

Surgery Combined With Peritonectomy Procedures and Intraperitoneal Chemohyperthermia in Abdominal Cancers With Peritoneal Carcinomatosis: A Phase II Study

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Purpose: To evaluate the tolerance of peritonectomy procedures (PP) combined with intraperitoneal chemohyperthermia (IPCH) in patients with peritoneal carcinomatosis (PC), a phase II study was carried out from January 1998 to September 2001.

Patients and Methods: Fifty-six patients (35 females, mean age 49.3) were included for PC from colorectal cancer (26 patients), ovarian cancer (seven patients), gastric cancer (six patients), peritoneal mesothelioma (five patients), pseudomyxoma peritonei (seven patients), and miscellaneous reasons (five patients). Surgeries were performed mainly on advanced patients (40 patients stages 3 and 4 and 16 patients stages 2 and 1) and were synchronous in 36 patients. All patients underwent surgical resection of their primary tumor with PP and IPCH (with mitomycin C, cisplatinum, or both) with a closed sterile circuit and inflow temperatures ranging from 46° to 48°C. Three patients were included twice.

Results: A macroscopic complete resection was performed in 27 cases. The mortality and morbidity rates were one of 56 and 16 of 56, respectively. The 2-year survival rate was 79.0% for patients with macroscopic complete resection and 44.7% for patients without macroscopic complete resection ($P = .001$). For the patients included twice, two are alive without evidence of disease, 54 and 47 months after the first procedure.

Conclusion: IPCH and PP are able to achieve unexpected long-term survival in patients with bulky PC. However, one must be careful when selecting the patients for such an aggressive treatment, as morbidity rate remains high even for an experienced team.

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MOST PATIENTS with peritoneal carcinomatosis (PC) die within 6 months. In a recent multicentric prospective study including 370 patients with PC from nongynecologic malignancies¹ the median overall survival was 3.1 months: 3.1 months for gastric cancer patients, 5.2 months for colorectal cancer patients, 2.1 months for pancreatic cancer patients, and 1.5 months for patients with PC from unknown primary cancer. Research protocols using palliative systemic chemotherapy have been conducted with encouraging tumor response rates, but with no improvement on survival rates.^{2,3}

However, since the end of the 1980s, there has been a renewed interest in PC, and new aggressive and multimode therapeutic approaches have been proposed as intraperitoneal injection of anticancer drugs as OK432,⁴ intracavitary immunotherapy,⁵ photodynamic therapy,⁶ and intraperitoneal chemohyperthermia (IPCH).⁷ After an experimental study on dogs,⁸ IPCH has been used since 1989 in our department. In a phase II study⁹ dedicated to IPCH evaluation in digestive tract cancer patients with PC we reported that the best efficacy of IPCH was achieved for stage 1 or 2 PC (Table 1), whereas stage 3 and 4 did not benefit from IPCH.

In 1995, peritonectomy was first described as a new possible surgical approach for PC.¹⁰ Peritonectomy was then reported as an aggressive procedure with high postoperative morbidity rates,¹¹ but resulting in downstaging the PC and to improve the long-term survival for selected patients.^{7,12}

After a feasibility study on 18 patients in 1997,¹³ in 1998, a prospective nonrandomized phase II trial was initiated using peritonectomy combined with IPCH for abdominal cancer patients with PC.

MATERIALS AND METHODS

Protocol

The type of study was an open, prospective, nonrandomized, monocentric phase II study performed at Centre Hospitalo-Universitaire Lyon-Sud. It was initiated in January 1998 and closed in September 2001.

The inclusion criteria were age younger than 65 years, abdominal cancer patients including malignant peritoneal mesothelioma as well as pseudomyxoma peritonei, PC confirmed by pathologic examination, synchronous or metachronous PC, absence of extraabdominal metastases, no liver metastases on preoperative explorations, satisfactory cardiorespiratory and renal status, and signed informed consent.

The exclusion criteria were unresectable primary tumors, renal or myocardial failures, administration of systemic chemotherapy 1 month before inclusion, CNS disease (vascular or neoplastic), and World Health Organization (WHO) index more than 2.

Before inclusion in the protocol, all patients underwent a physical examination, blood cell count, serum electrolytes, hepatic function test, Quick's test, kaolin-activated partial thromboplastin time test, blinding test, cardiac ultrasound, spirometry, cerebral and thoracic computed tomography

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Table 1. Peritoneal Carcinomatosis Staging

Stage	Peritoneal Carcinomatosis Description
Stage 0	No macroscopic disease
Stage 1	Malignant granulations less than 5 mm in diameter localized in one part of the abdomen
Stage 2	Malignant granulations less than 5 mm in diameter diffuse to the whole abdomen
Stage 3	Malignant granulations 5 mm to 2 cm in diameter
Stage 4	Large malignant cakes (more than 2-cm diameter)

(CT) scan, abdominal ultrasonography for liver exploration and abdominal CT scan for PC exploration, and biologic renal and hemostasis exploration.

The protocol required that for synchronous PC, surgical resection of the primary tumor had to be performed before or at the same time as peritonectomy and IPCH with a maximal allowed delay of 5 weeks; peritonectomy had to minimize as much as possible the residual tumor volume exposed to IPCH; and postoperative systemic chemotherapy was recommended, according to the general status of the patient, at least 6 weeks after IPCH and following the rules for palliative systemic chemotherapy.

This protocol was performed in accordance with the precepts established by the Helsinki declaration, and has been approved by the Lyon Human Investigation Committee.

Surgical Procedures

Under general anesthesia and complete hemodynamic monitoring, careful abdominal exploration and cytological as well as pathologic samples were taken through a median laparotomy (from xyphoid to pubis). Surgical resection of the primary tumor was performed according to oncologic surgical rules (lymphadenectomy, acceptable margins). Once the primary tumor had been removed, a peritonectomy was performed, adapted to the location of the malignant granulations as guided by the surgeon, exploration, and extemporaneous biopsies (systematic, extensive peritonectomies were not performed). These peritonectomies were performed according to Sugarbaker's surgical.¹⁰ Locations of peritonectomy performed were preoperatively recorded on a specific form: right diaphragmatic cupula, left diaphragmatic cupula, greater omentum, lesser omentum, omental bursa, right paracolic gutter, left paracolic gutter, Douglas' pouch, anterior wall peritoneum, posterior wall peritoneum, Glisson capsula, and mesenteric peritoneum (mesenteric peritoneum was not extensively removed, but after acceptable small bowel resections guided by maximal tumor volume locations, remaining malignant granulations were destroyed using electro-surgical fulguration).

Type of IPCH

At the end of each surgical procedure, an IPCH infusion was carried out under general anesthesia and general hypothermia (32°C induced by duration of peritonectomy procedure, cold wraps on the legs, and ice hat). Before closure of the laparotomy, two inflow drains were inserted under the left and right diaphragmatic cupula (30 French silicone drainage, William Harvey, Bard Cardiopulmonary Division, USA), whereas a third drain (outflow drainage) was inserted in the Douglas' pouch (32 French). Thermic probes (Mallinckrodt SA and Cair SA, Lozanne, France) were also inserted within the abdominal cavity (behind the liver pedicula and near the first jejunal loop). Other thermic probes were set up outside the abdominal cavity on the inflow and outflow drains (8 cm from the skin) and inside the bladder with a Foley catheter. Laparotomy was then closed and inflow and outflow drains were connected to a closed sterile circuit in which a 4 to 6 L perfusate (Travenol laboratory, Norfolk, England) was circulated by means of an electromagnetic pump at a flow rate of 500 mL/mn. The closed sterile circuit was heated by means of a thermal exchanger (Dideco, France) connected to a heating circuit. Intra- and extraabdominal temperatures were connected to a thermic reader (Cair SA, Lozanne, France) and monitored every 10 minutes (Fig 1). IPCH was performed for 90 minutes with close monitoring of respiratory and hemodynamic parameters at inflow temperatures ranging between 46°C and 48°C.

Type of Intraperitoneal Chemotherapy (IPC)

For PC from digestive origin, mitomycin C (MMC) was used at the dose of 0.7 mg/kg (maximum dose of 60 mg). For PC from ovarian origin, cisplatin (CDDP) was used at the dose of 1 mg/kg (maximum dose of 80 mg). For PC from peritoneal malignant mesothelioma and pseudomyxoma, MMC and CDDP were combined intraperitoneally at the dose of 0.5 mg/kg and 0.7 mg/kg, respectively. MMC and/or CDDP were inserted in the peritoneal dialysis liquid at the beginning of IPCH.

Laboratory Data

Samples of blood, urine, and perfusate were collected during IPCH at 45 and 90 minutes, and MMC and CDDP concentrations were measured by high-performance liquid chromatography.¹⁴ After the end of IPCH, MMC concentrations were measured at 24 hours and CDDP concentrations at 12, 24, and 72 hours, in blood, urine, and abdominal drainages.

Patients

From January 1998 to September 2001, 56 patients were included in the present study. A great number of selection factors (according to the inclusion and exclusion criteria of the protocol) were used before and after referral and

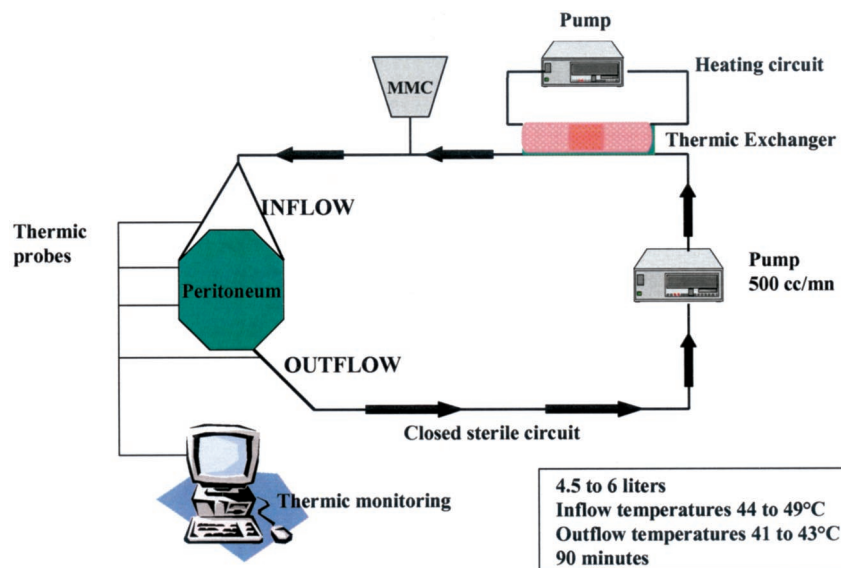


Fig 1. Intraperitoneal chemohyperthermia device.

Table 2. Details on Patient Population

Type	N	Sex	Mean Age	pT	pN	Liver Meta	PC Stage 1	PC Stage 2	PC Stage 3	PC Stage 4	Clinical Presentation	Diff
Right colon	15	8F	49.5	1pT2 9pT3 5pT4	7pN1 7pN2 1pN3	0	4	2	4	8	2 ascitis 2 occlusions 1 perforation	3WD 8MD 4PD
Left colon	11	7F	47.8	5pT3 6pT4	4pN1 7pN2	3	0	2	1	8	1 ascitis	3WD 4MD 4PD
Gastric	6	4F	49.8	2pT3 4pT4	2pN1 4pN2	0	1	1	1	3	2 ascitis	2WD 1MD 3PD
Mesothelioma	5	2F	50.2			0	1	2	0	3	2 ascitis	
Pseudomyxoma	7	5F	51.7			0	1	1	2	3		
Ovarian	7	7F	51.1	1 III a 2 III b 4 III c		0	0	3	1	4		
Miscellaneous	5	2F	45.2			1	0	1	3	1		
Total	56	35F				4	4	12	12	28	7 ascitis	

NOTE. For ovarian carcinoma, FIGO classification is used.

Abbreviations: F, female; N, number; Meta, metastase; PC, peritoneal carcinomatosis; Diff, differentiation; WD, well differentiated; MD, moderately differentiated; PD, poorly or not differentiated.

strongly influenced the composition of this patient population: during the 45-month period of the study, 240 patients with PC were referred to our department for treatment, whereas only 56 met the selection criteria and gave their informed consent. Unfortunately, no data in regard to the follow-up of the 184 excluded patients was obtained. Exclusions were mainly decided according to age, WHO index less than 2, unsatisfactory cardiac or renal functions, clear evidence of massive and total abdominal cavity involvement on clinical examination, and presence of extraabdominal metastasis. The 184 excluded patients were then followed by the referring hospital.

The 56 selected patients were 35 females and 21 males, mean age 49.3 years (SD = 10.7 years, range, 25 to 65). Locations of primary tumor were right colon adenocarcinoma (n = 15), left colon adenocarcinoma (n = 11), gastric adenocarcinoma (n = 6), peritoneal malignant mesothelioma (n = 5), pseudomyxoma peritonei (n = 7), ovarian carcinoma (n = 7), and miscellaneous malignancies (n = 5: three small bowel adenocarcinoma and two adenocarcinoma from unknown primary origin). Details on age and sex according to tumor type, differentiation, pTNM (using 1988 American Joint Committee on Cancer and International Union Against Cancer TNM staging criteria), PC staging according to the PC staging described in Table 1, and clinical presentation are detailed in Table 2.

For 36 patients, PC were synchronous ones and for 20 PC were metachronous ones (diagnosed during the follow-up of a previously resected primary abdominal cancer). Four patients had liver metastases that were removed at the time of treatment. These patients had a normal preoperative liver CT scan and normal liver ultrasonography. They were not excluded from the study. Seven patients presented with abundant ascitis (> 1 L).

Fifteen patients underwent peritonectomy and IPCH 15 to 30 days after surgical resection of their primary tumors (these patients underwent surgery at a different hospital and postoperatively were referred to our center for peritonectomy and IPCH treatments), whereas 21 underwent peritonectomy and IPCH immediately at the end of the surgical removal of their primary tumor. The remaining 20 patients presented metachronous PC and were treated 4 to 46 months (mean 18.0 months, SD = 14.6) after the resection of their primary tumor. All surgical anastomoses were fashioned before the perfusion.

Three patients were included twice in the present study: one 61-year-old female underwent a peritonectomy first and IPCH in March of 1998 for a pseudomyxoma peritonei (PC 4 surgically reduced to PC 3), and a second course treatment in February 1999 (PC 3 surgically reduced to PC 0), one 57-year-old female underwent a first course in July 1998 for a pT3N1 left colon adenocarcinoma (PC 1 surgically reduced to PC 0) and a second course in November 1999 (PC 4 surgically reduced to PC 1), and a third patient, a 31-year-old female underwent a first course in January 1998 for a right colon

adenocarcinoma (PC 2 surgically reduced to PC 0) and a second course in June 2000 (PC 1 surgically reduced to PC 0). The decision to perform a second peritonectomy and IPCH course was based on the persistence of an excellent performance status and evidence of recurrent peritoneal disease (increase in tumor markers, abdominal CT scan findings, abdominal pain episodes, vomiting, and partial bowel obstruction). Details of peritonectomies and digestive organ resections performed are outlined in Tables 3 and 4.

Patient Follow-up

All the patients included in this study were postoperatively transferred to an intensive care unit for 24 hours and then to the surgical department. Mean duration of hospital stay was 15.7 days (SD = 6.4; range, 8 to 41). Clinical, biologic, and radiologic follow-up of the patients was repeated on a monthly basis after discharge from the hospital. Thirty-two of the included patients received postoperative palliative systemic chemotherapy during their follow-up, as indicated in Table 5.

Statistical Analysis

Data were collected and analyzed on a commercially available compute program (Statview 4.5, Abacus Inc., Berkeley, CA) and are expressed as mean, SD, median, and range. The two-tailed Student's *t*-test was used to take into account differences in the mean survival of the different groups. The log-rank and Kaplan and Meier tests were used for analysis of the censored survival rates.

RESULTS

Peritonectomy Results

At the end of the surgical procedures, 27 patients were considered as R0 or R1 resection, whereas 29 underwent an R2 resection.

Pre- and Postoperative Course

No preoperative death occurred. Mean duration of surgery was 6.11 hours (SD = 1.73; range, 4 to 13.5) excluding the duration of IPCH.

Postoperative mortality was 1 of 56 (a 49-year-old man with left colon adenocarcinoma and PC stage 4, treated by left

Table 3. Details on Peritonectomy Locations

	Right Colon	Left Colon	Gastric	Mesothelioma	Pseudomyxoma	Ovary	Miscellaneous	Total
RDC	3	5	1	2	3	4	2	20
LDC	1	1	1	2	2	1	1	9
GO	12	11	7	5	6	6	4	51
LO	3	3	4	3	3	1	1	18
OB	2	0	2	1	3	0	0	8
RCG	11	7	5	3	5	4	2	37
LCG	3	9	1	2	4	1	2	22
DP	3	6	3	2	5	6	3	28
AWP	3	3	2	0	2	2	1	13
PWP	0	3	1	0	2	1	1	8
Glisson	1	0	0	0	3	2	0	6
MF	10	9	4	5	7	5	4	44

Abbreviations: RDC, right diaphragmatic cupula; LDC, left diaphragmatic cupula; GO, great omentum; LO, lesser omentum; OB, omental bursa; RCG, right colon gutter; LCG, left colon gutter; DP, Douglas pouch; AWP, anterior wall peritoneum; PWP, posterior wall peritoneum; MF, mesenteric fulguration.

colectomy, cholecystectomy, omentectomy, R2 resection and IPCH with 60 mg total dose of MMC) died from peritonitis and septicemia on the twenty-seventh postoperative day (massive leakage of colorectal anastomosis).

Postoperative morbidity was 16 of 56 (28.6%), mainly represented by seven of 56 digestive fistulas. There were two colocutaneous fistula medically treated, one ileocolic fistula, and three ileal fistula surgically treated, and one biliary fistula after Glisson's exeresis surgically treated. Other complications were two postoperative prolonged ileus (up to the eleventh and fourteenth days), two right pleurisy (treated by external drainage), one pelvic abscess on the twenty-first postoperative day (treated by external drainage), one patient with severe and prolonged respiratory distress syndrome requiring ventilation up to the twenty-fifth postoperative day, two grade 3 leucopenia (day 5 to day 15), and one temporary renal insufficiency (day 4 to day 12).

Delayed Complications

Two patients complained of sexual troubles 6 months after the treatment: one 54-year-old male with mesothelioma complained of impotence after small bowel resection, left colectomy, poste-

rior wall peritonectomy, and IPCH with MMC and CDDP; one 38-year-old male with gastric adenocarcinoma complained of retrograde ejaculation after total gastrectomy, small bowel resection, Douglas pouch, and anterior wall peritonectomy, and IPCH with MMC.

Thermic and Pharmacokinetics Results

No thermal intolerance occurred, and the mean maximal temperature in the pulmonary artery was 38.5°C (SD = 0.7; range, 37.0 to 39.5). In all patients, the temperature in the pulmonary artery dropped to normal values within 2 to 5 hours after the end of IPCH. Mean maximal inflow, outflow and peritoneal temperatures were 45.0°C (SD = 2.2; range, 41.0 to 49.0), 42°C (SD = 0.9; range, 39.5 to 43.0) and 42.1°C (SD = 0.5; range, 41.0 to 43.0), respectively (Fig 2). Mean maximum values of liver, first jejunal loop, and bladder temperatures were 38.5°C (SD = 0.5; range, 37.0 to 39.0), 42.1°C (SD = 2.1; range, 39.5 to 44.0), and 37.5°C (SD = 0.4; range, 36.0 to 38.1), respectively.

Kinetic studies concerning MMC showed a maximum serum concentration 45 minutes after the beginning of IPCH (mean value 0.251 mg, SD = 0.146 mg; range, 0.200 to 0.577), whereas

Table 4. Details on Digestive Organ Resection

	Right Colon	Left Colon	Gastric	Mesothelioma	Pseudomyxoma	Ovary	Miscel	Total
Right colectomy	13	4	1	1	4	0	1	24
Left colectomy	0	9	0	0	1	0	1	11
Transverse colectomy	0	1	2	0	1	0	0	4
Subtotal colectomy	0	0	0	1	1	0	0	2
Gastrectomy	0	0	6	0	1	0	1	8
Splenectomy	0	1	2	1	1	0	0	5
Cholecystectomy	0	2	3	2	2	1	2	12
Liver resection	1	2	0	0	0	0	0	3
Left pancreatectomy	0	0	0	1	0	0	0	1
Small bowel resection	9	7	0	1	3	2	3	25
Diaphragmatic resection	1	0	0	0	1	1	0	3
Low anterior resection	0	1	0	0	1	0	0	2
Right nephrectomy	1	0	0	0	0	0	0	1
Oophorectomy	2	4	2	0	1	7	1	17
Total hysterectomy	2	2	0	0	2	1	1	8

Abbreviation: Miscel, miscellaneous.

Table 5. Details on Postoperative Systemic Palliative Chemotherapy

	Number of Patients	Type of Chemotherapy
Right colon cancer	8	Fluorouracil Oxaliplatinium Irinotecan
Left colon cancer	8	Fluorouracil Oxaliplatinium Irinotecan
Gastric cancer	3	Fluorouracil Oxaliplatinium
Mesothelioma	4	VP 16 Cisplatinium Gemcitabin
Pseudomyxoma	1	Fluorouracil
Ovarian cancer	3	Carboplatinium Taxol Topotecan Navelbin
Miscellaneous	5	Cisplatinium Oxaliplatinium Fluorouracil

MMC concentration in the perfusate showed a 60% decrease during the time of IPCH. In all patients, MMC disappeared from the blood and urine within 2 hours at the conclusion of IPCH, and MMC was not detectable in the postoperative abdominal fluids.

Kinetic studies concerning CDDP showed a maximum serum concentration 90 minutes after the beginning of IPCH (mean

value 0.555 mg; SD = 0.216; range, 0.364 to 0.913), whereas CDDP concentration in the perfusate showed a 65% decrease during the time of IPCH. In all patients, CDDP was detectable in blood and urine up to 3 days after the end of IPCH, whereas CDDP was detectable in postoperative abdominal fluids up to the fifth day.

Survival Results

Up to the end of August 2002, 14 patients had died (one from myocardial necrosis, 13 from peritoneal recurrences). Mean follow-up was 544.4 days (range, 133 to 1,680). Using the Kaplan and Meier method, the overall 30 month actuarial survival rate was 54.2%. R0 patients mean survival was 558.3 days, whereas it was 360.1 days for R2 patients (*P* = .006). The 2-year actuarial survival rate was 79% for R0 patients (Fig 3) and 44.7% for R2 patients (*P* = .03).

Survival in the Different Subgroups is Detailed in Table 6

Six of the seven patients with preoperative abundant ascitis were free of ascitis up to their death or up to the end of the follow-up (as judged by clinical examination and abdominal ultrasonography). The three patients included twice (two with colon adenocarcinoma and one with pseudomyxoma peritonei) had their second inclusion 16, 29, and 11 months after the first procedure, respectively. They were alive 20, 22, and 36 months after the second procedure. One is alive with disease recurrence and two with no evidence of recurrence.

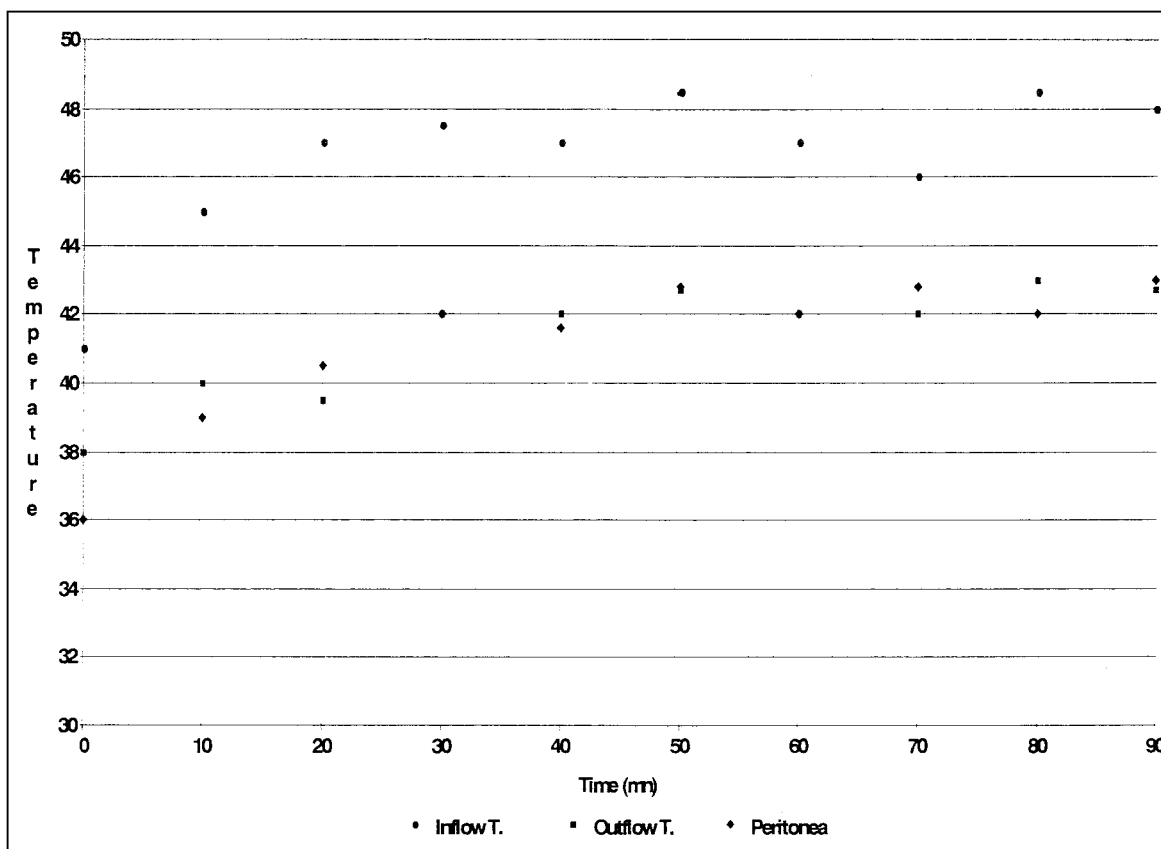


Fig 2. Mean temperatures during intraperitoneal chemohyperthermia .

Survival

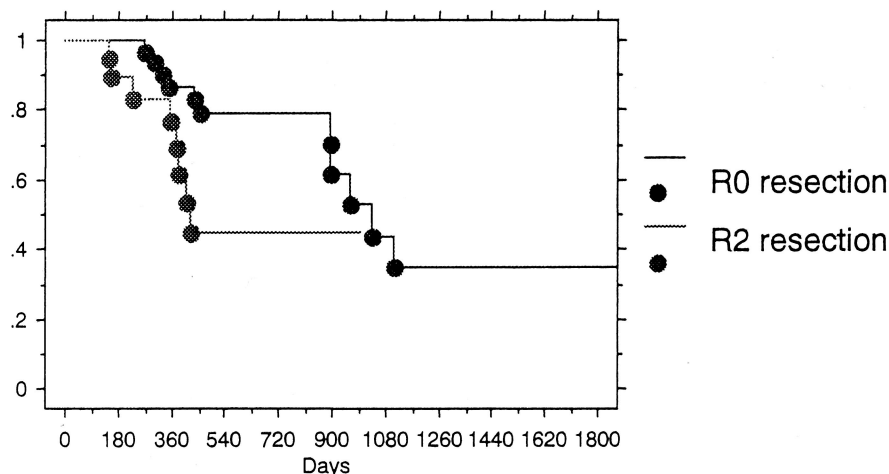


Fig 3. Actuarial survival of R0 and R2 patients with the Kaplan and Meier method.

DISCUSSION

PC has long been considered a fatal clinical entity, and has been treated palliatively. Since the 1980s, there has been a renewed interest in novel therapeutic approaches to PC, especially with IPC and IPCH combined with peritonectomy procedures (PP). The first aim of IPC or IPCH is to rinse out free intraperitoneal cancer cells and to damage peritoneal metastases by simultaneous exposure to heated anticancer drugs.

Up to now, several teams all over the world have reported their experience with IPCH using different devices¹⁵ (open or closed circuit, low or high flow rate) with encouraging preliminary results.^{9,16-19} However, best results were achieved for small volume PC (stage 1 or 2) and the concept of combining IPCH with a surgical procedure maximally reducing the tumor volume seems correct.^{9,20}

Reducing tumor volume has always been considered an important factor in achieving tumor response to chemotherapy.^{16-17,21} The idea of reducing tumor volume in PC has been reported in the past for ovarian cancer. The combination of both peritonectomy and IPCH (with or without hyperthermia) could

act as a “dose intensification device” leading to better results. Theoretically, cytoreductive surgery is performed to treat the macroscopic disease and IPCH to treat the microscopic residual disease to eradicate the disease completely during a single procedure. However, combining two aggressive procedures can lead to greater mortality and morbidity rates with rates as high as 60% morbidity.^{7,22} Of course, performing surgery and IPCH at the same time exposes the patient to anastomotic leakage rates that are higher than with surgery alone. But delaying IPCH after surgery is not very logical when taking into account the free malignant cancer cells remaining inside the abdomen at the end of the surgery.²³ Adhesions induced by prior operations will entrap tumor cells and allow them to progress.²⁴ Tumor cells fixed within scar tissue may not be reached by systemic or by IPC. Delay in definitive treatment of carcinomatosis until disease progression is evident allowing superficial seeding to progress into an invasive process is much more difficult and often impossible to eradicate. The concept indicates that peritonectomy procedures and cytoreductive surgery should remove gross disease, and that intraperitoneal chemotherapy used during the same operative setting will eliminate microscopic residual disease. It is important to note that patients of the reported study were selected using strict criteria (56 patients selected out of a group of 240 patients with PC); therefore, there is an important selection bias in this trial. But this select group (inclusion limited to young patients with good general status, acceptable renal and myocardial function, no systemic chemotherapy administration 1 month before the inclusion, no extraabdominal metastases, no previous abdominal radiation therapy, PC stage evaluation on abdominal CT scan) may achieve improved survival results with an acceptable morbidity rate. This morbidity rate (28.6%) was higher than in the previous reported studies^{9,20} when IPCH was not combined with extensive cytoreductive surgery.

When the primary tumor is not amenable to resection or when the resection does not allow a sufficient reduction in tumor volume, IPCH does not seem to be indicated as the gain in terms of survival is minimal.⁹ In the previous reported studies^{9,13,20} IPCH was performed without extensive cytoreductive surgery. It achieved a morbidity rate of less than 10%. But even when the

Table 6. Mean survival in different subgroups

Subgroups	Mean Survival (Range) (Days)	P
Metachronous PC	459.5 (133 to 1680)	.24
Synchronous PC	593.0 (147 to 1610)	
Chemotherapy post yes	612.0 (139 to 1680)	.17
Chemotherapy post no	463.4 (133 to 1561)	
R0 patients	558.3 (139 to 1680)	.006
R2 patients	360.1 (133 to 991)	
PC before 1	572.0 (269 to 1141)	
PC before 2	785.9 (204 to 1680)	
PC before 3	525.2 (147 to 1561)	
PC before 4	453.5 (133 to 1037)	
Colon adenocarcinoma	525.0 (133 to 1610)	
Gastric adenocarcinoma	356.0 (139 to 556)	
Mesothelioma	975.2 (356 to 1680)	
Pseudomyxoma	647.4 (283 to 1561)	
Ovarian carcinoma	421.2 (156 to 543)	
Miscellaneous	452.6 (317 to 587)	

Abbreviation: PC, peritoneal carcinomatosis.

primary tumors were resected, PC with gross residual tumor (stage 3 or 4) treated by IPCH had a poor prognosis with no patient alive at 1 year. Our experience and also the other reported data^{7,16-18} showed that the best indications of IPCH are when cytoreductive surgery achieves an R0 or R1 resection, with the intent to cure. But its indications can be discussed for the palliative treatment of PC with malignant and debilitating ascites. At the beginning of our experience, we demonstrated, as other teams have,²⁵ that IPCH can lead to ascites regression in 70% of cases and to enhance quality of life. McQuellon et al²⁶ recently reported a better or similar quality of life in 64 patients with PC of digestive origin, 3 months after IPCH. Other issues to be taken into account are realistic survival gains in conjunction with quality of life experienced by the patient as well as cost.

In the reported study, the 2-year survival rates were 79% after complete cytoreductive surgery and 44.7% after incomplete cytoreductive surgery. In gastric cancer, the combination of aggressive surgery with IPCH for the treatment of all stages prolonged survival. Yonemura et al¹⁹ reported survival to 5 years for 11% of 83 patients treated by this combination, with 5 surviving in the long term. The same team also reported survival rates to 3 years in nearly 40% of the cases treated by the combination of peritonectomy-IPCH, compared with only 10% in cases treated by IPCH only.²⁷ For colorectal tumors, the most important experience is that reported by Sugarbaker et al.⁷ In their studies the combination of peritonectomies, extensive resections, and IPCH in cases where surgical reduction of the tumor volume was complete, had survival rates of 3 years in more than 70%. Their survival rates are greater than 20% in cases of incomplete surgical reduction. However, a number of important cases of pseudomyxoma peritonei are included in their studies (for which this combined therapy is the treatment of choice), which does not have the same evolution, nor the same prognosis as colorectal adenocarcinomas.^{28,29} Witkamp et al³⁰ recently reported a survival rate of 81% at 3 years in 46 patients with pseudomyxoma peritonei after combining optimal cytoreductive surgery and IPCH. But the same team as well as Elias et al^{16,18} reported survival rates to 3 years in nearly 40% of patients

with PC of colorectal origin with this aggressive combined treatment. Mesotheliomas and the malignant primary tumors of the peritoneum seem to be good indicators for this combined therapy, peritonectomy-IPCH; allowing survival rates to 3 years for more than 50%.³¹ Finally, it seems that for all these indications a complete cytoreductive resection is needed to achieve improved survival rates, whereas sometimes incomplete cytoreductive resection give unexpected long-term survivals.

In regard to the repeat IPCH and peritonectomy, three patients underwent two procedures and two are alive 54 and 47 months after the first procedure, respectively (22 and 36 months after the second procedure, respectively). These repeated aggressive therapeutic interventions have also been reported by other authors.^{12,32} This second-look surgery seems to be possible in a strictly selected group of patients, especially with PC from appendiceal malignancy and not contraindicated by a first procedure.¹² These are two principal limiting factors for the surgical reduction: the small bowel is only resectable to a certain degree and exposes the patients to a short small bowel postoperatively; the pelvic invasion for which pelvic exenteration are required are too extreme and seem invalid for treatment of PC.

In conclusion, peritonectomy procedures and IPCH are feasible with a high but acceptable morbidity in strictly selected patients, and are able to achieve unexpected long-term survival in patients with PC, especially after complete cytoreductive surgery. Other peritoneal surface malignancy centers have reported similar interesting survival results with this aggressive therapeutic approach of PC in phase II studies. The preliminary results of the Dutch trial comparing IPCH and cytoreductive surgery with intravenous chemotherapy alone in patients with PC of colorectal origin have statistically demonstrated the benefit of this aggressive procedure, which was stopped for ethical reasons.³³ This combined treatment still raises the problems of standardization, in both its indications and techniques, as well as the problem of patient's selection.

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REFERENCES

1. Sadeghi B, Arvieux C, Glehen O, et al: Peritoneal carcinomatosis from non gynecologic malignancies: Results of the EVOCAPE 1 multicentric prospective study. *Cancer* 88:358-363, 2000
2. Chu DZ, Lang NP, Thompson C, et al: Peritoneal carcinomatosis from non gynecologic malignancies. *Cancer* 63:364-367, 1989
3. Briasoulis E, Kalofonos H, Bafaloukos D, et al: Carboplatin plus paclitaxel in unknown primary carcinomas: A phase II Hellenic Cooperative Oncology Group Study. *J Clin Oncol* 18:3101-3107, 2000
4. Torisu M, Katano M, Kimura Y, et al: New approach to management of malignant ascites with a streptococcal preparation OK 432: Improvement of host immunity and prolongation of survival. *Surgery* 93:357-364, 1983
5. Sartori S, Nielsen T, Tassinari D, et al: Evaluation of a standardized protocol of intracavitary recombinant interferon alpha-2b in the palliative treatment of malignant peritoneal effusions. A pilot study *Oncology* 61:192-196, 2001
6. Hendren SK, Hahn SM, Spitz FR, et al: Phase II trial of debulking surgery and photodynamic therapy for disseminated intraperitoneal tumors. *Ann Surg Oncol* 8:65-71, 2001
7. Sugarbaker P, Jablonski KA: Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* 221:124-132, 1995
8. Gilly FN, Carry PY, Sayag AC: Intraperitoneal chemohyperthermia with mitomycin C in dogs. *Int J Hyperthermia* 8:659-666, 1992
9. Beaujard AC, Glehen O, Caillot JL, et al: Intraperitoneal chemohyperthermia with mitomycin C for digestive tract cancer patients with peritoneal carcinomatosis. *Cancer* 88:2512-2519, 2000
10. Sugarbaker P: Peritonectomy procedures. *Ann Surg* 221:29-42, 1995
11. Jacquet P, Stephens AD, Averbach AM, et al: Analysis of morbidity and mortality in 60 patients with PC treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer* 77:2622-2629, 1996
12. Esquivel J, Sugarbaker PH: Second-look surgery in patients with peritoneal dissemination from appendiceal malignancy: Analysis of prognostic factors in 98 patients. *Ann Surg* 234:198-205, 2001
13. Gilly FN, Beaujard AC, Glehen O, et al: Peritonectomy combined with intraperitoneal chemohyperthermia in abdominal cancer with peritoneal carcinomatosis: A phase I-II study. *Anticancer Res* 19:2317-2321, 1999

14. Panteix G, Guillaumont M, Chapin L: Study of the pharmacokinetics of MMC in humans during intraperitoneal chemohyperthermia with special mention of the concentration in local tissues. *Oncology* 50:366-370, 1993
15. Elias D, Antoun S, Goharin A, et al: Research on the best chemohyperthermia technique of treatment of peritoneal carcinomatosis after complete resection. *Int J Surg Investig* 1:431-439, 2000
16. Elias D, Blot F, El Otmány A, et al: Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 92:71-76, 2001
17. Cavaliere F, Perri P, Di Filippo F, et al: Treatment of peritoneal carcinomatosis with intent to cure. *J Surg Oncol* 74:41-44, 2000
18. 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* 37:979-984, 2001
19. Yonemura Y, Fujimura T, Nishimura G, et al: Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. *Surgery* 119:437-449, 1995
20. Beaujard AC, François Y, Glehen O, et al: Intraperitoneal chemohyperthermia with mitomycin C for gastric cancer patients with peritoneal carcinomatosis. *Anticancer Res* 19:1375-1382, 1999
21. Barakat RR, Sabbatini P, Bhaskaran D, et al: Intraperitoneal chemotherapy for ovarian carcinoma: Results of long-term follow-up. *J Clin Oncol* 20:694-698, 2002
22. Elias D, Gachot B, Bonvallot S: Carcinomes péritonéales traitées par résection complète et chimiothérapie post-opératoire immédiate: Etude de phase II chez 54 patients. *Gastroenterol Clin Biol* 11:181-187, 1997
23. Pestieau SR, Sugarbaker PH: Treatment of primary colon cancer with peritoneal carcinomatosis: Comparison of concomitant vs. delayed management. *Dis Colon Rectum* 43:1347-1348, 2000
24. Jacquet P, Sugarbaker PH: Influence of wound healing on gastrointestinal cancer recurrence. *Wounds* 7:40-47, 1995
25. Mansvelt B, Bertrand C, Nackermann P: Study of the toxicity and results of intraperitoneal hyperthermic chemotherapy in 28 patients with peritoneal carcinomatosis. *Ann Chir* 51:60-67, 1997
26. McQuellon RP, Loggie BW, Fleming RA, et al: Quality of life after intraperitoneal hyperthermic chemotherapy (IPCH) for peritoneal carcinomatosis. *Eur J Surg Oncol* 27:65-75, 2001
27. Yonemura Y, Fujimura T, Fushida S, et al: A new surgical approach (Peritonectomy) for the treatment of peritoneal dissemination. *Hepatogastroenterology* 46:601-609, 1999
28. Esquivel J, Sugarbaker PH: Clinical presentation of the pseudomyxoma peritonei syndrome. *Br J Surg* 87:1414-1418, 2000
29. Ronnett BM, Shmookler BM, Sugarbaker PH, et al: Pseudomyxoma peritonei: New concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of the ovary. *Anat Pathol* 2:197-226, 1997
30. Witkamp AV, de Bree E, Kaag MM, et al: Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei. *Br J Surg* 88:458-463, 2001
31. Sebbag G, Yan H, Shmookler BM, et al: Results of treatment of 33 patients with peritoneal mesothelioma. *Br J Surg* 87:1587-1593, 2000
32. Porcheron J, Talabard JN, Breton C, et al: Intraperitoneal chemohyperthermia for peritoneal carcinomatosis: Original modeling, clinical tolerance and results study about 30 patients. *Hepatogastroenterology* 47:1411-1418, 2000
33. Witkamp AJ, Verwaal V, van Ruth S, et al: Preliminary results of a randomised study comparing hyperthermic intraperitoneal chemotherapy with mitomycin C in addition to i. v. 5FU/leucovorin, with i. v. 5FU/leucovorin alone in patients with peritoneal carcinomatosis of colorectal origin. Presented at XXIV International Congress on Clinical Hyperthermia, Rome, September 24-29, 2001