Identification of a Subgroup of Patients at Highest Risk for Complications After Surgical Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy

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Objective: To assess the influence of parietal and visceral peritonectomy procedures on moderate/severe morbidity in patients undergoing surgical cytoreducion and hyperthermic intraperitoneal chemotherapy (HIPEC) and to identify subgroups of patients at highest operative risk.

Background: Cytoreducion with HIPEC is an effective but potentially morbid treatment option for peritoneal surface malignancies. Although complication rates have recently decreased with increasing experience, risk-factors for adverse operative outcome are still poorly understood.

Methods: A prospective database of 426 combined procedures was reviewed. Multivariate analysis tested the correlation between major morbidity and 6 peritonectomies (greater and lesser omentectomy, pelvic, parietal anterior, left and right diaphragmatic peritonectomy), 14 visceral resections, 5 other operative factors, and 12 clinical variables. The extent of peritoneal involvement was quantified by peritoneal cancer index (PCI).

Results: Mortality and major morbidity were 2.6% and 28.2%. PCI, number of visceral resections, poor performance status, and cisplatin dose more than 240 mg independently correlated to morbidity. The type and number of parietal peritonectomies and the type of visceral resections did not correlated to complications. Major morbidity rate was 65.7% in 35 (8.2%) patients with at least 2 of the following factors: PCI greater than 30, more than 5 visceral resections, poor performance status. Morbidity was 100% in 9 patients presenting all the risk factors.

Conclusions: Acceptable morbidity and low mortality may be achieved in high-volume centers. Operative outcome is mainly affected by a complex interplay of tumor, patient, and treatment-related factors. Preoperative and early intraoperative assessment of operative risk may identify a subset of patients unlikely to tolerate aggressive management.

Keywords: peritoneal surface malignancies, cytoreductive surgery, hyperthermic intraperitoneal, chemotherapy, HIPEC, complications

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Peritoneal dissemination is a common manifestation of disease progression in gastrointestinal or gynecological tumors, and rare primary peritoneal cancers.[1] Once regarded as end-stage metastatic conditions only amenable to palliative options, peritoneal surface malignancies (PSM) are increasingly recognized as local-regional disease entities. Better understanding of their natural history, with symptoms, site of progression, and cause of death, which are commonly confined to the abdominal-pelvic cavity, has recently evolved into a novel treatment approach with curative intent.[2] A similar paradigm shift has occurred in the management of colorectal cancer liver metastases.[3]

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An innovative strategy aiming at definitive disease eradication combines aggressive surgical cytoreduction with hyperthermic intraperitoneal chemotherapy (HIPEC).[2] Peritonectomy procedures and organ resections are used to remove the macroscopic tumor on parietal and visceral peritoneal surfaces, and HIPEC to treat the microscopic residual disease. Observational studies, phase I and II trials, multi-institutional series, and literature reviews are currently the best evidence that an improved outcome is associated with the combined treatment, as compared to contemporary or historical controls.[4–10] Furthermore, 2 randomized and 2 controlled studies have demonstrated the superiority of cytoreduction and HIPEC over systemic therapy in the treatment of colorectal and gastric cancer carcinomatosis.[11–14]

Patients with PSM are often referred with massive tumor load or after extensive surgical and medical therapies. Their definitive management involves further demanding surgical procedures, intraperitoneal chemotherapy, and hyperthermia. Not surprisingly, earlier trials reported high morbidity and mortality rates.[15] Although impressive reductions in complications have more recently occurred in high-volume centers with increasing experience, many unanswered questions remain, such as the predictive factors for morbidity and relative contribution to operative risk of the different components of the combined treatment.[16] In addition, remarkable differences among centers, with regard to clinical indications, cytoreductive surgical procedures, and intraperitoneal chemotherapy techniques, still hamper any meaningful conclusion about the optimal surgical and comprehensive management of PSM.[17]

To date, many peritoneal malignancy treatment centers have been established in the United States, Japan, Australia, and Europe. Furthermore, new randomized trials are presently ongoing or being planned to define the role of cytoreduction and HIPEC in colorectal, gastric, and ovarian cancer carcinomatosis.[18–20] This scenario reinforces the need to optimize both short- and long-term outcomes through a more knowledgeable selection of patient for treatment and safer operative procedures. In our institution, previous morbidity analyses have contributed to standardize HIPEC administration, as cisplatin dose more than 240 mg was demonstrated to increase both surgical morbidity and systemic toxicity.[21,22] In the present study, we critically reviewed our institutional prospective database of 426 combined procedures, in an attempt to define the impact of the extent and quality of the surgical cytoreduction on major operative complications.

PATIENTS AND METHODS

All the patients included in the present study were treated according to a protocol approved by our institutional ethics committee and signed an informed consent form. Data for the present analysis were collected from a prospective database. Additional information was retrieved from medical charts.

Eligibility requirements included the following: diagnosis of PSM made or confirmed in our Pathology Department, age 75 years or younger, performance status 2 or less according to Eastern Cooperative Oncology Group (ECOG),[23] no significant comorbidities, no

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extra-abdominal or hepatic metastases, and preoperative computed tomographic (CT) scan showing peritoneal disease amenable to potentially complete surgical cytoreduction.

Operative Treatment

Patients were admitted 1 day before surgery. On admission, subcutaneous calcium heparin (5000 units twice daily) or nadroparin (3800 units once daily) were administered. Mechanical bowel preparation was given. Cefotaxime 1000 mg and metronidazole 500 mg were administered 30 minutes before skin incision and repeated every 6 hours during surgery.

The peritoneal cancer index (PCI) was used to score the extent of peritoneal involvement at surgical exploration.[24] PCI combines tumor implant size and distribution in 13 abdominal-pelvic regions, resulting in a numeric score (PCI 0–39). Cytoreductive surgery was based on the technique described by Sugarbaker,[2] with some modifications.[25] Briefly, the goal of the cytoreduction was to remove all visible tumor by means of 1 to 6 of the following procedures: right diaphragmatic peritonectomy; left diaphragmatic peritonectomy; pelvic peritonectomy; parietal anterior peritonectomy; greater omentectomy; and lesser omentectomy. Small and scattered localizations on visceral surfaces were resected by local excision or electrocoagulation. In case of massive involvement, visceral resections were performed. Bowel anastomosis techniques were described previously.[26,27] Anastomoses were performed at the completion of the cytoreduction and before HIPEC because both in the literature and our experience there was no evidence of increased risk for anastomotic complications or isolated disease recurrence on suture lines, which represent the theoretical drawbacks of such time setting for their construction. Protective ostomies were performed only in high-risk patients after HIPEC, to prevent perfusate leak from ostomy tracts through the abdominal wall.

HIPEC was performed according to the closed-abdomen technique, at temperature of 42.5°C, with cisplatin (45 mg/L) plus doxorubicin (15 mg/L) for 90 minutes, or cisplatin (25 mg/m^2/L) plus mitomycin-C (3.3 mg/m^2/L) for 60 minutes.[17,28] Perfusate volume was 4 to 6 L; average flow was 700 mL/min. The Performer LRT [RAND, Medolla (MO), Italy] extracorporeal circulation device was used. After 2007, upper limit for cisplatin total dose was set at 240 mg, as a result of our previous morbidity analyses.[21,22] A 30% dose reduction was applied to patients older than 70 years, with previous chemotherapy and/or extensive surgical cytoreduction.

The completeness of cytoreduction (CCR) was classified at the end of the surgical phase, as macroscopically complete (CCR-0); nearly complete: residual disease 2.5 mm or less in any region (CCR-1); or suboptimal: residual disease more than 2.5 mm (CCR-2).[24]

Postoperative Management

Following surgery, patients were admitted to the intensive care unit (ICU) for continuous monitoring. Laboratory and instrumental examinations were performed daily. Patients were then discharged to the surgical ward for recovery. Doppler ultrasound was ordered if deep venous thrombosis was suspected. Patients developing respiratory signs suggestive of pulmonary embolus, underwent ventilation/perfusion scan, or CT pulmonary angiogram. Oral contrast-enhanced abdomen CT scan was performed in patients with a clinical suspicion of intra-abdominal abscess. Parenteral and/or enteral nutrition was administered to patients with prolonged inadequate caloric intake.

Study Design and Statistical Analysis

Adverse events within 30 days of surgery or during the same hospital admission were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Surgical complications were rated as minor, when no or only medical treatment was required for resolution (grade 1/2); major complications included those requiring interventional endoscopy or CT-scan/ultrasound-guided procedures (grade 3), return to the operating room or ICU (grade 4), and operative death (grade 5).

Primary study endpoint was the correlation between major adverse events (grade 3–5) and 20 cytoreductive surgical procedures. Each of the 6 peritonectomies (lesser and greater omentectomy, pelvic, parietal anterior, right and left diaphragmatic peritonectomy), and the following surgical procedures were analyzed as dichotomous variables (done vs not done): splenectomy, liver capsulectomy, cholecystectomy, total gastrectomy, any gastrectomy, appendectomy, sigmoid, right, transverse and total colectomy, small bowel resection, total abdominal hysterectomy (TAH) ± bilateral salpingo-oophorectomy (BSO), diaphragm resection, protective ostomy. Patients who had infracolic omentectomy previously and underwent gastrocolic ligament resection at the time of combined treatment were considered as having greater omentectomy. The number of peritonectomies and visceral resections performed in each patient was also analyzed as continuous variables, with possible values of 0 to 6 and 0 to 8, respectively.

In addition, the following operative and clinical factors were analyzed as control variables: HIPEC regimen (cisplatin and doxorubicin vs cisplatin and mitomycin-C), cisplatin total dosage ($\leq$240 mg vs $>$240 mg), transfused blood red cell units, transfused frozen plasma units, number of anastomoses, age, sex, ECOG performance score (0 vs 1–2), serum albumin ($\leq$3.2 vs $>$3.2 g/dL), lymphocytes ($>$800 vs $\leq$800), histology (nongastrointestinal vs gastrointestinal origin), previous systemic chemotherapy, previous surgery ($\leq$1 vs $>$1 abdominal-pelvic region dissected), primary versus repeated combined treatment, treatment period (after vs. before 12/31/2002), and CCR (0 vs 1 vs 2). Four PCI subgroups were arbitrarily created for the analysis: 1–6, 7–12, 13–18, and $>$18.

Categorical variables were described in terms of frequencies and percentages, and continuous variables in terms of mean, standard error, median, and first and third quartiles. The influence of patient, disease, and treatment-related factors was related to the risk of postoperative complications using univariate and multivariate logistic regression models. Continuous variables were categorized into 2 classes using their median value as cutoff. Variables deemed statistically significant by univariate analysis were included in the multivariate analysis; both number and type of visceral resections and peritonectomy procedures were included in the model regardless of the statistical significance. PCI was entered in the multivariate analysis as continuous variable due to its linear relationship with the risk of adverse events. $P < 0.05$ were considered significant. All statistical analyses were conducted by using SPSS software version 8.0.0 (SPSS Inc, Chicago, IL).

RESULTS

Between February 1995 and March 2011, 426 consecutive combined procedures were performed in 420 patients by the same surgical team (see Table 1). Six patients underwent the procedure twice due to disease recurrence. Some of these patients were included in previous morbidity analyses.[21,22,26,27]

Mortality and Morbidity

Mortality rate was 11/426 (2.6%). The cause of death was sepsis and multiorgan failure in 9 patients, due to bowel complications (n = 8) or abdominal abscess (n = 1). The remaining two patients died of myocardial infarction (n = 1) and respiratory failure (n = 1). In

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TABLE 1. Clinical Characteristics of 426 Patients With Peritoneal Surface Malignancies

Variables	Categories	No. Patients	Percentage of Patients
Sex	Male	157	36.9
	Female	269	63.1
Age, yrs	Mean (SD), median (IQ range)	53.4 (12.7)	54 (44–64)
PSM	Pseudomyxoma peritonei	159	37.3
	Peritoneal mesothelioma	132	31.0
	Ovarian cancer carcinomatosis	53	12.5
	Colorectal cancer carcinomatosis	21	4.9
	Gastric cancer carcinomatosis	12	2.8
	Papillary serous carcinoma	6	1.4
	Abdominal sarcomatosis	37	8.7
	Other	6	1.4
ECOG score	0	350	82.2
	1	67	15.5
	2	10	2.3
Previous surgery	Only biopsy	151	35.5
	1 abdominal region dissected	90	21.1
	2–5 abdominal regions dissected	176	41.3
	>5 abdominal regions dissected	9	2.1
Previous systemic chemotherapy	Done	189	44.4
	Not done	237	55.6
PCI	Mean (SD), median (IQ range)	18.7 (10.8)	17 (10–26)
Completeness of cytoreduction	No visible residual tumor	257	57.6
	Residual tumor ≤2.5 mm	132	29.6
	Residual tumor >2.5 mm	37	8.7
Peritonectomy procedures	Mean (SD), median (IQ range)	4.41(2.27)	6 (2–6)
Visceral resections	Mean (SD), median (IQ range)	2.71 (1.99)	2 (1–4)
HIPEC drug schedule	cisplatin + mitomycin-C	245	57.5
	cisplatin + doxorubicin	181	42.5
Cisplatin dose	Mean, mg (SD), median (IQ range)	189.6 (45.8)	200 (150–240)
Mitomycin-C dose	Mean, mg (SD), median (IQ range)	28.0 (7.2)	28 (25–30)
Doxorubicin dose	Mean, mg (SD), median (IQ range)	64.4 (13.5)	60 (60–75)
Operative time	Mean, min. (SD), median (IQ range)	562.7 (155.9)	540 (480–660)
Blood loss	Mean, unit (SD), median (IQ range)	2.763 (3.59)	2.0 (0–4)
Frozen plasma	Mean, unit (SD), median (IQ range)	5.93 (5.17)	4 (3–8)
Hospital stay	Mean, days (SD), median (IQ range)	23.1 (15.1)	18 (14–28)

IQ indicates interquartile; SD, standard deviation.

addition, 134 patients (31.5%) had an uneventful recovery, 102 patients (23.9%) had grade 1, 71 patients (16.6%) had grade 2, 50 patients (11.7%) had grade 3, and 58 patients (13.6%) had grade 4 postoperative complications. Overall, 172 major complications (grade 3–5) occurred in 120 procedures (28.2%). Reoperation rate was 10.7%.

Postoperative adverse events are summarized in Table 2. The most common surgical morbidities were bowel complications, either in the form of anastomotic dehiscence or bowel perforation away from anastomotic suture lines. Forty-seven bowel complications occurred in 44 procedures (10.3%). Hemorrhage occurred in 3.3% of procedures and respiratory tract complications in 3.5%. Renal and hematologic systemic toxicity rates were 5.4% and 5.9%, respectively.

Risk Factors for Grade 3–5 Postoperative Complications

Figures 1 and 2 are forest plots showing the impact on major morbidity of the type and number of peritonectomy procedures and visceral resection, respectively, adjusted by control variables, as assessed by the multivariate logistic model. The number of organ resections performed in each patient significantly increased the risk for major complications ($P = 0.004$), whereas the number of parietal peritonectomies did not ($P = 0.776$). Regarding the type of surgical procedures, no statistically significant association was detected between operative morbidity and any visceral resection or parietal peritonectomy.

The results of the univariate analysis of factors associated with a poor operative outcome are shown in Figure 3. The final model of Cox multivariate analysis is shown in Table 3. Four independent predictors of grade 3–5 morbidity were identified: ECOG score higher than 0 ($P = 0.017$), PCI ($P = 0.044$), number of visceral resections ($P = 0.004$), and cisplatin total dose more than 240 mg ($P = 0.001$). Each single point increase on PCI increased the risk for complications by 3.5%.

Identification of High-Risk Groups

Three independent risk factors retained by the multivariate analysis (ECOG score, PCI, and number of visceral resections) were retrospectively combined to identify patients at higher risk for operative morbidity. Cisplatin dose was excluded because of no value in the preoperative/early intraoperative risk-assessment process. For each variable, different cutoffs were analyzed: PCI greater than 30, more than 5 visceral resections, ECOG score higher than 0 was the combination that better correlated to operative risk. Figure 4 shows the major morbidity pattern according to the number of the previously described predictive factors present in the single patients. Grade 3–5 morbidity and mortality were 65.7% and 16.6%, respectively, in 35 patients with at least 2 risk factors. This high-risk group accounted for

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TABLE 2. Postoperative Adverse Events According to NCICTCAE Severity Score

Adverse Events	n	Grade 3	Grade 4	Grade 5
Abdominal abscesses	7	6		1
Anastomosis dehiscence	22	1	16	5
Bowel perforation	25		22	3
Hemorrhage	15	6	9	
Biliary leakage	1		1	
Pancreatic leakage	5	3	2	
Pancreatitis	2	2		
Ureteral leakage	4	2	2	
Abdominal wall dehiscence	1		1	
Gastric volvulus	1	1		
Pulmonitis	9	6	3	
Pleural collection	4	4		
Respiratory failure	3		2	1
Pulmonary embolism	3	1	2	
Sepsis (unrelated to abdominal complications)	9	9		
Lower limb acute ischemia	2		2	
Acute myocardial infarction	1			1
Diarrhea	1	1		
Abdominal fluid collection	1	1		
Central line infection	3	3		
Neurological complications	2		2	
Cardiac arrest	1		1	
Lower limb compartmental syndrome	2		2	
Renal toxicity	23	18	5	
Hematological toxicity	25	20	5	
Total	172	84	77	11

NCICTCAE indicates National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

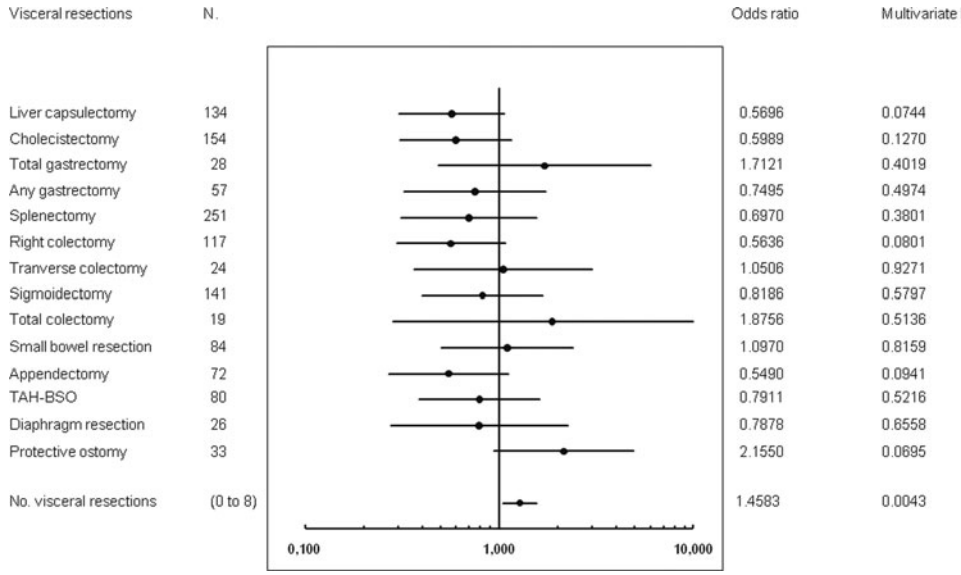

FIGURE 1. Forest plot showing the impact of the type of and number of visceral resections on grade 3–5 morbidity. For each visceral resection, the number of patients who had the procedure, odds ratios of presence versus absence of morbidity, estimated by binary logistic models, and adjusted *P* value are shown. The horizontal bars represent 95% confidence intervals (CIs); when the number of patients undergoing a particular organ resection is low, the corresponding 95% CI is wide, denoting high imprecision of odds ratio estimate.

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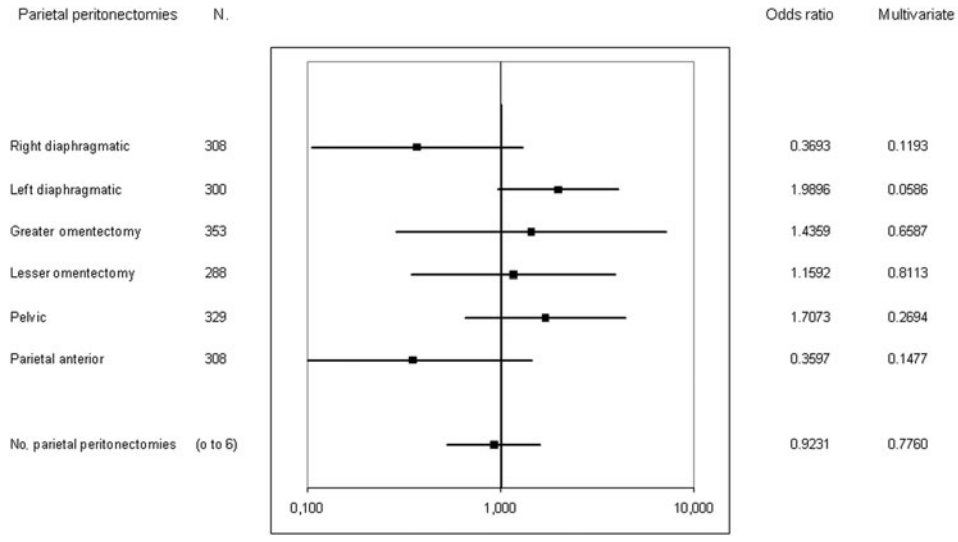

FIGURE 2. Forest plot showing the impact of the type and number of parietal peritonectomies on grade 3–5 morbidity. For each peritonectomy, the number of patients who had the procedure, odds ratios of presence versus absence of morbidity, estimated by binary logistic models, and adjusted *P* value are shown. The horizontal bars represent 95% CIs.

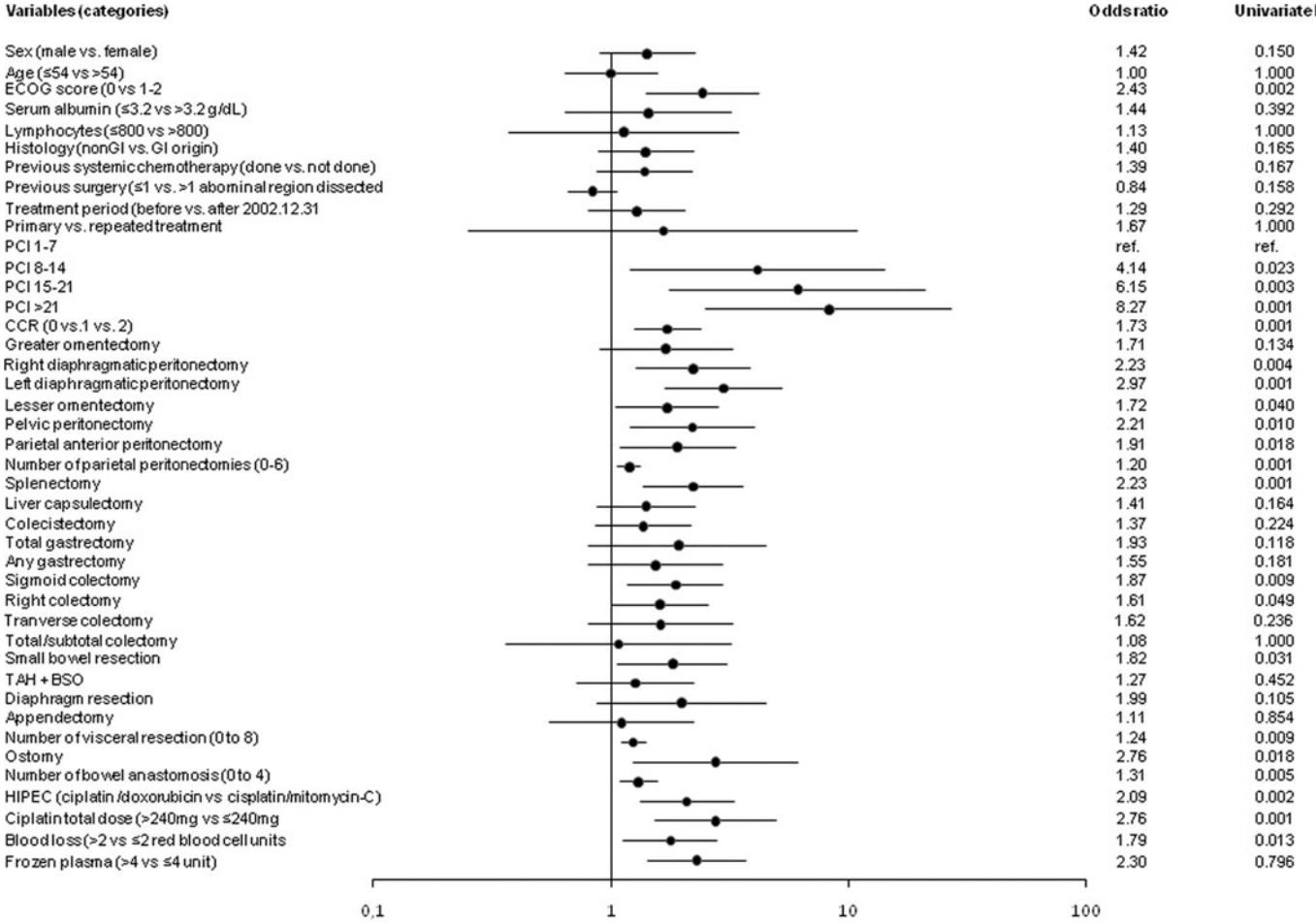

FIGURE 3. Forest plot showing the results of univariate logistic models assessing the influence of each patient, disease, and treatment-related factor on operative risk. For each variable, odds ratios and univariate *P* value are shown. The horizontal bars represent 95% CIs.

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TABLE 3. Multivariate Analysis of Factors Influencing Major Morbidity

	Odds Ratio	(95% CI)	Multivariate *P*
PCI (0–39)	1.035	1.001–1.071	0.044*
Visceral resections (0–8)	1.458	1.129–1.883	0.004*
Cisplatin dose (≤240 mg vs >240 mg)	4.288	2.159–8.520	0.001*
ECOG score (0 vs 1–2)	2.028	1.137–3.621	0.017*
CCR (0 vs 1 vs 2)	1.249	0.848–1.838	0.234
Number of anastomosis (0–4)	1.001	0.695–1.442	0.784
Red blood cell units (≤2 vs >2)	0.826	0.454–1.505	0.749
Fresh frozen plasma units (≤4 vs >4)	1.342	0.777–2.319	0.392

*Statistically significant.

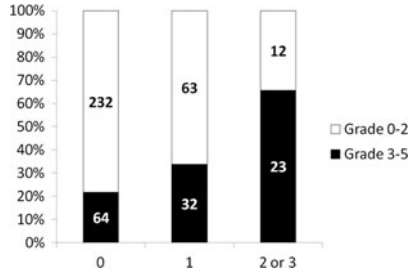

FIGURE 4. Major morbidity pattern according to the number of independent risk factors in the single patients. Patients are categorized according to the number of the following factors they present: PCI >30, more than 5 visceral resections, ECOG > 0. Operative complications are scored according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

8.2% of the overall series. In 9 patients presenting all 3 risk factors, morbidity and mortality were 100% and 22.2%.

DISCUSSION

The fundamental purpose of cancer therapy is to maximize both survival and quality of life. As the treatment of peritoneal surface malignancies is evolving from a minimalist approach to aggressive management, critical assessment of operative morbidity is essential to allow the transition from experimental therapy to standard of care. One of the unique findings of the present study is the identification of a subset of patients in whom higher operative risk may be expected and need to be carefully weighed against the potential benefit of an aggressive approach of surgical cytoreduction and HIPEC.

Complication rates of the present series were comparable to those of the literature.[29–35] A recent review has reported morbidity of 12% to 52% and mortality of 0.9% to 5.8% in 10 international high-volume centers (including our institution), selected to avoid possible biases deriving from small sample size and less experienced teams. These figures, although not negligible, are similar to those of major gastrointestinal operations, such as duodenopancreatectomy and esophagectomy.[15] Interestingly, the present series is comparable to retroperitoneal sarcomas treated in our institution by aggressive surgery with extensive organ resections, regarding major morbidity (28.2% vs 18%), mortality (2.6% vs 3%), and reoperation rates (10.7% vs 12%).[36]

Peritoneal tumor load (PCI > 30), more than 5 visceral resections, and poor performance status (ECOG > 0), combined together, were the most powerful predictors of morbidity. Patients presenting at least 2 independent risk factors were exceedingly prone to experience major adverse effects. The risk associated with the number prevailed over the risk associated with the type of resected organs, presumably because the number better reflected an extensive cytoreduction.

Clearly, widespread peritoneal involvement entails extensive cytoreduction, but the results of the multivariate model suggest that both PCI and number of visceral resections affected morbidity independently from each other. This may be explained by the fact that the number of resected organs is related not only to tumor volume, but also to other disease features, such as tumor location in anatomic sites where a conservative approach is technically difficult, and an infiltrative growth pattern. Analogously, health status is related to patients' ability to withstand demanding operations, but also to tumor load and biological aggressiveness.

The present study highlights the value of imaging studies and initial laparoscopic or surgical exploration suggestive of extensive disease and extensive cytoreduction, along with patient clinical conditions, to assess the operative risk. More knowledgeable risk stratification allows surgical oncologists and patients to make informed decisions regarding treatment planning, thus avoiding unnecessary morbidity and economic costs of care. Despite the current limitations in quantifying accurately the amount of peritoneal disease, CT-scan appears to depict massive tumor involvement.[37] Furthermore, CT-scan has been demonstrated to foresee severe complications and poor survival in patients with pseudomyxoma peritonei.[38] Future studies are needed to explore the adjunctive value of positron emission and magnetic resonance imaging, and the ability of radiological tools to predict the type and number of visceral resections.

In the present series, the morbidity pattern was thoroughly assessed according to the number and type of both peritonectomies and organ resections performed in the single patient. Although the magnitude of surgery has been repeatedly associated to operative complications, far fewer data are available on the relationship between the quality of the surgical cytoreduction and morbidity. Several nonstandardized surrogate markers of surgical complexity have been inconsistently used in previous studies, including operative time and number of anastomoses, organ resections, parietal peritonectomies, or the mixed parietal-visceral cytoreductive procedures originally described by Sugarbaker.[29–35] Furthermore, only few authors have reported on the safety of specific resections as part of combined treatment,[39,40] and, finally, multivisceral resections were not associated to an increased risk for complications in a recent study of the Pittsburgh University.[34]

This study provided additional information that may impact the surgical decision making. First, imaging studies suggestive of high PCI or early intraoperative determination can be used for better patient selection and adverse event prevention. PCI has been demonstrated to affect prognosis in peritoneal carcinomatosis from colorectal and gastric cancer.[7,10] Our results may question the value of cytoreduction and HIPEC for massive disease even in those PSM, for whom high PCI is a less defined contraindication, such as peritoneal mesothelioma and pseudomyxoma peritonei.[41,42] A systematic

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second-look approach has been proposed to treat colorectal cancer carcinomatosis at an early asymptomatic stage. The evidence that limited peritoneal involvement can minimize the risk for complications is a further strong argument to support such a policy.[19] In our institution, patients with massive disease and poor clinical conditions are currently excluded from combined treatment, regardless of tumor histology.

Second, no single visceral resection significantly affected morbidity at multivariate analysis. The accomplishment of macroscopically complete surgery remains an absolute requirement for successful treatment. Consequently, the concern about operative risk is no longer an acceptable justification for avoiding even the most technically demanding single visceral resections, such as total gastrectomy or proctocolectomy, if necessary to remove macroscopic disease. On the contrary, caution is needed whenever approaching widespread peritoneal disease and restrictions have to be made on the number of organ resections.

Third, in contrast to organ resections, the number of parietal peritonectomies did not increase the risk for major complications. This finding might be specific of our series. Most centers perform both parietal peritonectomies and organ resections only when massive involvement makes superficial excision ineffectual, to preserve sufficient postoperative function.[29–35] In contrast, we developed over the year a more liberal approach to parietal peritonectomy, comprising formal peritonectomies of surfaces harboring relatively little disease. Furthermore, some patients were included in an ongoing trial assessing systematic complete versus selective parietal peritonectomy.[25] Our results would confirm the hypothesis that removing minimally affected parietal peritoneum (rather than performing multiple limited excisions of small scattered nodules) might add a negligible risk for complication, being a relatively simple and safe procedure.

To our knowledge, this is the largest study on operative outcomes of cytoreduction and HIPEC. Two series of 510 and 1290 procedures have been reported, but these studies did not focus on complications as primary endpoints.[10,33] Nevertheless, our study might lack statistical power to detect weaker associations with morbidity. Other HIPEC-related variables, namely exposure techniques, duration, and temperature, could affect operative outcome, but our standardized protocol made possible only to determine the association of cisplatin dose with morbidity. An additional criticism may involve the retrospective nature of the study, leading to a likely underestimation of complication rates. This potential drawback, however, was partially overcome by taking advantage of our prospective and exhaustive clinical database and limiting our analysis to complications requiring invasive therapeutic procedures.

Although other groups report decreased complications in most recent updates, thus suggesting the existence of a learning curve,[31,35] lower morbidity (12%) and mortality (0.9%) were observed in the first 209 combined procedures performed in our center.[21] This may be partly explained by the adoption of a more accurate adverse event classification. Furthermore, in recent years, we started a rare PSM treatment program. Because high PCI in pseudomyxoma and mesothelioma is not necessarily associated with worse prognosis, the increased proportion of patients at higher risk for moderate/severe morbidity, because of extensive disease, may have masked any improvement in surgical management. The issue of the learning curve was assessed in a parallel study using more sophisticated statistical analyses.

In conclusion, combined treatment is associated with low mortality and acceptable morbidity, when performed in a high-volume center. Operative outcome is mainly affected by a complex interplay of tumor, patient, and treatment-related factors. Careful analysis identified a subset of patients unlikely to tolerate aggressive management.

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