent of the disease within all regions of the abdomen and pelvis is indicated by a numerical score from 0 to 39.

Morbidity and mortality were assessed according to the Washington Cancer Institute system, as previously described by Sugarbaker et al. Table 1 summarizes all the possible postoperative adverse events [4]. This system was constructed to specifically evaluate patients treated for PC and consisted of 47 adverse events arranged in 8 categories by organ system.

For each adverse event, a grade is assigned. For grade I adverse event, the diagnosis is established, but no treatment is required; for grade II, the adverse event requires medical treatment. For grade III, the adverse event is potentially serious but is resolved conservatively, often with invasive CT or ultrasound-guided diagnostic or therapeutic intervention. For grade IV, the adverse event requires reoperation or intensive care unit. Grade V adverse event leads to patient's death (Table 2).

Table 1. Peritoneal surface malignancy: postoperative adverse events correlated with morbidity (modified from Sugarbaker et al. [4])

Systems/organs	*Adverse event*
Gastrointestinal	Postoperative bleeding
	Anastomotic leak
	Enteric fistula
	Pancreatic fistula
	Pancreatitis
	Biliary fistula
	Oral pain/ulcer
	Stomia complications
	Vomiting
	Diarrhea
	Ascites
	Other
Pulmonary	Pleural effusion
	Pneumonia
	ARDS
	Chest tube complications
	Other
Catheter status	Line sepsis
	Line thrombosis
	Insertion pneumothorax
	TPN intolerance
	Other
Cardiovascular	Rhythm disturbances
	Hypotension
	Pulmonary embolism
	Myocardial ischemia
	Venous thrombosis
	Pulmonary edema
	Cardiotoxicity
Genitourinary	Urinary tract infection
	Urine leak
	Hematuria
	Other
Hematological	Neutropenia
	Thrombocytopenia
	Anemia
	PT, PTT elevation
Neurological	Orientation/ intellect
	State of communication
	Stroke
	Other
Infection	Intra-abdominal sepsis
	Wound infection
	Other

ARDS: acute respiratory distress syndrome, TPN: total parenteral nutrition, PT: prothrombin time, PTT: partial thromboplastin time

The aim of operation in these patients was to render the abdomen and pelvis free of macroscopic disease. This required a series of peritonectomies and visceral resections, as previously described [5].

The peritonectomy procedures are classified as greater and lesser omentectomy, cholecystectomy,

Table 2. Peritoneal surface malignancy: postoperative severity grade of adverse events (From Sugarbaker et al. [4])

Grade	*Criteria*
0	Absence of events
I	Diagnosis established: no intervention required for resolution
II	Diagnosis established: medical treatments sufficient for resolution
III	Diagnosis established: conservative measures, like radiological intervention required for resolution
IV	Diagnosis established: Urgent return to the operating room or intensive care unit
V	Postoperative death

stripping of the omental bursa, splenectomy, left and right upper quadrant peritonectomy and pelvic peritonectomy. All these procedures are associated with the appropriate hollow viscera resections and reconstructions.

Preoperatively, a mechanical bowel cleansing with an osmotic laxative was carried out in all patients. Intrajugular or subclavian central venous catheters were used during surgery and the postoperative period in all patients. One hour before the operation cefazolin 1 g every 4 h and metronidazole 500 mg every 4 h were administered intravenously and continued for the first week postoperatively.

Prophylaxis for venous thrombosis and pulmonary embolism was limited to the use of compression devices throughout the hospitalization. Suction drains remained in place after surgery in all patients, one in the right hemidiaphragm, one in the left, and two in the pelvis.

Thoracostomy tubes were placed whenever a patient had a diaphragmatic peritonectomy and all tubes were removed in the 2nd postoperative week as drainage diminished. All patients received postoperative total parenteral nutrition (TPN) until their caloric intake was adequate to allow its discontinuation.

After the cytoreductive operation was complete and before intestinal anastomoses we administered HIPEC using the open abdomen technique which was recently described by our team [3]. One inflow catheter was placed below the epigastrium between the small bowel loops, and 3 outflow catheters were positioned in the right and left subphrenic area and in the cul-de-sac. Temperature probes were placed next to the outflow catheters. Up to 3 liters of dextrose 5% were used to fill the abdominal cavity before the circulation of the fluid was started. A heater device (Thermochem, ST Medical, Greece) with a pump allowed a continuous distribution of the fluid within the abdominal space at 42° C.

The chemotherapy used depended on the tumors' histology: cisplatin (80 mg/m^2) plus doxorubicin (15 mg/m^2) for ovarian cancer; mitomycin (15 mg/m^2) plus cisplatin (50 mg/m^2) for gastric cancer; and mitomycin (15 mg/m^2) or oxaliplatin (360 mg/m^2) plus irinotecan (360 mg/m^2) for colorectal cancer. All these drugs were added in the heated circulation and maintained for 90 min except oxaliplatin and irinotecan protocol in colorectal cancer which were used for 30 min.

Results

Demographic data

The median age of 39 patients was 58 years (range 20-74). Seventy-seven percent of the patients had no prior abdominal surgery. Table 3 shows the kinds of malignancies treated.

The median number of peritonectomy procedures was 4 (range 2-6).

Seventeen percent of the patients had a temporary ileostomy and 11% a temporary colostomy. Thirty percent of the patients had positive mesenteric lymph nodes.

The median duration of the operation, including HIPEC, was 7 h and 50 min (range 5-12.30 h). The mean blood product transfusion requirements per patient was 2.2 units of red blood cells (range 0-4) and 4 units of fresh frozen plasma (range 0-8).

Regarding the completeness of cytoreduction (CC), 62% of the patients achieved a CC_0 (no macroscopic residual disease) score, 23% had a CC_1 score (no residual nodule greater than 5 mm in diameter) and 15% a CC_2 score (diameter of residual nodules greater than 5 mm).

Mortality

Two (5.1%) patients died. One patient died of pulmonary infection due to candida albicans and one of intraabdominal sepsis due to fistula formation.

Table 3. Malignancies treated

Kind of tumor	*n*	*%*
Ovarian cancer	20	51.2
Gastric cancer	5	12.8
Colon cancer	7	17.9
Rectal cancer	4	10.3
Peritoneal mesothelioma	1	2.0
Pseudomyxoma peritonei	2	5.2
Total	39	

Morbidity/adverse events

Grade III-IV adverse events occurred in 17 out of 39 (43.5%) patients (Table 4). In many of these patients there was more than a single grade III or IV event. Venous line sepsis occurred in 11% of the patients and hematologic toxicity in 16%. Pulmonary embolism occurred in 10.2% of the patients between the 22nd to 43rd postoperative day and required re-hospitalization. Other pulmonary complications, such as acute respiratory distress syndrome (ARDS), pleural effusion, pneumonia, and chest tube complications occurred in 31% of the patients.

The major predisposing factors for adverse events were the general condition of the patient, preexisting chronic conditions, PC index ≥20 ($p<0.004$), the duration of the operation ($p<0.001$) and the volume of blood transfusion (>6 units; $p<0.001$) (Table 5). Postoperative bleeding requiring reoperation (grade IV event) occurred in 11% of the cases.

Table 4. Morbidity after cytoreductive surgery plus HIPEC in our patients

System/organ	*Patients n (%)*	*Grade*
Gastrointestinal (34%)		
Postoperative bleeding	11 (28.2)	IV
Anastomotic leak	2 (5.1)	III
	1 (2.5)	IV
Enteric fistula	6 (15.4)	III
	1 (2.5)	IV
Pancreatic fistula	1 (2.5)	IV
Pancreatitis	1 (2.5)	III
Pulmonary (31%)		
Pleural effusion	3 (7.6)	III
Pneumonia	2 (2.5)	III
	1 (5.1)	IV
ARDS	4 (10.2)	IV
	1 (2.5)	III
Catheter status (11%)		
Line sepsis	5 (12.8)	III
Line thrombosis	1 (2.5)	III
Cardiovascular (25%)		
Rhythm disorders	8 (20.5)	III
	2 (5.1)	IV
Pulmonary embolism	3 (7.6)	III
	1 (2.5)	IV
Genitourinary (7%)		
Urine leak	1 (2.6)	III
Infection	3 (7.6)	III
Hematuria	3 (7.6)	III
Hematological (16%)		
Neutropenia	3 (7.6)	III
	1 (2.5)	IV
Thrombocytopenia	1 (2.5)	III
Infection (7%)		
Intra-abdominal sepsis	1 (2.5)	V
Wound infection	4 (10.2)	III

Discussion

Cytoreductive surgery and HIPEC have shown that this treatment modality may result in improved survival of PC patients compared with standard treatments which consist of systemic chemotherapy combined with palliative or emergency surgery [6].

On the other hand, this procedure is associated with high morbidity and mortality and this fact has questioned if the high rate of complications limits the value of this modality as a therapeutic option [7-10].

It is well known from historical studies from Sugarbaker and other investigators that persistent cancer cells within the abdomen and pelvis are responsible for the death of 30-50% of the patients who die of disease and for quality of life consequences that result from intestinal obstruction caused by cancer recurrence at the resected site and on peritoneal surfaces. In these patients intraoperative and postoperative intraperitoneal chemotherapy before the occurrence of fibrous entrapment of the cancer cells can be expected to improve both survival and quality of life [11]. Yet the effects of this regional chemotherapy are not limited to the peritoneal

Table 5. Predisposing factors for morbidity and mortality

	Group A Morbidity / Mortality	*Group B Morbidity / Mortality*	*Statistical significance Morbidity / Mortality*
ASA P score	P1, P2 35% / 1.8%	≥ P3 38% / 2.4%	NS / NS
PCI	≤20 20% / 2.3%	>20 42% / 5.9%	p<0.004/p<0.003
Operative time	≤ 5 hours 25% / 2.1%	> 5 hours 37% / 5.6%	p<0.001/p<0.001
Blood transfusion	≤ 6 units 27% / 3.4%	> 6 units 42% / 6.8%	p<0.001/p<0.001

ASA: American Society of Anesthesiologists physical status, PCI: peritoneal cancer index, NS: non significant

space but also impact wound healing, as can be concluded by the increased incidence of fistula formation and anastomotic leakage reported to date.

The goal of this retrospective study was to demonstrate that, despite high morbidity, cytoreductive surgery plus HIPEC can be performed with minimal mortality in specialized centers.

Abdominal complications, such as anastomotic leak or fistula formation, were the grade III and IV adverse events most observed in our study. Only 2 of 6 patients with fistulas demanded reoperation and were tabulated as grade IV event and one of them died due to this complication.

Similar findings concerning morbidity were seen in several other series with cytoreductive surgery plus HIPEC [2,12-14].

The clinical features that correlated with anastomotic leak and fistula formation were preoperative bowel obstruction and the high PC index ($p<0.004$).

To limit these complications we performed all gastrointestinal anastomoses after HIPEC and normally used proximal loop ileostomy to protect left-sided colonic anastomoses. We planned a closure within 3-4 months after the initial operation under local anesthesia.

In our study grade III and IV hematological toxicity was 16% of the patients treated, a fact showing that intraperitoneal chemotherapy may have profound systemic manifestations. The immune suppression from leucopenia/neutropenia combined with septic surgical complications can be a lethal event [15]. The rate of hematologic toxicity after HIPEC varies depending on the cytotoxic drugs used during intraperitoneal chemotherapy.

The rate of systemic toxicity may be attributable to the use of mitomycin C which achieves high concentrations within the peritoneal cavity and tumor with minimal systemic absorption [16]. On the other hand, severe hematological toxicity was observed in centers which use oxaliplatin combined with irinotecan in HIPEC [2].

In the absence of a major gastrointestinal complication, patients with hematological toxicity recover from neutropenia within 5-7 days with the administration of G-CSF.

Pulmonary complications are less serious but occurred in 31% of our patients. These complications are usually grade I-III and the conservative management includes oxygen administration, respiratory therapy, drainage of pleural effusions, diuretics, and antibiotics in case of postoperative pneumonia.

The more serious grade IV pulmonary complications with respiratory failure demand admission to intensive care unit, re-intubation, and mechanical ventilation and tracheostomy (Table 4).

One patient in our study developed ARDS due to candida albicans infection with co-existing neutropenia and died in the 12th postoperative day in the intensive care unit.

A high incidence of subclavian venous line infection was noted in our patients (11%); this complication was also reported by other investigators [17,18].

Sugarbaker et al. notes also an unexpectedly high incidence of thrombosis of the subclavian vein catheter [4]. However, this adverse event was not confirmed in our or other studies [15,17,18].

Cardiovascular complications are rare and in the majority of the cases are connected with pre-existing cardiovascular disease. The most common grade II adverse event was rhythm disorders in 25% of our patients. This condition may lead to sudden unexplained death [19], so prolonged cardiac monitoring is necessary in this group of patients.

Table 6 displays data from peritoneal surface malignancy treatment centers in Europe and USA in the last 5 years. Morbidity ranges from 12 to 66% and mortality from 0.9-12%.

In conclusion the management of PC with cytoreductive surgery and HIPEC demands a well-organized center with the collaboration of different specialties

Table 6. Comparison of morbidity / mortality data from different centers in USA and Europe with peritoneal surface malignancy programs 2005-2008

Author	No. of *patients*	Morbidity (%)	Mortality (%)
Schmidt et al [18] 2005	67	34	45
Kusamura et al [13] 2006	209	12	0.9
Roviello et al [19] 2006	61	35	1.6
Moran et al [20] 2006	65	40	6.2
Smeenk et al [21] 2006	103	54	11
Sugarbaker et al [4] 2006	356	19	2
Elias et al [2] 2007	106	55	4
Levine et al [22] 2007	501	43	4.8
Gusani et al [1] 2008	122	56.5	1.6
Spiliotis et al.* 2008	39	43.5	5.1

* present study

such as medical oncologist, surgeon, anesthesiologist, cardiologist, radiologist and nurse [20].

But the most important factor for a rewarding outcome is team-spirit and considering the patient not as candidate for death but as candidate for improved survival and quality of life.

References

1. Gusani N, Cho S, Colovos Ch et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol 2008; 15: 754-763.
2. Elias D, Goere D, Blot F et al. Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43° C after complete cytoreductive surgery: mortality and morbidity in 106 consecutive patients. Ann Surg Oncol 2007; 14: 1818-1824.
3. Spiliotis J, Tentes AA, Vaxevanidou A et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal carcinomatosis. Preliminary results and cost from two centers in Greece. J BUON 2008; 13: 205-210.
4. Sugarbaker P, 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; 3: 635-644.
5. Sugarbaker PH. Peritonectomy procedures. Cancer Treat Res 2007; 134: 247-264.
6. Glehen O, Osinsky D, Beaujard AC, Gilly FN. Natural history of peritoneal carcinomatosis from non gynecologic malignancies. Surg Oncol Clin N Am 2003; 12: 729-739.
7. 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: 4560-4567.
8. Shen P, Levine EA, Hall J et al. Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. Arch Surg 2003; 138: 26-35.
9. Deraco M, Baratti D, Inglese MG et al. Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. Ann Surg Oncol 2004; 11: 393-398.
10. Elias D, Blot F, El Otmany A et al. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. Cancer 2001; 92: 71-76.
11. Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol 1999; 43: 515-525.
12. 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: 863-869.
13. Kusamura S, Younan R, Boratti D et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer 2006; 106: 1144-1153.
14. Stephens AD, Alderman R, Chang D et al. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol 1999; 6: 790-796.
15. Witkamp AJ, deBree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. Cancer Treat Rev 2001; 27: 365-374.
16. Kecmanovic DM, Pavlor MJ, Ceranic MS et al. Treatment of peritoneal carcinomatosis from colorectal cancer by cytoreduction and hyperthermic perioperative intraperitoneal chemotherapy. Eur J Surg Oncol 2005; 31: 147-152.
17. Verwaal J, van Tinteren H, Ruth SV, Zoetmulder FAN. Toxicity of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol 2004; 85: 61-67.
18. Schmidt U, Dahlke M, Klempnauer J et al. Perioperative morbidity and quality of life in long-term survivors following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol 2005; 31: 53-58.
19. Roviello F, Marrelli D, Neri A et al. Treatment of peritoneal carcinomatosis by cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion: postoperative outcome and risk factors for morbidity. World J Surg 2006; 30: 2033-2040.
20. Moran BJ, Meade B, Murphy E. Hyperthermic intraperitoneal chemotherapy and cytoreductive surgery for peritoneal carcinomatosis of colorectal origin: a novel treatment strategy with promising results in selected patients. Colorectal Dis 2006; 8: 544-550.
21. Smeenk RM, Verwaal VJ, Zoetmulder FAN. Toxicity and mortality of cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei – a report of 103 procedures. Eur J Surg Oncol 2006; 32: 186-190.
22. Levine EA, Stewart J, Russel G et al. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: experience with 501 procedures. J Am Coll Surg 2007; 204: 943-953.