Cytoreductive Surgery Followed by Intraperitoneal Hyperthermic Perfusion

Analysis of Morbidity and Mortality in 209 Peritoneal Surface Malignancies Treated with Closed Abdomen Technique

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BACKGROUND. The purpose of this prospective Phase II study was to analyze morbidity and mortality of cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP) in the treatment of peritoneal surface malignancies.

METHODS. A total of 205 patients (50 with peritoneal mesothelioma, 49 with pseudomyxoma peritonei, 41 with ovarian cancer, 32 with abdominal sarcomatosis, 13 with colon cancer, 12 with gastric cancer, and 8 with carcinomatosis from other origins) underwent 209 consecutive procedures. Four patients underwent the intervention twice because of disease relapse. There were 70 men and 135 women. Mean age was 52 years (range, 22–76 yrs). CRS was performed by using peritonectomy procedures. IPHP through the closed abdomen technique was conducted with a preheated (42.5 °C) perfusate containing cisplatin + mitomycin C or cisplatin + doxorubicin.

RESULTS. Major morbidity rate was 12%. The most significant complications were 23 anastomotic leaks or bowel perforations, 4 abdominal bleeds, and 4 sepses. Operative mortality rate was 0.9%. On logistic regression model multivariate analysis, extent of cytoreduction (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.29–6.40) and dose of cisplatin for IPHP ≥ 240 mg (OR, 3.13; 95% CI, 1.24–7.90) were independent risk factors for major morbidity. Ten patients presented with Grade 3 to 4 toxicity.

CONCLUSIONS. CRS + IPHP presented acceptable morbidity, toxicity, and mortality rates, all of which support prospective Phase III clinical trials. ***Cancer* 2006;106: 1144–53.** © *2006 American Cancer Society.*

KEYWORDS: peritonectomy, intraperitoneal hyperthermic perfusion, morbidity.

The evolution of locoregional therapy in the last 2 decades has changed the paradigm that has supported management of patients affected by peritoneal surface malignancies (PSM). In fact, results from Phase II studies that tested the efficacy of combination cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP) in the treatment of carcinomatosis of various origins have been somewhat encouraging. In our previous experience with CRS + IPHP, we reported 5-year overall survival rates of 97% and 67%, respectively, for pseudomyxoma peritonei[1] and peritoneal mesothelioma.[2] Other groups have reported 5-year overall survival rates of 63.4% and 19%, respectively, in ovarian[3] and colorectal cancers.[4] Moreover, results of a Phase III trial have confirmed the superiority of CRS + IPHP in the treatment of patients with carcinomatosis from rectal cancer over other standard surgical and/or systemic chemo-

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TABLE 1
Patient Characteristics

Characteristic	No.
Total no. of patients	205
Total no. of procedures	209
Mean age (range)	52 yrs (22–76)
Male/female	70/135
Body mass index in kg/m^2 (range)	25 (15.9–40)
Histologic type distribution	
Peritoneal mesothelioma	50
Pseudomyxoma peritonei	49
Ovarian cancer	41
Abdominal sarcomatosis	32
Adenocarcinoma of the colon	13
Gastric cancer	12
Carcinomatosis from other origins	8
Performance status(ECOG)	
0	160
1	41
2	8
Carcinomatosis extension, mean PCI (range)	20 (5–39)

PCI: peritoneal cancer index.

therapy modalities.[5] More prospective randomized trials are ongoing to test the efficacy of this treatment in other tumor types.[6]

Nevertheless, CRS + IPHP still suffers from a broad range of variability, with no consensus on its various technical aspects. Thus, we attempted to make a contribution to this debate by providing results of a Phase II study in which we analyzed morbidity, toxicity, and mortality of CRS followed by IPHP (closed abdomen technique) in the treatment of patients affected by PSM.

MATERIALS AND METHODS

Patient Characteristics

All patients included in this study were treated under an institutionally approved protocol with written informed consent. The eligibility requirements for treatment were as follows: histologically confirmed diagnosis of peritoneal carcinomatosis or sarcomatosis; age $\leq$ 75 years; no distant metastasis; adequate renal, hematopoietic, and liver functions; and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Data on patient characteristics are summarized in Table 1. A total of 205 patients (50 with peritoneal mesothelioma, 49 with pseudomyxoma peritonei, 41 with ovarian cancer, 32 with abdominal sarcomatosis, 13 with adenocarcinoma of the colon, 12 with gastric cancer, and 8 with carcinomatosis from other origins) underwent 209 consecutive procedures from February 1995 to November 2004. Four patients underwent the intervention twice because of disease relapse. There were 70 men and 135 women. The mean age was 52 years (range, 22–76 yrs). The mean body mass index was 25 (range, 15.9–40). A total of 160 (75%) cases presented with an ECOG performance status of 0.

Cytoreductive Surgery

The technique of cytoreductive surgery has been described elsewhere.[7] Briefly, the surgical procedure was carried out with 1 or more of the following steps, depending on disease extension: 1) greater omentectomy, right parietal peritonectomy $\pm$ right colon resection; 2) pelvic peritonectomy $\pm$ sigmoid colon resection $\pm$ hysteroadnexectomy; 3) lesser omentectomy and dissection of the duodenal–hepatic ligament $\pm$ antrectomy $\pm$ cholecystectomy; 4) right upper quadrant peritonectomy $\pm$ Glisson capsule; 5) left upper quadrant peritonectomy $\pm$ splenectomy; 6) other intestinal resection and/or abdominal mass resection. A ball-tip electrosurgical hand piece was used to dissect the tumor on peritoneal surfaces from normal tissue.[8] Electrosurgery was used on pure cut at high voltage. The 2 mm ball-tip electrode was used for dissection on visceral surfaces, including stomach, small bowel, and colon. When more rapid tumor destruction is required, the 5 mm ball-tip can be used.

Anastomotic Techniques

Whether a partial or total gastrectomy is performed, we always use a Roux-en-Y reconstruction. In cases of partial gastrectomy, the stomach and proximal duodenum are, respectively, transected using a GIA stapler (GIA™, United States Surgical, a division of Tyco Healthcare Group LP, Pembroke, Bermuda). In case of total gastrectomy, the distal esophagus is divided 2 cm above the cardia with the scalpel. The lower part of the GIA-stapled line of the gastric remnant is then cut with scissors, and the ensuing end-to-end gastrojejunal anastomosis is hand sewn with 1 layer of extramucosal continuous polyglyconate 4-0 sutures. The distal terminolateral jejunojejunal anastomosis is also hand sewn in the same fashion as above. When a total gastrectomy is completed, a terminolateral esophagojejunal anastomosis is performed with a circular stapler usually of size 21–25 mm. A GIA stapler is applied to the remaining proximal end of the jejunal limb. The distal anastomosis is similar to the one described above.

Small bowel and colic anastomoses are always hand sewn in an end-to-end fashion using single-layer extramucosal continuous polyglyconate 4-0 or 3-0 suture. For all anastomoses, we start a running stitch on the antimesenteric border for the anterior layer and then start a second running stitch at the mesenteric

side for the posterior layer. This allows completion of the anastomosis on the free antimesenteric border, avoids the mesentery, and allows better observation of the bowel wall.

Most of the time, we, as well as other investigators, have found that the Douglas pouch area is filled with coalescing tumor implants that also include much of the sigmoid colon. A complete pelvic peritonectomy with a low anterior resection is frequently needed to completely remove these tumor implants. In a few selected cases, however, we were able to preserve the rectum and only resect the overlying visceral peritoneum, including the peritoneal reflection. In case of low anterior resection, the lower margin of bowel transection is usually below the level of the peritoneal reflection. The low colorectal anastomosis is performed with an intraluminal stapler of 29–33 mm diameter after a distal washout of the rectal remnant with a proviodine iodine. We then test the integrity of the anastomosis with air insufflation from below.

All patients who underwent intestinal resections received an anastomosis just after completion of CRS and before initiation of IPHP. Our initial policy was to perform diverting ostomies only in high-risk patients. Peritoneal carcinomatosis was quantified according to the Peritoneal Cancer Index (PCI).[9] The mean PCI was 20 (range, 6–39). Cytoreduction was classified into 3 levels according to the number of procedures performed: Level I, 1 to 2 procedures; Level II, 3 or 4 procedures; Level III, 5 procedures or more. Residual disease after surgery was classified according to Sugarbaker[9] criteria: cc-0, no residual disease; cc-1, minimal residual disease of 0–2.5mm; cc-2, residual disease of 2.5 mm–2.5 cm; cc-3, residual disease of > 2.5 cm.

IPHP Technique

After cytoreduction, 4 silicone catheters are placed in the abdominal cavity; 1 in the right subphrenic cavity, 1 in the deep pelvis, 1 in the left subphrenic cavity, and 1 in the superficial pelvic site cavity. To continuously monitor peritoneal temperature during IPHP, thermocouples are placed in the abdominal cavity. After the closed abdomen technique is performed, the skin is closed with a running suture. The catheters are then connected to the extracorporeal circuit Performer LRT®, (RAND, Medolla, MO, Italy). Intraperitoneal chemotherapy regimens were as follows: cisplatin (CDDP, 25 mg/m^2/L) and mitomycin C (MMC, 3.3 mg/m^2/L)[10] for pseudomyxoma peritonei, colorectal, and gastric carcinomatosis; cisplatin (CDDP, 43 mg/L of perfusate) and doxorubicin (Dx, 15.25 mg/L of perfusate)[11] for mesothelioma, ovarian carcinomatosis, and abdominal sarcomatosis. A heat exchanger kept the perfusate at 44 °C as it was being administered, so the intracavitary perfusate temperature was maintained at 42–43 °C. The IPHP lasted 60–90 minutes, depending on the drug schedule. After perfusion, the perfusate was quickly drained, and the abdomen closed after careful intracavitary inspection.

Study Parameters

We defined bowel complications as any of the following categories: 1, Bowel perforation; 2, anastomotic leak. A bowel perforation occurs at a site away from an anastomosis. An anastomotic leak is a breach and/or complete dehiscence at the suture line. We adopted a criteria scale, which was coined by Bozzetti et al.,[12] to grade surgical morbidity. This scale has been followed historically by the surgical department of the National Cancer Institute of Milan. It classifies the postoperative complications as G1, no complications; G2, minor self-limiting complications; G3, major complications (requiring reoperation or intensive care unit admission or interventional radiology); and G4, in-hospital mortality.[12] Grading of toxicity was performed according to World Health Organization (WHO) criteria. Dependent variables were classified in 2 groups, major or combined Grade 3/4 morbidity and combined Grade 3/4 IPHP-related toxicity. We considered only those unfavorable events (both for morbidity and mortality) occurring within 30 days after the procedure.

Independent variables were taken into consideration for potential association with postoperative major complications as follows: histology of the primary tumor (tumor of gastrointestinal origin vs. non-GI origin), gender, performance status (WHO: 0 vs. 1 or 2), age ($<$ 52 yrs vs. $\geq$ 52 yrs), body mass index ($<$ 25 vs. $\geq$ 25), previous chemotherapy, previous radiation therapy, extension of carcinomatosis, number of intestinal anastomoses ($<$ 2 vs. $>$ 2), duration of the procedure ($<$ 530 min vs. $\geq$ 530 min), extent of cytoreduction (Level 1/2 vs. 3), completeness of cytoreduction (cc 0/1 vs. 2/3), IPHP drug schedule (CDDP + MMC vs. CDDP + Dx), and dose of CDDP in the IPHP ($<$ 240 mg vs. $\geq$ 240 mg). Continuous variables were categorized in 2 classes using their mean value as cutoff.

Follow-Up and Statistical Analysis

During the postoperative period, patients were admitted to the intensive care unit, where they were evaluated daily with laboratory and instrumental examinations. They were then discharged to the surgical ward for recovery. Long-term follow-up was carried out by physical examination, tumor markers (Ca125, CEA, CA19.9), and thoracic and abdominal computed to-

mography (CT) scans every 3 months in the first year and every 6 months thereafter. Analysis of treatment-related toxicity was performed according to WHO criteria.[13] A univariate analysis of each clinical variable was performed by Fisher exact test or chi-square test to determine a probability of association with each morbidity variable. A logistic regression model was used in a multivariate analysis to determine correlation between clinical variables and morbidity variables. All clinical variables that presented a $P \leq 0.05$ were included in the model. The backward elimination method was used to determine which clinical variables best predicted the presence of morbidity. All statistical analyses were conducted using SPSS for Windows Version 8.0.0 (SPSS, Chicago, IL).

RESULTS

CRS + IPHP

We submitted 37 (17.7%), 86 (41.1%), and another 86 (41.1%) patients to Levels I, II, and III cytoreduction, respectively. The mean number of peritonectomy procedures for each patient was 4.9. Details of cytoreductive surgery are outlined in Table 2. Accordingly, 182 (87%) cases were optimally cytoreduced (cc, 0/1). The mean duration of the procedure was 532 minutes (range, 240–1320 min). The mean number of blood units received was 2.4 (range, 0–18 units). With respect to the IPHP, 84 (40.2%) and 125 (59.8%) cases received CDDP + MMC and CDDP + Dx regimens, respectively. The mean doses of drugs administered were 218 mg (range, 100–300 mg) for CDDP, 31 mg (range, 15–50 mg) for MMC, and 63 mg (range, 25–90 mg) for Dx. The mean length of intensive care unit stay was 3 days, and the mean hospitalization was 23 days (range, 7–73 days).

TABLE 2
Surgical Results with Description of Peritonectomy and Resection Procedures

Surgical procedures and results	No.
Peritonectomy	
Left diaphragm	101
Right diaphragm	106
Glissonian capsule	82
Lesser omentectomy	92
Pelvic peritonectomy	123
Greater omentectomy	148
Other surgical procedures	
Great bowel resection	132
Small bowel resection	20
Subtotal gastrectomy	8
Total gastrectomy	18
Marginal gastrectomy	3
Cholecystectomy	41
Splenectomy	71
Diaphragm resection	8
Hysterectomy	24
Bilateral oophorectomy	22
Other resections	19
Bowel anastomosis	
Esophagojejunal	18
Jejunoileal	26
Gastrojejunal	8
Ileoileal	20
Ileocolic	50
Colocolic	9
Colorectal	58
Ileorectal	2
Protective ostomy	2
Mean duration of the procedure (minutes)	532 (240–1320)
Mean No. of Blood units transfused	2.4 (0–18)
Mean No. of peritonectomy procedures/patient	4.9
Level of peritonectomy procedure (%)	
I	37 (17.7)
II	86 (41.1)
III	86 (41.1)
No. of optimally cytoreduced cases in cc0/1 (%)	182 (87)

Morbidity and Mortality

Major morbidity occurred in 25 (12%) cases. The most significant morbidities were 17 anastomotic leaks, 6 intestinal perforations, 6 with fever, 4 abdominal bleeds, and 4 sepses. Other complications were 1 pulmonary embolism, 2 with pancreatic fistula, and 1 with biliary fistula. One patient presented an acute hypotensive episode, clinically diagnosed as cardiac arrest, on the 8th day after the procedure; he was urgently resuscitated without any short- or long-term sequelae. Examples of postoperative main complications (G1-4), their anatomic location, description, and management are outlined in Table 3.

Two patients died in the early postoperative period. The first one on the 21st day after the procedure because of a duodenal perforation associated with abdominal bleeding. The second patient died on the 26th day after the procedure because of a colic perforation, bronchial bleeding, and sepsis. The overall mortality rate was 0.9%.

By univariate analysis, the following variables were proven to have a statistically significant correlation with major morbidity: male gender ($P = 0.016$), ECOG performance status ($P = 0.05$), no previous systemic chemotherapy ($P = 0.004$), carcinomatosis extension ($P = 0.027$), number of bowel anastomoses > 2 ($P = 0.028$), duration of procedure ($P = 0.014$), extent of cytoreduction ($P = 0.019$), and dose of CDDP for IPHP ≥ 240 mg ($P = 0.02$). Multivariate analysis was performed with a logistic regression model, and after the backward elimination method, no previous systemic chemotherapy (odds ratio [OR], 2.719; 95% confidence interval [CI], 0.984–7.512; $P = 0.054$), extent of cytoreduction (OR, 2.877; 95% CI, 1.292–6.404;

TABLE 3
Anatomic Location, Description, and Management of Main Complications

Type of complication	Anatomic location	No. of complications	Surgical treatment or ICU recovery	Conservative management
Anastomotic leak	Ileocolic anastomoses	7	5	2
	Small bowel anastomoses	3	1	2
	Colocolic anastomoses	3	3	0
	Colorectal anastomoses	2	1	1
	Not available	2	2	0
Digestive tract perforation	Duodenum	1	1	0
	Small bowel	3	3	0
	Colon	1	1	0
	Stomach	1	1	0
Other gastrointestinal complications	Biliary fistula	1	1	0
	Pancreatic fistula	2	0	2
	Ileus/gastric stasis	4	0	4
Pulmonary	Pneumonia	9	0	9
	Pleural effusion	4	0	4
	Pulmonary embolism	1	1	0
	Respiratory failure	1	1	0
Infectious	Abdominal infection (abscess)	3	1	2
	Sepsis	4	0	4
	Fever[a]	6	0	6
Bleeding	Abdominal	4	4	0
Other clinical complications		10	0	10

ICU: intensive care unit.
[a] Unrelated to infectious problems.

$P = 0.010$), and dose of CDDP for IPHP $\geq$ 240 mg (OR, 3.128; 95% CI, 1.239–7.900; $P = 0.016$) remained in the model (Table 3).

TOXICITY

Ten (4.8%) patients presented Grade 3/4 toxicity. There were 3 cases of G3 hematologic toxicity, 1 case with G3 gastrointestinal toxicity, 2 cases of Grade 3 nephrotoxicity, 2 cases of Grade 4 nephrotoxicity, 1 case of G4 pulmonary toxicity, and 1 case of G3 alopecia. The 2 cases of G4 nephrotoxicity were peritoneal mesothelioma patients who required hemodialysis in the postoperative period and developed chronic renal failure.

DISCUSSION

The locoregional treatment for PSM is attracting an increased interest from the scientific community. However, the procedure of CRS + IPHP is both time- and labor-intensive. The institution of a program in PSM requires not only highly specialized human resources but also complex technological facilities[14] to perform the CRS + IPHP safely, to minimize treatment-related morbidity and mortality, and to maximize their results in terms of survival and quality of life. In this context, the identification of risk factors for postoperative complications is one major concern. As outlined in Table 4, we found that only no previous systemic chemotherapy, extent of cytoreduction, and dose of CDDP for IPHP remained in the model after multivariate analysis. However, no previous systemic chemotherapy presented a borderline significance ($P = 0.054$), and, thus, only the extent of cytoreduction and dose of CDDP for IPHP could be considered the best predictors of major morbidity after CRS and IPHP.

The most significant complication in our series was digestive fistula due to anastomotic leak and/or digestive perforation. This morbidity constituted about 70% of all cases with major morbidity, and the rate of fistula in the whole series was 11%. There were 17 (9%) dehiscences occurring in 191 fashioned anastomoses. This figure is somewhat higher than the 5% postoperative fistula rate reported for common elective surgeries with bowel anastomoses.[15,16] Several factors could be responsible for this difference, including the effects of locoregional chemotherapy and of hyperthermia on suture healing, the biologic aggressiveness of the neoplastic diseases being treated in our series, and the magnitude of surgical trauma with fairly longer procedures. The influence of chemotherapy on the suture-line healing depends on the type of drug. In animal studies, anastomotic healing can be impaired by intraperitoneal MMC[17] and cisplatin[18]

TABLE 4
Univariate and Multivariate Analysis of Clinical Risk Factors for Major Morbidity

		Univariate[a]		Multivariate[b]	
	Independent variables	OR_{crude}	*P*	OR_{adj} 95% CI	*P*
1	Tumor histology of GI origin	1.54	0.213		
2	Male gender	2.76	0.016		
3	Performance status (ECOG) ≥ 1	0.43	0.050		
4	Age ≥ 52 yrs	1.02	0.571		
5	BMI ≥ 25 kg/m^2	0.76	0.343		
6	No previous CHT	3.69	0.004	2.72 0.98–7.51	0.054
7	Previous RT	1.49	0.539		
8	Carcinomatosis extension (PCI ≥ 20)	2.88	0.027		
9	No. of anastomoses ≥2	2.65	0.028		
10	Procedure duration ≥ 530 minutes	3.35	0.014		
11	Extent of cytoreduction: Levels 1/2 vs. Level 3[c]	2.68	0.019	2.88 1.29–6.40	0.010
12	Completeness of cytoreduction: cc0/1 vs. cc2/3	1.27	0.439		
13	CDDP IPHP dose ≥240 mg	2.70	0.020	3.12 1.24–7.90	0.016

OR: odds ratio; GI: gastrointestinal; BMI: body mass index; CHT: chemotherapy; RT: radiotherapy; CDDP: cisplatin; IPHP: intraperitoneal hyperthermic perfusion.

[a] Chi square test or Fisher's exact test.

[b] logistic regression model with backward elimination method.

[c] Cytoreduction was classified into 3 levels according to the number of procedures performed: Level I: 1–2 procedures; Level II: 3 or 4 procedures; Level III: more than 5 procedures.

but not by 5-fluorouracil[19] or paclitaxel.[20] Local hyperthermia in itself has no adverse effect on anastomotic healing in animal models.[21] Our rate of anastomotic fistula, however, is not significantly different from data reported by other authors who performed CRS + IPHP. Data from the literature report rates ranging from 7.2% to 17.4%.[22–25]

The higher incidence of anastomotic leak or of intrabdominal abscess in locoregional treatment of PSM with respect to common elective surgical procedures has guided several surgeons to perform protective proximal ostomies more liberally. Indications are not uniform, suffering a range of variation. Verwaal et al. recommend colostomy for all rectal resections.[26] Moran et al. and Sugarbaker et al. advocate a proximal diverting stoma in cases of low anterior resections in which the preservation of the rectum is not possible.[27,28] Conversely, Shen et al., despite having found an unacceptably high rate of sepsis correlated with bowel anastomoses, adopted a more flexible policy that suggested the surgical performance of protective stoma is an alternative.[29] In our series, we performed only 2 diverting ostomies in the 58 low colorectal anastomoses and found only 2 (3.4%) anastomotic fistulae. Therefore, to primarily perform unprotected colorectal anastomoses can be considered a feasible option.

Digestive tract perforations occurred in 6 cases in our series, and they could be attributed to partial-thickness mechanical and/or thermal damage to intestinal surfaces. This, in turn, could have been aggravated by subsequently administered heated chemotherapy. Other possible explanations for digestive perforation are 1) the focal heat injury at the tip of the inflow catheter, 2) the mechanical trauma elicited by the suctioning effect of the outflow catheter, 3) postoperative shrinking of infiltrating metastatic nodules on the intestinal wall because of the antiblastic effect of heated chemotherapy. The risk for such complications should be minimized by a careful lysis of adhesions and dissection, with a judicious use of the ball-tip electrocautery on the serosal surfaces of the intestine in case the cytoreduction requires an extensive fulguration of metastatic disseminated implants. Another important surgical step is the final inspection of the abdominal cavity after the drainage of perfusate at the end of IPHP. This phase should be performed as accurately as possible to identify and treat all the risky damaged areas on the organs and intestinal tract.

One noteworthy finding in our study was the dose of CDDP used for IPHP as an independent risk factor for major procedure-related morbidity. As already outlined in the Materials and Methods section of this article, 2 IPHP drug schedules were used, according to the tumor type, namely, CDDP (25 mg/m^2/L of perfusate) + MMC (3.3 mg/m^2//L of perfusate), and CDDP (43 mg/L of perfusate) + Dx (15.25 mg/L of perfusate). The second combination was established

formally by a Phase I dose-finding study conducted by Rossi et al.,[11] although this does not hold true for the first combination. The dose of CDDP for IPHP in each of the combinations is calculated in different ways and, in our study, ranged from 100 to 300 mg. We chose 240 mg as the cutoff value CDDP dose for IPHP, as it represents the theoretical maximum for a tolerable dose, in our series, according to the schedule proposed by Rossi et al. It is the approximate result of the product of 43 mg by 6 liters (maximal volume of perfusate used in our series). Patients receiving CDDP $\geq$ 240 mg presented a significantly higher rate of combined major morbidity. However, they presented 3 times higher risk of developing a GIII–IV postoperative complication compared with those who were submitted to IPHP with a lower CDDP dose, when adjusted for the other variables. This finding, at first glance, should not be surprising as it can be supported by an experimental study, which demonstrated the negative influence of CDDP on healing of bowel anastomosis after IPHP.[18] In addition, the digestive complications due to anastomotic leaks and/or bowel perforations were the most frequent type of major morbidity in the present series, as already discussed. However, the correlation between CDDP dose during IPHP and the occurrence of procedure-related bowel complications did not present a statistical significance, not even by univariate analysis in a parallel study.[30] Whether the experimental evidence of adverse effect of CDDP on bowel anastomotic healing could have a clinical significance on postoperative evolution of patients submitted to CRS + IPHP is still to be evaluated by a formal controlled trial.

Following the gastrointestinal tract, the respiratory tract was the second most affected system by postoperative complications. In fact, according to Table 3, pulmonary morbidity was found in 15 cases. Fortunately, most of them were of Grade 1 or 2, with the exception of 1 case of pulmonary embolism and 1 case of respiratory failure. This finding is in line with reports in the literature.[31,32] Several factors can account for this fact. The stripping of the diaphragmatic peritoneum elicits a mechanical and thermal injury on the muscle, with the formation of clinically nonevident communications between the abdominal and pleural cavities that allow passage of perfusate inside the thorax during IPHP. Moreover, inflammatory reaction secondary to tissue injury could be responsible for continuous production of exudates by the pleura during the postoperative period. The possibly impaired contractive function of the diaphragmatic muscle due to surgical trauma, formation of pleural effusion, along with general causes related to any major surgery (prolonged anesthesia time, inappropriate postoperative analgesia) should all be considered as potential factors for the emergence of pulmonary morbidities. The prevention and management of such complications include careful inspection of the integrity of diaphragmatic muscle after the stripping of its peritoneum and the prompt repair of eventual macroscopic holes, the prophylactic insertion of thoracic drains after the cytoreduction,[33] an aggressive control of postoperative pain, a judicious management of respiratory rehabilitation, and administration of antibiotics.

Jacquet et al. conducted a study on 60 patients with peritoneal carcinomatosis from adenocarcinoma of the colon or appendix treated with CRS, IPHP with MMC followed by 1 cycle of early postoperative intraperitoneal 5-fluorouracil.[24] They used the closed abdomen technique for IPHP, and after a multivariate analysis including 11 clinical variables, gender, intrabdominal temperature, and duration of surgery were identified as the best predictors of major morbidity. Stephens et al.[34] reported on 200 cases of peritoneal carcinomatosis treated with CRS + IPHP using the coliseum technique. After performing multivariate analysis, they found that the number of peritonectomy procedures and resections was the only variable significantly associated with presence of major morbidity (OR = 1.32; $P = 0.0002$). Glehen et al.[35] conducted a study on 216 consecutive treatments of peritoneal carcinomatosis by IPHP by using a closed abdomen procedure combined with cytoreductive surgery when needed. The postoperative mortality and morbidity rates were 3.2% and 24.5%, respectively. The most frequent complications were digestive fistula (6.5%) and hematologic toxicity (4.6%). After univariate analysis, morbidity was proven to be linked with the carcinomatosis stage ($P = 0.016$), the duration of surgery ($P = 0.005$), and the number of resections and peritonectomy procedures ($P = .042$). Verwaal et al.[26] conducted a study of complications and toxicity in 102 patients treated by CRS + IPHP. Grade 3, 4, or 5 toxicity (National Cancer Institute, Cancer Therapy Evaluation Program) rate was 65%. Eight patients died of treatment-related causes. Surgical complications (defined as any postoperative event that needed reintervention) rate was 35%. Fistulae were observed in 18 patients. The risk of a complicated recovery was higher in the following situations, 1) carcinomatosis with recurrent colorectal cancer ($P = 0.009$), 2) more than 5 regions affected ($P = 0.044$), 3) Simplified Peritoneal Cancer (the Netherlands Cancer Institute) score = 13 ($P = 0.012$), 4) incomplete initial cytoreduction ($P = 0.035$), 5) blood loss exceeding 6 L ($P = 0.028$), and 6) 3 or more anastomoses ($P = 0.018$). Table 5 presents an overview of the main studies that

TABLE 5
Overview of Operative Complications Associated with CRS+IPHP (Series with More Than 50 Patients)

Author	Yr	No. of procedures	% of males	Predominant. histology	Protective ostomy (%)	IPHP modality	Timing of anastomosis[a]	Duration of procedure (hrs)	Morbidity (%)	Mortality (%)	Main complications	Risk factors	Statistical analysis
Jacquet et al.[24]	1996	60	62	Appendix, colon	None	Closed	After	10.9[b]	35	5	Bowel, bleeding	Sex, intrabdominal temperature, duration of surgery	Multivariate
Stephens et al.[34]	1999	200	53	PMP, colon	NA	Open	After	NA	27	1.5	Peripancreatitis, bowel, bleeding	No. of peritonectomy procedures	Multivariate
Glehen et al.[35]	2003	216	37	Colon, PMP, ovarian	NA	Closed	Before	6.1[b]	24.5	3.2	Digestive fistula; hematologic, toxicity	Carcinomatosis extension, duration of surgery, No. of peritonectomy procedures	Univariate
Verwaal et al.[26]	2004	102	56	Colon	42	Open	After	7.5[c]	35	8	Bowel, intraabdominal abscess	Recurrent form, carcinomatosis extension, CC, blood loss, No. of suture lines	Univariate
Shen et al.[29]	2004	77	58	Colon	13	Closed	After	9[c]	30	12	Bowel infection, respiratory failure, sepsis	Bowel anastomoses (with sepsis)	Univariate
Present series	2005	209	33	MP, PMP, ovarian	0.5	Closed	Before	8.2[c]	12	0.9	Bowel	Extent of cytoreduction; CDDP IPHP dose	Multivariate

NA: not available; IPHP: intraperitoneal hyperthermic perfusion; PM: peritoneal mesothelioma; PMP: pseudomyxoma peritonei; CC: completeness of cytoreduction.

[a] Whether the anastomoses were performed before or after the IPHP.

[b] Mean.

[c] Median.

addressed the issue of operative complications associated with CRS + IPHP.

All studies agree on the predictive value for postoperative complications of the variables directly or indirectly correlated with extent of cytoreductive procedure (such as number of anastomoses, number of peritonectomy procedures, and duration of the surgery). However, no consensus has been reached on other variables related to clinical data and surgical techniques. Several factors could account for this contrast, such as differences between cohorts concerning gender distribution, tumor type distribution, and IPHP techniques, thus rendering comparison of results somewhat problematic. In addition, different criteria defining postoperative morbidity and mortality were used in different series, and not all authors performed multivariate analysis to assess risk factors for procedure-related complications. The analysis performed in the present study comprised only clinical and surgical variables related to preoperative and intraoperative phases of the procedure. The search for risk factors for complications should be continued, analyzing other aspects of locoregional therapy. If other perioperative parameters are included in multivariate analysis, new independent risk factors for morbidity could emerge. The possible perioperative parameters to be studied are those related to nutritional status and hemodynamic and respiratory variables during and after the procedure.

Investigators have not achieved agreement on open or closed abdomen techniques of IPHP. Proponents of the coliseum technique (open abdomen)[34,36] claim better drug and heat distribution by continuous manipulation of the abdominal organs. Deficiencies were noted in the distribution of methylene blue dye with the closed abdomen technique, which, in turn, was blamed for a higher rate of complications.[37] Conversely, the closed technique permits an increase in the intrabdominal pressure that may lead to increased convection-driven drug penetration of macromolecular agents such as TNF-α inside the tumor.[38–40] Moreover, Jacquet et al. reported that, in animal models, an intraabdominal pressure of 20 and 30 mm Hg increased tissue uptake of doxorubicin in bladder, diaphragm, and abdominal wall during the first 10 minutes of intraperitoneal administration.[41] Furthermore, a recent study carried out by Glehen et al. reported morbidity and mortality results on 216 procedures of intraperitoneal chemohyperthermia using the closed abdomen technique.[35] They observed a postoperative mortality rate of 3.2% and morbidity of 24.5%, comparable to other reports. Since, up to now, no prospec-

tive controlled clinical trial has been conducted that specifically addresses the superiority of 1 technique over the other, the issue remains unclear with no striking differences between the 2 techniques in terms of operative morbidity.

Another technical variation of CRS + IPHP is the optimal timing for performing bowel anastomoses. They can be performed during the CRS just before IPHP or after completion of IPHP. Proponents of the second alternative argue that delaying the anastomosis permits a better distribution of heat and drugs inside the peritoneal cavity during IPHP and treatment of eventually implanted neoplastic cells on the intestinal end-surfaces that are to be sutured. In addition, they state that risk of postoperative bowel complications can be diminished because of avoidance of potential adverse effects of heat and chemotherapy on suture-line healing. Conversely, others have proposed the first alternative by reporting data of no increased morbidity due to postoperative bowel fistula and/or anastomotic leak when anastomoses are performed before IPHP.[44–46]

Thus, our low and acceptable morbidity, toxicity, and mortality rates suggest that CRS + IPHP performed by an experienced surgical team with primary intestinal anastomosis, closed abdomen technique, and no liberal indication of ostomies is safe. Although the present study was conducted in a large cohort of patients, it suffers from the methodologic limitation of the absence of a control group. In this sense, it is premature to defend categorically 1 technique over other(s), as any attempt to establish a technical guideline for CRS + IPHP on the basis of experimental and uncontrolled clinical evidence is condemned to fail. A definitive clarification of technical variations will be possible only by adequately designed prospective randomized trials.

REFERENCES

1. 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.
2. Deraco M, Casali P, Inglese MG, et al. Peritoneal mesothelioma treated by induction chemotherapy, cytoreductive surgery, and intraperitoneal hyperthermic perfusion. *J Surg Oncol.* 2003;83:147–153.
3. Ryu KS, Kim JH, Ko HS, et al. Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. *Gynecol Oncol.* 2004;94:325–332.
4. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol.* 2004;22:3284–3292.
5. Verwaal VJ, van Ruth S, de Bree E, 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;21:3737–3743.
6. Raspagliesi F, Deraco M, Rossi CR. Stage III/IV epithelial ovarian cancer with macroscopic residual disease after 1st line chemotherapy: a multicentric prospective randomized study comparing locoregional approach + systemic chemotherapy vs. systemic chemotherapy alone. Available from URL: http://www.sitilo.org [Accessed August 1, 2005].
7. Sugarbaker PH. Peritonectomy procedures. *Ann Surg.* 1995; 221:29–42.
8. Sugarbaker PH. Laser-mode electrosurgery. *Cancer Treat Res.* 1996;82:375–385.
9. Jacquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res.* 1996;15:49–58.
10. Fujimoto S, Takahashi M, Kobayashi K, et al. Combined treatment of pelvic exenterative surgery and intra-operative pelvic hyperthermochemotherapy for locally advanced rectosigmoid cancer: report of a case. *Surg Today.* 1993;23: 1094–1098.
11. Rossi CR, Foletto M, Mocellin S, et al. Hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin in patients who undergo cytoreductive surgery for peritoneal carcinomatosis and sarcomatosis: phase I study. *Cancer.* 2002;94:492–499.
12. Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. *Lancet.* 2001;358:1487–1492.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting the results of cancer treatment. *Cancer.* 1981;47:207–214.
14. Gonzalez Bayon L, Sugarbaker PH, Gonzalez Moreno S, Vazquez Vde L, Alves S, Moran BJ. Initiation of a program in peritoneal surface malignancy. *Surg Oncol Clin N Am.* 2003; 12:741–753.
15. Abete M, Ronchetti V, Casano A, Pescio G. [Anastomotic leakage after traditional surgery of the colon and rectum]. *Minerva Chir.* 2003;58:167–174. Review. Italian.
16. Montesani C, De Milito R, Chiappalone S, Narilli P, D'Amato A, Ribotta G. Critical evaluation of the anastomoses in large bowel surgery: experience gained in 533 cases. *Hepatogastroenterology.* 1992;39:304–308.
17. Fumagalli U, Trabucchi E, Soligo M, et al. Effects of intraperitoneal chemotherapy on anastomotic healing in rats. *J Surg Res.* 1991;50:82–87.
18. Makrin V, Lev-Chelouche D, Even Sapir E, Paran H, Rabau M, Gutman M. Intraperitoneal heated chemotherapy affects healing of experimental colonic anastomosis: an animal study. *J Surg Oncol.* 2005;89:18–22.
19. Kuzu M, Koksoy C, Kale T, Demirpence E, Renda N. Experimental study of the effect of preoperative 5-fluorouracil on the integrity of colonic anastomoses. *Br J Surg.* 1998;85:236–239.
20. Arikan AY, Gunal O, Pehlivan M, Alper M. The effect of intraperitoneal paclitaxel administration on colonic anastomosis. *Hepatogastroenterology.* 2000;47:1273–1276.
21. Shimizu T, Maeta M, Koga. Influence of local hyperthermia on the healing of small intestinal anastomoses in the rat. *Br J Surg.* 1991;78:57–59.
22. Elias D, Laurent S, Antoun S, et al. Pseudomyxoma peritonei treated with complete resection and immediate intraperitoneal chemotherapy. *Gastroenterol Clin Biol.* 2003;27:407–412.

23. 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.
24. Jacquet P, Stephens AD, Averbach AM, et al. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer.* 1996; 77:2622–2629.
25. Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. *Br J Surg.* 2004;91:747–754.
26. Verwaal VJ, van Tinteren H, Ruth SV, Zoetmulder FA. Toxicity of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. *J Surg Oncol.* 2004;85:61–67.
27. Moran BJ, Cecil TD. The etiology, clinical presentation, and management of pseudomyxoma peritonei. *Surg Oncol Clin N Am.* 2003;12:585–603.
28. Sugarbaker PH, Ronnett BM, Archer A, et al. Pseudomyxoma peritonei syndrome. *Adv Surg,* 1997;30:233–280.
29. Shen P, Hawksworth J, Lovato J, et al. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma. *Ann Surg Oncol.* 2004;11:178–186.
30. Younan R, Kusamura S, Baratti D, et al. Bowel complications in 203 cases of peritoneal surface malignancies treated with peritonectomy and closed-technique hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2005;12:910–918.
31. Loggie BW, Fleming R. Complications of heated intraperitoneal chemotherapy and strategies for prevention. In: Sugarbaker PH, editor. Peritoneal carcinomatosis: principles of management. Boston: Kluwer Academic, 1996:222–223.
32. Chen MY, Chiles C, Loggie BW, Choplin RH, Perini MA, Fleming RA. Thoracic complications in patients undergoing intraperitoneal heated chemotherapy with mitomycin following cytoreductive surgery. *J Surg Oncol.* 1997;66:19–23.
33. Ahmad SA, Kim J, Sussman JJ, et al. Reduced morbidity following cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion. *Ann Surg Oncol.* 2004;11:387–392.
34. 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.
35. 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.
36. Cavaliere F, Di Filippo F, Cosimelli M, et al. The integrated treatment of peritoneal carcinomatosis. A preliminary experience. *J Exp Clin Cancer Res.* 1999;18:151–158.
37. Sugarbaker PH, Jacquet P, Stephens AD, Stuart OA, Averbach AM. Comparison of covered versus closed technique for heated intraoperative chemotherapy for peritoneal carcinomatosis from gastrointestinal cancer. In: Abe O, Inokuchi K, Takasaki K, editors. XXX World Congress of the International College of Surgeons. Bologna, Italy: Monduzzi Editore, 1996;389–393.
38. Leunig M, Goetz AE, Dellian M, et al. Interstitial fluid pressure in solid tumors following hyperthermia: possible correlation with therapeutic response. *Cancer Res.* 1992;52:487–490.
39. Milosevic MF, Fyles AW, Hill RP. The relationship between elevated interstitial fluid pressure and blood flow in tumors: a bioengineering analysis. *Int J Radiat Oncol Biol Phys.* 1999; 43:1111–1123.
40. Jain RK, Baxter LT. Mechanisms of heterogeneous distribution of monoclonal antibodies and other macromolecules in tumors: significance of elevated interstitial pressure. *Cancer Res.* 1988;48(24 Pt 1):7022–7032.
41. Jacquet P, Stuart OA, Chang D, Sugarbaker PH. Effects of intra-abdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. *Anticancer Drugs.* 1996;7:596–603.
42. Deraco M, Vaglini M, Santinami M, Santoro N, Inglese MG, Spatti GB. Intraperitoneal hyperthermic perfusion (IPHP): analysis of morbidity and toxicity. *Oncol Rep.* 1996;3:1103–1106.
43. Deraco M, Rossi CR, Pennacchioli E, et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion in the treatment of recurrent epithelial ovarian cancer: a phase II clinical study. *Tumori.* 2001;87:120–126.
44. Zanon C, Clara R, Bortolini M, et al. Chemohyperthermia for advanced abdominal malignancies: a new procedure with closed abdomen and previously performed anastomosis. *Int J Hyperthermia.* 2001;17:456–464.