

# Treatment of Peritoneal Carcinomatosis by Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemoperfusion (IHCP): Postoperative Outcome and Risk Factors for Morbidity

Franco Roviello,<sup>1</sup> Daniele Marrelli,<sup>2</sup> Alessandro Neri,<sup>2</sup> Daniela Cerretani,<sup>3</sup> Giovanni de Manzoni,<sup>4</sup> Corrado Pedrazzani, MD,<sup>2</sup> Tommaso Cioppa, MD,<sup>2</sup> Giacomo Nastri, MD,<sup>2</sup> Giorgio Giorgi,<sup>3</sup> Enrico Pinto<sup>2</sup>

<sup>1</sup>Department of Human Pathology and Oncology, Advanced Surgical Oncology Unit, University of Siena, Policlinico Le Scotte, Viale Bracci, 53100 Siena, Italy

<sup>2</sup>Department of Human Pathology and Oncology, Surgical Oncology Unit, University of Siena, Policlinico Le Scotte, Viale Bracci, 53100 Siena, Italy

<sup>3</sup>Department of Pharmacology, University of Siena, Policlinico Le Scotte, Viale Bracci, 53100 Siena, Italy

<sup>4</sup>Department of General Surgery, University of Verona, Ospedale Borgo Trento, Verona, Italy

---

## Abstract

**Background:** Cytoreductive surgery with limited or extended peritonectomy associated with intraperitoneal hyperthermic chemoperfusion (IHCP) has been proposed for treatment of peritoneal carcinomatosis (PC) from abdominal neoplasms.

**Methods:** Fifty-nine patients with PC from abdominal neoplasms underwent 61 treatments using this technique from January 2000 to August 2005. Surgical debulking, completed by partial or total peritonectomy, was performed in most cases. In 16 patients with positive peritoneal cytology without macroscopic peritoneal disease, IHCP was performed in order to prevent peritoneal recurrence. IHCP was carried out throughout the abdominopelvic cavity for 60 minutes using a closed abdomen technique. Intra-abdominal temperature ranged between 41°C and 43°C; *mitomycin C* (25 mg/mq) and *cisplatin* (100 mg/mq) were the anticancer drugs generally used, and they were administered with a flow rate of 700–800 ml/minute.

**Results:** Mean hospital stay was 13 ± 7 (range 7–49) days. Postoperative complications occurred in 27 patients (44.3%); of these, major morbidity was observed in 17 (27.9%). The most frequent complications were wound infection (9 cases), grade 2 or greater hematological toxicity (5 cases), intestinal fistula (5 cases), and pleural effusion requiring drainage (5 cases). Reoperation was necessary in 5 patients (8.2%). One patient with multiorgan failure died in the postoperative period (mortality rate: 1.6%). Multivariate analysis of several variables identified completeness of cancer resection (CCR-2/3 vs. CCR-0/1, relative risk: 9.27) and age (relative risk: 1.06 per year) as

---

List of Abbreviations: PC, Peritoneal carcinomatosis; IHCP, Intra-peritoneal hyperthermic chemoperfusion; CCR, Completeness of cancer resection; MOF, Multiorgan failure

Correspondence to: Franco Roviello, Franco Roviello, via de Gasperi, 5, 53100 Siena, Italy, e-mail: roviello@unisi.it

independent predictors of postoperative morbidity. Preliminary follow-up data indicate that survival probability may be high in patients with ovarian or colorectal cancer and low in patients with gastric cancer.

*Conclusions:* IHCP combined with cytoreductive surgery involves a high risk of morbidity, but postoperative complications could be resolved favorably in most cases with correct patient selection and adequate postoperative care. Tumor residual and advanced age significantly increase the risk of morbidity after this procedure.

**P**eritoneal carcinomatosis (PC) is one of the most common routes of dissemination of abdominal neoplasms; it may be present at the time of diagnosis of the primary tumor, but it arises more frequently as a tumor recurrence after radical surgical treatment.<sup>1</sup> In gastric cancer, peritoneal recurrence occurs in about 20% of patients treated with radical surgery; this rate is much higher in some subgroups of patients (69% at 5 years in diffuse or mixed histotype involving the serosa, about 80% in patients with positive peritoneal cytology).<sup>2-4</sup> PC is less frequent in colorectal cancer with respect to gastric cancer; however, mucinous carcinoma, appendiceal cancer, and cases with positive peritoneal cytology show high rates of peritoneal dissemination.<sup>5</sup> Invasion of the ovarian capsule and dissemination in the peritoneal cavity is the main route by which ovarian carcinoma spreads.<sup>6</sup>

PC from nongynecological tumors is generally considered a lethal disease, with a mean survival time of 3–6 months after conventional chemotherapeutic treatments.<sup>7,8</sup> While systemic chemotherapy has little impact on the treatment of peritoneal disease, some centers have reported encouraging results with intraperitoneal hyperthermic chemoperfusion (IHCP).<sup>8-10</sup> The principle of locoregional treatments is to obtain an elevated and persistent drug concentration for the tumor while limiting systemic concentration. IHCP combines the direct effects of hyperthermia against the tumor cells with the effects of locoregional chemotherapy; anticancer activity of several chemotherapeutic agents and their tissue penetration is also enhanced by hyperthermia. Surgical procedures, including debulking of abdominal tumor mass, resection of organs involved by primary tumors, and partial or total peritonectomy, are often combined with IHCP in order to reduce tumor volume.<sup>8,11</sup>

In this study, we report the results of our experience with this type of treatment, with special reference to postoperative outcome and potential risk factors for morbidity.

## MATERIALS AND METHODS

For the present study, we considered 59 patients (16 men and 53 women, mean age  $55 \pm 11$  years, range

30–72) who underwent surgical treatment and IHCP between January 2000 and August 2005. Two patients were submitted to double treatment, making a total of 61 procedures. This series represents a selected population of patients with PC from abdominal neoplasms observed at the Department of Human Pathology and Oncology, Surgical Oncology Unit, University of Siena. The indication to perform this procedure was based upon the following criteria: absence of hepatic or extra-abdominal metastases, good general conditions, and patients aged 72 years or younger. Initially, 70 years was considered the age limit for patient eligibility. Recently, however, 2 patients aged 71 and 72 years with good general conditions were submitted to this treatment, thus increasing the age limit to 72 years.

Primary tumor was ovarian carcinoma in 24 patients, colorectal carcinoma in 19, gastric carcinoma in 12, pseudomyxoma in 3, and mesothelioma in 1. Preoperative evaluation always included a thoracic and abdominal computed tomography scan to stage peritoneal disease and exclude distant metastases; upper digestive endoscopy and colonoscopy generally completed tumor staging. A careful preoperative evaluation of the patients' general conditions was always performed and included complete blood tests, electrocardiogram, cardiac ultrasound, and spirometry. Informed consent was obtained from all patients.

Complete intraoperative staging of peritoneal disease was performed immediately after a midline laparotomy incision. Biopsy of peritoneal nodules and examination of peritoneal cytology or biopsy of hepatic lesions were performed in doubtful cases. In 45 cases, PC confirmed by histopathological examination was present; the presentation of PC was synchronous in 22 cases and metachronous in 23 cases. In 16 patients, on the contrary, (7 with colorectal cancer, 6 with gastric cancer, and 3 with ovarian cancer), positive peritoneal cytology without macroscopic peritoneal disease was observed. In this latter group, IHCP was performed in order to prevent peritoneal recurrence after radical surgery; 11 of these 16 patients were reoperated 1 month after surgical resection of the primary tumor because definitive peritoneal cytology was positive.

PC stage was classified according to the Lyon group criteria<sup>8</sup>, as follows: stage 0 in 16 cases, stage 1 in 5, stage 2 in 9, stage 3 in 19, and stage 4 in 12. Surgical debulking was carried out in order to reduce tumor volume where necessary. Including multiple resection cases, hysteroadnexectomy was performed in 19 patients, surgical resection of colon or rectum in 13, splenectomy in 7, small intestine resection in 6, partial or total gastrectomy in 5, partial cystectomy in 3, and nephrectomy in 1.

The peritonectomy procedure was conducted according to Sugarbaker's surgical guidelines,<sup>11</sup> and peritoneum was removed in the following number of abdominal regions: 1–3 regions (partial) in 21 cases, 4–6 regions (extended) in 17, and more than 6 regions (total) in 10; no peritonectomy was performed in 13 cases. Three patients with ovarian cancer and positive peritoneal cytology without evidence of PC were submitted to pelvic peritonectomy associated with hysteroadnexectomy because microscopic tumor implants to pelvic peritoneum were suspected even if not confirmed by definitive histopathological examination. Generally, in patients submitted to subdiaphragmatic peritonectomy, intrathoracic drainage was positioned during the operation. The completeness of cancer resection (CCR) was classified as: CCR-0 (no residual tumor) in 37 cases, CCR-1 (no residual nodule greater than 2.5 mm in diameter) in 14, CCR-2 (no residual nodules greater than 25 mm) in 5, and CCR-3 (residual nodules greater than 25 mm) in 5.<sup>8</sup>

After surgical debulking, 5 silicon drains were inserted in the abdomen, temperature probes were positioned above the mesocolon and in the pelvis, and the abdominal wall was then closed. IHCP was performed using a specific device (RAND Performer, Modena, Italy), with two pumps (inflow and outflow), a thermal exchanger, and a sterile closed circuit, as described elsewhere.<sup>12</sup> This device is equipped with software for continuous monitoring and management of temperatures (esophageal, inflow, outflow, subdiaphragmatic, pelvic), flow rate, volume of perfusate, and pressures (inflow, outflow, intraperitoneal). After reaching an intra-abdominal temperature of at least 41°C, chemotherapeutics were injected in the perfusate and circulated with a flow rate of 700–800 ml/minute for 60 minutes. Oxaliplatin (460 mg/mq) was administered in four patients with PC from colorectal cancer; in all other patients, mitomycin C (25 mg/mq) and cisplatin (100 mg/mq) were used. Intra-abdominal temperature during circulation was kept between 41°C and 43°C. A cooling and washing phase followed for 10 minutes. Anastomoses were always performed at the end of IHCP after abdominal relaparotomy. Mean duration of surgery was  $7.8 \pm 2.6$  (range 3–18) hours. At the end of operation,

patients were admitted to the intensive care unit for at least 48 hours and then returned to the surgical department when cardiovascular and pulmonary functions became stable. Continuous monitoring of hepatic and renal functions and hydroelectrolytic balance were performed afterward. Antibiotic and thromboembolic prophylaxes were administered to all patients.

## Statistical Analysis

In the present study, an analysis of postoperative complications was performed. All clinical, histopathological and follow-up data were stored in a database. The chi-squared test was used to assess statistical significance of the association between variables and incidence of complications. Nonparametric data were compared using variance analysis. Independent predictors of morbidity were assessed by means of a multivariate analysis using a logistic regression model, as described elsewhere.<sup>13</sup> The presence of postoperative complications was considered as the dependent variable whereas gender, age, body mass index, primary tumor, previous systemic chemotherapy, operative time, extent of peritonectomy, visceral anastomosis, stage of PC, and CCR were covariates. In the statistical program, parameters of the model were estimated using the maximum-likelihood method. Significant variables were included in the model by means of forward stepwise selection. Starting with a model containing only the constant, at each step, the variable with the smallest significance value entered the model, with a default level of  $P < 0.05$ . The significance value of each factor was reassessed at each step; if a variable in a forward stepwise block exceeded a significance level of 0.1, it was removed from the model. Removal testing was based on the probability of the likelihood-ratio statistic. Follow-up finished on 31 December 2005, and the mean follow-up period was  $25 \pm 19$  (range 1–68) months. Survival curves were calculated according to the Kaplan–Meier model. Deaths included those resulting from tumor recurrence as well as other causes. The Statistical Package for the Social Sciences software (version 11.0) (SPSS, Chicago, IL, USA) was used for statistical analysis.

## RESULTS

### Postoperative Complications

For morbidity rate, we considered postoperative complications that occurred during the hospital stay or within

**Table 1.**

List of postoperative complications observed in 27 patients.  
Multiple complications are included

Complication	No. of cases	Treatment (no. of cases)
<b>Surgical</b>		
Wound infection	9	Drainage
Pleural effusion requiring drainage	5	Percutaneous drainage
Intestinal fistula <sup>a</sup>	5	Reoperation (4); medical (1)
Abdominal abscess	2	US-guided drainage
Prolonged ileus	1	Medical
Bleeding from gastric ulcer	1	Endoscopic haemostasis
Intra-abdominal bleeding	1	Reoperation
MOF (death)	1	
<b>Medical</b>		
Grade $\geq 2$ hematological toxicity	5	Medical
Acute renal failure	2	Medical
Arrhythmias	2	Medical
Cutaneous rash	1	Medical

US: ultrasound; MOF: multiorgan failure.

<sup>a</sup>Duodenal stump leakage in two cases.

30 days from surgery. In 27 patients, we observed postoperative complications (morbidity rate: 44.3%); major morbidity was observed in 17 patients (27.9%), and in 5 patients (8.2%), a reoperation was necessary. One patient with multiorgan failure (MOF) died in the postoperative period (mortality rate: 1.6%). A list of all complications observed is reported in Table 1. Surgical morbidity, including multiple complications, was observed in 25 cases and medical complications in 10. The most frequent complications were wound infection, pleural effusion requiring drainage, intestinal fistula, and grade-2 or more hematological toxicity. Transient polyuria and slight pleural effusion were present in several patients and were not considered in the morbidity rate because they resolved spontaneously within a few days. Only patients with pleural effusion requiring drainage were considered in the morbidity rate.<sup>14</sup> Four patients with intestinal fistula were reoperated: a small bowel resection was performed in 2, 1 was treated with a colostomy, and 1 underwent closure of a duodenal stump leakage; another patient with duodenal stump leakage was conservatively treated. All these patients recovered, with a mean hospital stay of 29 days.

Two patients with an abdominal abscess underwent ultrasound-guided drainage, and one who was bleeding from a gastric ulcer was treated by endoscopic hemostasis. One patient with intra-abdominal bleeding was reoperated. All other complications were successfully

treated by medical therapy. Two cases of acute renal failure were resolved by medical therapy within a few days, and no dialytic treatment was required. Mean hospital stay was  $13 \pm 7$  (range 7–49) days; these values were  $16 \pm 9$  in patients with complications versus  $10 \pm 2$  in patients without complications ( $P < 0.001$ ). An analysis of potential risk factors for postoperative morbidity was performed. By univariate analysis, operative time ( $P = 0.039$ ) and residual nodules larger than 2.5 mm (CCR-2 or CCR-3) ( $P = 0.017$ ) were associated with an higher incidence of postoperative complications (Table 2). Morbidity rate was particularly high in the latter (80%). A trend to a more advanced age was observed in patients with postoperative complications even if not statistically significant. In 16 patients with positive peritoneal cytology, morbidity rate was 50% (8 cases). Major morbidity was present in 3 of these patients (one intestinal fistula and two duodenal stump leakages), but no mortality was observed. Multivariate analysis identified CCR-2/3 [relative risk (RR): 9.27] and advanced age (RR: 1.06 per year) as independent predictors of postoperative morbidity (Table 3).

## Preliminary Survival Data

At the follow-up end date, 58 patients were available for survival analysis whereas 1 patient was lost at follow-up. Of the 58 patients, 30 (51.7%) were alive without evidence of disease with a mean follow-up period of  $25 \pm 21$  months, 12 (20.7%) were alive with disease, and 16 (27.6) died of disease. Cumulative 5-year overall survival was 50.8%. Preliminary follow-up data from our experience indicate that survival probability may be good in patients with ovarian and colorectal cancer and low in patients with gastric cancer (Fig. 1).

## DISCUSSION

The modern approach to neoplastic disease includes the use of locoregional treatments, often combined with surgical debulking and systemic chemotherapy. IHCP associated with cytoreductive surgery is becoming a widely accepted procedure for the prevention or treatment of PC from abdominal cancer.<sup>8</sup> This indication is based upon the concept that PC may be considered a locoregional condition not necessarily associated with a systemic dissemination of the disease. Several biological and clinical studies support this hypothesis.<sup>15</sup>

**Table 2.**  
Association between morbidity and clinical variables

Variable	No. of cases	With complications	Without complications	P value
Gender				0.785
Male	17	8 (47%)	9 (53%)	
Female	44	19 (43%)	25 (57%)	
Age (years)		58 ± 9	53 ± 12	0.117
Body mass index (kg/m <sup>2</sup> )		26.0 ± 5.8	24.8 ± 4.3	0.337
Primary tumor				0.993
Colon–rectum	20	9 (45%)	11 (55%)	
Stomach	12	5 (42%)	7 (58%)	
Ovary	25	11 (44%)	14 (56%)	
Others	4	2 (50%)	2 (50%)	
Previous systemic chemotherapy				0.973
Performed	36	16 (44%)	20 (56%)	
Not performed	25	11 (44%)	14 (56%)	
Operative time (hours)		8.5 ± 3.0	7.1 ± 2.1	0.039
Peritonectomy (no. of removed areas)				0.661
> 6	10	6 (60%)	4 (40%)	
4–6	17	6 (35%)	11 (65%)	
1–3	21	9 (43%)	12 (57%)	
None	13	6 (46%)	7 (54%)	
Visceral anastomosis				0.355
Performed	21	11 (52%)	10 (48%)	
Not performed	40	16 (40%)	24 (60%)	
Stage of peritoneal carcinomatosis				0.346
0	16	8 (50%)	8 (50%)	
1–2	14	8 (57%)	6 (43%)	
3–4	31	11 (35%)	20 (65%)	
Completeness of cancer resection				0.017
CCR-0	37	16 (43%)	21 (57%)	
CCR-1	14	3 (21%)	11 (79%)	
CCR-2/3	10	8 (80%)	2 (20%)	

**Table 3.**

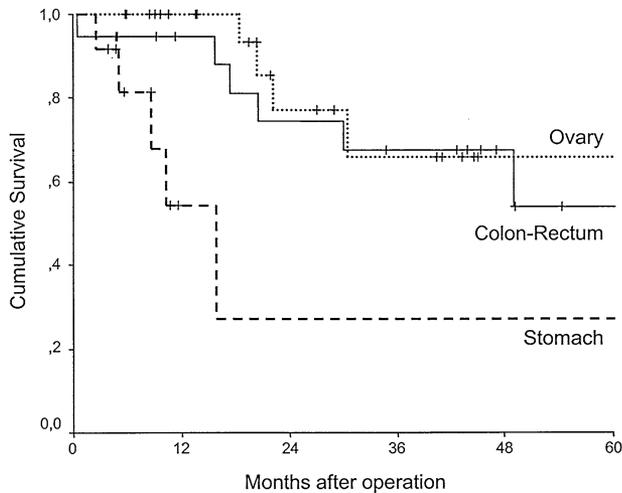
Independent predictors of postoperative complications (logistic regression model)

Variable	Coefficient	SE (coefficient)	P value	Relative risk
Completeness of cancer resection (CCR-2/3 vs. CCR-0/1)	2.22	0.89	0.012	9.27
Age (per year)	0.06	0.03	0.045	1.06

SE: standard error

Like reports in several studies, the results of our experience with IHCP indicate that, even when combined with an aggressive surgical procedure, this technique is associated with an acceptable risk of postoperative complications and mortality.<sup>8,10,14,16–18</sup> An extended surgical procedure was performed in most of our patients in order to reduce tumor volume, including several cases with visceral resections. Even though a fairly high incidence of postoperative complications was observed, this rate was similar to that of other reports.<sup>18–23</sup> Major morbidity and postoperative mortality occurred in 27.9% and

1.6% of patients, rates that overlap with the incidence reported by specialized centers.<sup>10,14,24,25</sup> In particular, the mortality rate in our patients was lower than other recent experiences.<sup>21,23,26</sup> One death due to MOF was observed; this patient had very advanced disease with a large residual tumor, and a long operative time was required. All other complications were successfully treated with surgical or medical therapy; as such, the lethality of complications in our patients was minimal. We believe that careful preoperative selection of patients and adequate postoperative monitoring and care are crucial in



**Figure 1.** Cumulative survival according to primary tumor in 54 patients.

order to minimize the incidence and the lethality of postoperative complications in patients submitted to IHCP. Additionally, the device we used, which was specifically designed for this treatment, allowed continuous monitoring of treatment phases, and this probably contributed to reducing the lethality of complications. Septic complications (wound infections, abdominal abscesses) were the most common causes of morbidity in our patients. These complications have frequently been observed by other authors.<sup>14,16,24</sup> Neoplastic disease in an advanced stage, immunodeficiency in patients previously subjected to chemotherapy, and extended surgical procedure associated with IHCP were all factors that probably contributed to the occurrence of septic complications. Two patients were subjected to percutaneous drainage of an abdominal abscess whereas all other patients were successfully treated with medical therapy.

Intestinal fistula has been reported to be an important cause of morbidity and mortality in patients submitted to IHCP, with an incidence rate ranging from 6% to 27%.<sup>14,17,20,24,27,28</sup> In a recent paper, Younan *et al.*<sup>27</sup> reported male gender, duration of surgery, and no previous systemic chemotherapy to be independent predictors of bowel complications. IHCP has a detrimental effect on the strength of visceral anastomosis, and in patients submitted to IHCP, even nonresective procedures can be associated with intestinal fistula in the postoperative period.<sup>28,29</sup> We always performed anastomotic suture following IHCP and relaparotomy; 2 duodenal stump leakages were observed, and three other cases of intestinal fistula were due to intestinal perforation not involving anastomosis. We immediately reoperated four patients when biliary or fecal drainage was observed whereas one

patient with duodenal stump leakage was conservatively treated. All these patients recovered favorably, and there was no mortality. An interventional approach should be considered when this life-threatening complication occurs in patients submitted to IHCP.

Recent studies have reported the duration and extent of surgery, visceral resections, carcinomatosis stage, and incomplete cytoreduction as important risk factors for postoperative complications after cytoreductive surgery and IHCP.<sup>14,20,24</sup> In our patients, the presence of residual nodules greater than 2.5 mm and advanced age were independent predictors of postoperative morbidity whereas duration of surgery was a significant factor only at univariate analysis. We excluded from treatment patients older than 72 years, but nonetheless, patient age influenced morbidity. In 80% of patients with CCR-2/3, we observed postoperative complications, including 1 patient who died and 3 who required reoperation. The presence of tumor residual is directly related to PC stage and often to the extent of surgery performed. In our series, the number of patients with CCR-2/3 was low (10 cases only); as a consequence, even if the morbidity rate was very high, the number of complicated events in this group represented a minority of the overall events observed (8 out of 27). The limited number of patients did not allow further stratifications (*i.e.*, extent of surgery by residual tumor), and for these reasons, the potential impact of other factors on morbidity cannot be excluded. Extended surgery is justified in order to obtain optimal surgical cytoreduction, which is associated with improved long-term survival.<sup>16,17,25,30</sup> As the extent of tumor residual influences both morbidity and long-term outcome of patients with PC, in our opinion, this factor should be carefully considered in the evaluation of risk/benefit ratio in individual patients.

Preliminary survival data from our experience indicate that high long-term survival could be achieved in patients with ovarian and colorectal cancer, as observed in larger studies reported in the literature.<sup>16,23,26,28,30,31</sup> A recent multicenter study from 28 institutions, performed on 506 patients with PC from colorectal cancer, reported a median survival of 19.2 months.<sup>30</sup> A Korean study compared IHCP with conventional treatments in stage Ic-III ovarian cancer and found a significant improvement in both disease-free and overall survival in the former.<sup>28</sup> Completeness of cytoreduction is a strong determinant of outcome in patients treated with IHCP.<sup>16,26,30,31</sup> Complete cytoreduction was obtained in most of our patients, which is indicative of an appropriate patient selection. This factor, together with the inclusion of patients with only microscopic peritoneal disease, could explain the high survival rates observed.

Survival was notably lower in our patients with gastric cancer. Ovarian and colorectal cancer are more sensitive to anticancer drugs with respect to stomach cancer, and this could justify the different results obtained. Although a limited group of patients with gastric cancer was analyzed, 5-year and median survival from our experience were very similar to those in recent larger studies.<sup>25,32,33</sup> We believe that, particularly in patients with gastric cancer, IHCP could play a more important role in the prevention of peritoneal recurrence after radical surgery for primary carcinoma rather than in treatment of PC. High-risk groups, such as diffuse-mixed type involving the serosa, or patients with positive peritoneal cytology, may particularly benefit from this treatment.<sup>2-4</sup> At present, a number of studies have been performed regarding prevention of PC from gastric cancer, with conflicting results.<sup>34,35</sup> However, none of these selected eligible patients according to these criteria.

In 16 patients with positive cytology in peritoneal washing, we performed IHCP with adjuvant intent. Eleven of these patients were reoperated and subjected to IHCP 1 month after surgical resection of the primary tumor. The operation was deferred because intraoperative cytological examination of peritoneal washing is not a standard procedure in our department, and it is associated with a high rate of false negative results. Morbidity rate in these patients was 50%, including 2 patients with duodenal stump leakage, 1 with intestinal fistula, and 5 who suffered from minor complications. Even if no macroscopic PC was present, in 5 cases, resective surgery for removal of the primary tumor was associated with IHCP, and in other patients, an extended viscerolysis was necessary. This could explain the postoperative complications observed. At present, the low number of patients and short follow-up time prevent evaluation of long-term results. In light of the very poor survival probability of patients with positive peritoneal cytology reported by other authors, we believe that these patients may be candidates for IHCP in order to prevent peritoneal recurrence of the disease.<sup>36,37</sup> Application of this technique with adjuvant intent may represent a new frontier in surgical oncology.

In conclusion, even if IHCP combined with cytoreductive surgery involves a high risk of morbidity, postoperative complications could be resolved favorably in most cases with correct patient selection and adequate postoperative care, thus minimizing mortality. Tumor residual and advanced age significantly increase the risk of morbidity after this procedure; as such, these factors should be carefully considered in the evaluation of risk/benefit ratio in individual patients.

## ACKNOWLEDGMENTS

This work was supported by grant from Fondazione Monte dei Paschi di Siena, 1999, Italy.

## REFERENCES

1. Sugarbaker PH. (1996) Peritoneal carcinomatosis: natural history and rational therapeutic interventions using intraperitoneal chemotherapy. In: Sugarbaker PH, editor. Peritoneal carcinomatosis: drugs and disease Kluwer, Boston, pp 149–168.
2. Marrelli D, Roviello F, De Manzoni G, *et al.* (Italian Research Group for Gastric Cancer). Different patterns of recurrence in gastric cancer depending on Lauren's histological type: longitudinal study. *World J Surg* 2002;26:1160–1165.
3. Roviello F, Marrelli D, de Manzoni G, *et al.* (Italian Research Group for Gastric Cancer). A prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg* 2003;90:1113–1119.
4. Bando E, Yonemura Y, Takeshita Y, *et al.* Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. *Am J Surg* 1999;178:256–262.
5. Pestieau SR, Sugarbaker PH. Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. *Dis Colon Rectum* 2000; 43:1341–1346.
6. Sugarbaker TA, Chang D, Koslowe P, *et al.* Pathobiology of peritoneal carcinomatosis from ovarian malignancy. *Cancer Treat Res* 1996;81:63–74.
7. Sadeghi B, Arvieux C, Glehen O, *et al.* Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000;88:358–363.
8. Glehen O, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. *Lancet Oncol* 2004;5:219–228.
9. Fujimoto S, Takahashi M, Mutou T, *et al.* Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer* 1997;79:884–891.
10. Witkamp AJ, de Bree E, Kaag MM, *et al.* Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin. *Eur J Cancer* 2001;37:979–984.
11. Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995;221:29–42.
12. Cerretani D, Nencini C, Urso R, *et al.* Pharmacokinetics of Mitomycin C after resection of peritoneal carcinomatosis and intraperitoneal chemohyperthermic perfusion. *J Chemother* 2005;17:56–61.

13. Marrelli D, De Stefano A, de Manzoni G, *et al.* Prediction of recurrence after radical surgery for gastric cancer. A scoring system obtained from a prospective multicenter study. *Ann Surg* 2005;241:247–255.
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. Nishimori H, Yasoshima T, Denno R, *et al.* A novel experimental mouse model of peritoneal dissemination of human gastric cancer cells: different mechanisms in peritoneal dissemination and hematogenous metastasis. *Jpn J Cancer Res* 2000;91:715–722.
16. 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.
17. Glehen O, Mithieux F, Osinsky D, *et al.* Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. *J Clin Oncol* 2003;21:799–806.
18. Ahmad SA, Kim J, Sussman JJ, *et al.* Reduced morbidity following cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion. *Ann Surg Oncol* 2004;11:387–392.
19. Pilati P, Mocellin S, Rossi CR, *et al.* Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from colon adenocarcinoma. *Ann Surg Oncol* 2003;10:508–513.
20. Verwaal VJ, van Tinteren H, Ruth SV, *et al.* Toxicity of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. *J Surg Oncol* 2004;85:61–67.
21. Cavaliere F, Perri P, Di Filippo F, *et al.* Treatment of peritoneal carcinomatosis with intent to cure. *J Surg Oncol* 2000;74:41–44.
22. Schmidt U, Dahlke MH, 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.
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. 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.
25. Yonemura Y, Kawamura T, Bandou E, *et al.* Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. *Br J Surg* 2005;92:370–375.
26. 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.
27. Younan R, Kusamura S, Baratti D, *et al.* Bowel complications in 203 cases of peritoneal surface malignancies treated with peritonectomy and closed-technique intraperitoneal hyperthermic perfusion. *Ann Surg Oncol* 2005;12:910–918.
28. Ryu KS, Kim JH, Ko HS, *et al.* Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. *Gynecol Oncol* 2004;94:325–332.
29. Makrin V, Lev-Chelouche D, Even Sapir E, *et al.* Intraperitoneal heated chemotherapy affects healing of experimental colonic anastomosis: an animal study. *J Surg Oncol* 2005;89:18–22.
30. 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.
31. Zanon C, Chiara R, Chiappino I, *et al.* Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. *World J Surg* 2004;28:1040–1045.
32. Glehen O, Schreiber V, Cotte E, *et al.* Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. *Arch Surg* 2004;139:20–26.
33. Hall JJ, Loggie BW, Shen P, *et al.* Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for advanced gastric cancer. *J Gastrointest Surg* 2004;8:454–463.
34. Yonemura Y, de Aretxabala X, Fujimura T, *et al.* Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. *Hepatogastroenterology* 2001;48:1776–1782.
35. Kunisaki C, Shimada H, Nomura M, *et al.* Lack of efficacy of prophylactic continuous hyperthermic peritoneal perfusion on subsequent peritoneal recurrence and survival in patients with advanced gastric cancer. *Surgery* 2002;131:521–528.
36. Bentrem D, Wilton A, Mazumdar M, *et al.* The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. *Ann Surg Oncol* 2005;12:347–353.
37. Koppe MJ, Boerman OC, Oyen WJ, *et al.* Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006;243:212–222.