

Peritoneal Carcinomatosis Treated With Surgery And Intraperitoneal Chemohyperthermia: 14 Years Experience In Lyon

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Citation

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Abstract

INTRODUCTION

In the past, carcinomatosis from non gynaecologic malignancies has been regarded as a terminal disease, most oncologists have regarded it as a condition only to be palliated. Literature concerning the natural history of this condition is not extensive. However, three studies document a median survival of approximately 6 months.^{1,2,3} Research protocols using palliative systemic chemotherapy have been conducted with encouraging tumour response rates, but with no improvement in survival rates.^{2,4,5} In the 1980s, a renewed interest in peritoneal surface malignancies developed in an attempt to find benefit for patients through new multimodal therapeutic approaches. Publications regarding previously unexplored treatment options such as peritonectomy procedures,⁶ intraperitoneal injection of anticancer drug OK432,⁷ intracavitary immunotherapy,⁷ photodynamic therapy,⁸ intraperitoneal chemohyperthermia (IPCH),^{9,10} and early postoperative intraperitoneal chemotherapy,¹¹ have appeared.

Promising results are reported by groups using the combination of a comprehensive cytoreductive surgery with perioperative intraperitoneal chemotherapy. This new management plan may be used with a palliative intent for the treatment of carcinomatosis not accessible to a macroscopic complete cytoreduction. It is the only plan that has shown curative results for carcinomatosis in phase II and a few phase III trials. Although these data were viewed with great scepticism for many years, it seems impossible to ignore that a significant proportion of carcinomatosis patients are long-term survivors.^{9,12,13,14,15,16}

In 1989, the first loco-regional treatment using IPCH was performed in Lyon-Sud for the treatment of a young patient

with unresectable peritoneal carcinomatosis from gastric cancer. Fourteen years later, more than 200 procedures combining surgery and IPCH have been performed for the treatment of peritoneal surface malignancies in the same institutions. The purpose of this work is to review the entire experience of this single institution.

NATURAL HISTORY OF DIGESTIVE CARCINOMATOSIS: A PROSPECTIVE MULTICENTRIQUE STUDY OF 370 PATIENTS

Prospective studies to document the clinical features and natural history of carcinomatosis from non-gynaecologic malignancies remain limited. Data comes from three prominent studies in the literature. The first study by Chu et al. (in 1989), included 100 patients and observed an overall median survival of 6 months.¹ A decade later, we conducted a multicentric prospective study called EVOCAPE 1.² It included 370 patients who all underwent surgery. Synchronous carcinomatosis occurring with primary cancer was found in 57% of patients and carcinomatosis documented in following occurred in the other 43%. The overall operative mortality and morbidity rates were 21% and 16% respectively. The overall median survival was 3.1 months: 5.2 months for colorectal cancer patients, 3.1 months for gastric cancer patients, 2.1 months for pancreatic cancer patients and 1.5 months for patients with carcinomatosis from unknown primary cancer. Shortest survival was seen when the diagnosis of carcinomatosis was made synchronously with the primary cancer and also when it was diagnosed at follow-up. This study also showed the profound prognostic implications of the carcinomatosis extent. More recently, Jayne et al. published a retrospective analysis of 3019 patients with colorectal cancers. Thirteen per cent of patients were identified with peritoneal

carcinomatosis and the median survival of patients with synchronous disease was 7 months.³ All these studies identify the inability to reliably diagnose carcinomatosis, either with the primary malignancy or with recurrent cancer, as a major diagnostic shortcoming.

QUANTITATIVE PROGNOSTIC INDICATORS

Quantitative prognostic indicators have been successfully utilized in several surgical disciplines and serve as guidelines in the selection of patients for treatments in order to maximize benefits. Often the major value of the quantitative prognostic evaluation is to exclude patients who have little or no chance of benefit from expensive, high risk management protocols. Our team have identified a series of clinical assessments that are currently used to select patients for treatment with surgery and IPCH.

ASSESSMENT OF CARCINOMATOSIS EXTENT: GILLY PERITONEAL CARCINOMATOSIS STAGING

This staging was described in 1994⁴ and takes into account the size of malignant granulations and their distribution (Table 1). Its two principal advantages are simplicity and reproducibility. Its utility was demonstrated in the multicentric prospective study, EVOCAPE 1, which gathered data from 370 patients with peritoneal carcinomatosis from non-gynaecologic malignancies, who had surgery in 9 different treatment centers by more than 30 surgeons.² This staging system has also demonstrated itself as an important prognostic indicator in several clinical trials.^{2, 5, 6, 7} A significant difference in survival rates was observed between peritoneal carcinomatosis stage 1 and 2 (carcinomatosis with malignant granulations less than 5 mm) and stage 3 and 4 (carcinomatosis with malignant granulations more than 5 mm). Figure 1 contrasts stage 1 and 2 versus stage 3 and 4 carcinomatosis.

Figure 1

Figure 1: IPCH device

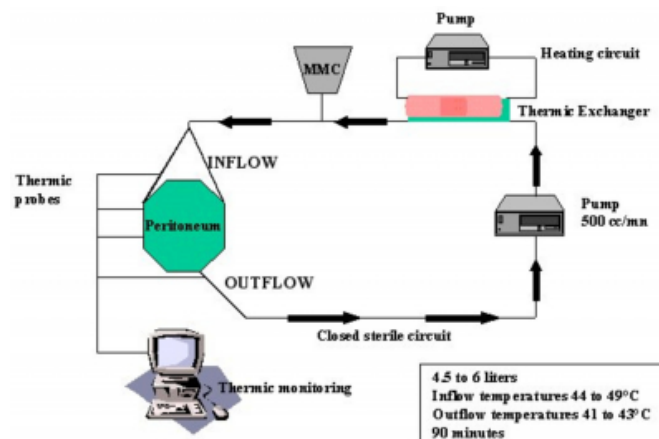


Figure 2

Table 1 :Gilly Peritoneal carcinomatosis staging

Stage	Peritoneal Carcinomatosis Description
Stage 0	No macroscopic disease
Stage 1	Malignant granulations less than 5mm 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	Localized or diffuse malignant granulations 5mm to 2 cm in diameter
Stage 4	Localized or diffuse large malignant masses (more than 2 cm in diameter)

ASSESSMENT OF COMPLETE CYTOREDUCTION

The size of tumour nodules remaining after cytoreduction has been shown to profoundly influence prognosis by estimating the possibility of cancer eradication by IPCH. Several studies have shown a direct relationship between the completeness of cytoreductive surgery and survival rates for carcinomatosis from all primary cancer locations.^{8, 9, 10, 11} We first successfully used “complete (R0-R1) or incomplete (R2) cytoreduction” to assess the completeness of surgical clearance of cancer. In patients with carcinomatosis, it is difficult to confirm an a R0 resection. Data shows that it is acceptable to group R0 and R1 together because the outcome of these two groups is very similar.^{5, 7, 12} In the second part of our experience we précised this assessment by using a completeness of cancer resection score (CCR) which classified residual tumor nodules into three categories: CCR-0 indicated no macroscopic residual cancer remained; CCR-1 indicated no residual nodule greater than 5 mm in diameter remained; CCR-2 indicated that the diameter of residual nodules was greater than 5 mm.

THERAPEUTIC STRATEGY

IPCH was first used for the treatment of carcinomatosis at the surgical department of Lyon-Sud Hospital Center in February 1989. One hundred and sixty patients were enrolled in a phase II clinical trial between 1989 and 1997.^{5,7} Before treatment, all patients underwent a physical examination, blood tests, serum electrolytes, serum creatine, and hepatic function test. Diagnostic tests included: cardiac ultrasound, spirometry, cerebral and thoracic computed tomography (CT) scan, abdominal ultrasonography of the liver, and abdominal CT scan for carcinomatosis assessment.

The inclusion criteria were 1) age younger than 70 years, 2) peritoneal carcinomatosis confirmed by cytological and/or pathological examination, 3) synchronous or metachronous peritoneal carcinomatosis, 4) absence of extra abdominal metastases, 5) no liver metastases on preoperative investigations. The exclusion criteria were 1) renal or myocardial failure, 2) administration of systemic chemotherapy 1 month prior to inclusion, 4) central nervous system disease (vascular or tumour), and 5) World Health Organization (WHO) performance status more than 1.¹³ These protocol was performed in accordance with the Helsinki declaration and was approved by the Lyon Human Investigation Committee.

Informed consent was obtained from all patients before surgery. Patients underwent IPCH without extensive cytoreductive surgery. IPCH was performed with mitomycin C (MMC) for carcinomatosis of gastrointestinal origin, with cisplatin (CDDP) for carcinomatosis of ovarian origin and with both drugs for mesothelioma, pseudomyxoma peritonei or carcinomatosis from carcinoma of unknown origin. After this initial phase II study, in light of the interesting survival results published by Sugarbaker,¹⁴ we decided to perform more extensive cytoreductive surgery and peritonectomies.^{9,12}

SURGICAL PROCEDURE

Under general anesthesia and hemodynamic monitoring, abdominal exploration was performed through a midline laparotomy (from xyphoid to pubis). Surgical resection of the primary tumor was performed whenever possible according to surgical oncologic principles (lymphadenectomy, acceptable margins). Once the primary tumor was removed, peritonectomies were performed, adapted to the location of the peritoneal malignant nodules as guided by the surgeon's exploration and frozen section

biopsies. Peritonectomies were only performed for peritoneal surfaces involved by tumor. These peritonectomy procedures were performed according to Sugarbaker's surgical guidelines.¹⁴ Locations of peritonectomies performed were recorded preoperatively on a specific form: 1) right diaphragmatic cupola, 2) left diaphragmatic cupola, 3) greater omentum, 4) lesser omentum, 5) omental bursa, 6) right colon gutter, 7) left colon gutter, 8) Douglas' pouch, 9) anterior wall peritoneum, 10) posterior wall peritoneum, 11) Glisson capsula and 12) mesenteric peritoneum.

IPCH DEVICE

At the end of each surgical procedure, an IPCH infusion (Figure 1) was carried out under general anaesthesia and general hypothermia (32°C induced throughout the peritonectomy procedure, by cold wraps on both lower extremities, and an ice hat). Before closure of the laparotomy, two inflow drains were inserted under the left and right diaphragmatic cupola (30 French silicone drain, William Harvey, Bard Cardiopulmonary Division, USA) while a third drain (outflow) was inserted in the pouch of Douglas (32 French). Temperature probes (Thermic probes, Mallinckrodt SA and Cair SA, Lozanne, France) were also inserted within the abdominal cavity (behind the liver pedicle and near the 1st jejunal loop). Other temperature probes were set up outside the abdominal cavity; on the inflow and outflow drains (8 cm from the skin), inside the bladder within a Foley catheter. The laparotomy incision was then closed and the inflow and outflow drains were connected to a closed sterile circuit in which a 4 to 6 litre perfusate (Travenol laboratory, Norfolk, England) was circulated by means of an electromagnetic pump at a flow rate of 500 ml/min. The closed sterile circuit was heated by means of a thermal exchanger (Dideco, France) connected to a heating circuit. Intra and extra abdominal temperature probes were connected to a digital thermometer (Cair SA, Lozanne, France) and monitored every 10 minutes (Figure 1). IPCH was performed for 90 minutes with careful close monitoring of respiratory and hemodynamic parameters at inflow temperatures ranging between 46 and 48 °C.

From 1999, we are using a new perfusion apparatus: the CavithermTM (EFS Electronique, Millery, France). It is designed to program, autoregulate, and collect all the variables of temperature, flow, and pressure, allowing better standardisation, control and reproducibility of the procedure.

TYPE OF INTRAPERITONEAL CHEMOTHERAPY

For peritoneal carcinomatosis from gastrointestinal origin, MMC was used at the dose of 0.7 mg/kg (maximum dose of 60 mg). For peritoneal carcinomatosis from ovarian origin, CDDP was used at a dose of 1 mg/kg (maximum dose of 80 mg). For peritoneal carcinomatosis from peritoneal malignant mesothelioma, pseudomyxoma peritonei, and of unknown origin, 0.5 mg/kg of MMC and 0.7 mg/kg of CDDP were combined intraperitoneally. MMC and/or CDDP were added to the peritoneal dialysis liquid at the beginning of IPCH.

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.¹⁵ MMC concentrations were measured at 24 hours and CDDP concentrations at 12, 24 and 72 hours following IPCH, in blood, urine and abdominal drainage.

MORBIDITY AND MORTALITY OF CYTOREDUCTIVE SURGERY COMBINED WITH IPCH: ANALYSIS OF 216 CONSECUTIVE PROCEDURES

Between February 1989 and August 2001, 207 patients who underwent 216 IPCH procedures using a closed abdominal procedure with mitomycin C and/or cisplatin were prospectively studied. The postoperative mortality and morbidity rates were 3.2% and 24.5%, respectively. The most frequent complications were digestive fistula (6.5%) and hematological toxicity (4.6%). Morbidity was statistically linked with the carcinomatosis stage ($p=0.016$), the duration of surgery ($p=0.005$), and the number of resections and peritonectomy procedures ($p=0.042$). Duration of surgery, and carcinomatosis stage were the most common predictors of morbidity. The morbidity and mortality rates of the present study (24.5% and 3.2%, respectively) are comparable to those previously reported by other teams. In a study analyzing 200 treatments with cytoreductive surgery and IPCH with the Coliseum technique (open abdominal technique), Stephens et al. reported morbidity and mortality rates which were 27% and 1.5% respectively.¹⁷ In smaller studies the reported morbidity rates were higher, between 38% and 54%.^{8, 11, 18, 19, 20}

The complication rates decreased with experience. Morbidity should improve through routine use of the optimum hyperthermia procedure, improvements in the composition of the perfusate and better patient selection. The

effectiveness of treatments has remained stable or improved during this evolution, and morbidity has not increased. In the reported study, most of the prolonged ileus occurred in the first years of our experience. Moreover we no longer include patients with unresectable primary tumors as we did at the beginning of the study.

As observed by Sugarbaker,¹⁷ the extent of cytoreductive surgery influences morbidity. The number of resections, peritonectomy procedures, anastomoses, and especially the duration of surgery, statistically increase the complication rate. It would be expected that morbidity would correlate with the magnitude of surgery. Many patients had a moderate to extensive surgery before presenting at our department. They required extensive dissection of all adhesions, stripping of peritoneum, and organ resections to maximize the benefits of this treatment. Surgical expertise and judgment were required to find a balance between the postoperative risk of extensive surgery and benefit in survival and quality of life. Patients have to be more strictly selected for a second procedure because of the high risk of complication.

SURGERY COMBINED WITH PERITONECTOMY PROCEDURES AND IPCH IN ABDOMINAL CANCERS WITH PERITONEAL CARCINOMATOSIS: PHASE II STUDY

From January 1998 to September 2001, 56 patients were included in a phase II study in Lyon-Sud for carcinomatosis from colorectal cancer ($n=26$), ovarian cancer ($n=7$), gastric cancer ($n=6$), peritoneal mesothelioma ($n=5$), pseudomyxoma peritonei ($n=7$) and miscellaneous reasons ($n=5$). Carcinomatosis were mainly extensive (40 patients with stage 3 or 4). Complete macroscopic resection was attempted for 27 patients whereas 29 patients had residual tumor nodules more than 5 mm in diameter. The mortality and morbidity rates were 2% and 29%, respectively. The 2-year survival rate was 79% for patients with macroscopic complete resection and 45% for patients without macroscopic complete resection ($p=0.001$).

Reducing tumor volume has always been considered an important factor in achieving tumor response to chemotherapy.^{8, 20, 21} The idea of reducing tumor volume in peritoneal carcinomatosis 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 in order to eradicate the disease completely during a single procedure.

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 appear to be indicated as the gain in terms of survival is minimal.⁵ In the previous reported studies^{5,7,12} IPCH was performed without extensive cytoreductive surgery. It achieved a morbidity rate of less than 10 %. But even when the primary tumors were resected, carcinomatosis 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^{8,11,22,23,24} 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 peritoneal carcinomatosis with malignant and debilitating ascitis. At the beginning of our experience, we demonstrated, as other teams have¹⁹ that IPCH can lead to ascitis regression in 70% of cases and to enhance quality of life. Mac Quellon et al. recently reported a better or similar quality of life in 64 patients with carcinomatosis of digestive origin, 3 months after IPCH.²⁵ 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.

SURVIVAL RESULTS

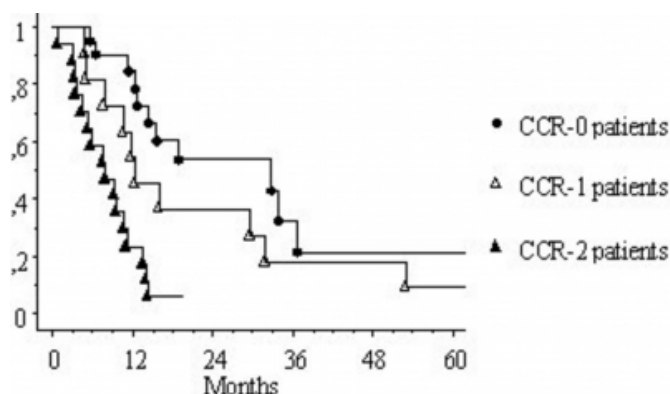
COLORECTAL CARCINOMATOSIS

We recently updated our experience.²⁶ From January 1989 to August 2002, 53 patients with colorectal carcinomatosis were treated by IPCH with mitomycin C in Lyon-Sud. In 34 patients, IPCH was performed following extensive cytoreductive surgery. At the end of the surgical procedure, 23 patients were considered to have undergone a CCR-0 resection (complete cytoreduction), 11 patients a CCR-1 (residual tumor nodule less than 5 mm) and 19 patients a CCR-2 (residual tumor nodule more than 5 mm). With a median follow up of 59.5 months, the overall median survival was 12.8 months. The extent of carcinomatosis extent, completeness of cytoreduction and histological differentiation were significant prognostic indicators by univariate analysis. Completeness of cytoreduction was the only significant independent predictor of survival by multivariate analysis. For patients treated with CCR-0 resection (complete cytoreduction), the 1-year, 2-year and 5-year survival rates were 85%, 54%, and 22%, respectively

with a median survival of 32.9 months. For patients treated with CCR-2 resection, the 1-year survival rate was 24% and median survival was 8.1 months ($p < 0.0001$). No patients with CCR-2 was alive at 2 years following treatment (Figure 2).

Figure 3

Figure 2: Actuarial survival of 56 patients with colorectal carcinomatosis treated with surgery and IPCH according to the completeness of cytoreductive surgery, with the Kaplan Meier method.



As previously reported in phase II studies,^{5,9,27} carcinomatosis with localized or small tumour nodules (stage 1 or 2) seems to be the best indication for IPCH. Other authors have reported that cancer distribution and cancer implant size were important quantitative prognostic indicators. These indicators were most commonly assessed by the means of Peritoneal Cancer Index (PCI).^{8,23,28} For carcinomatosis from colon cancer treated by the combination of cytoreductive surgery and IPCH or early postoperative intraperitoneal chemotherapy, Elias et al.⁸ reported that the survival results were significantly better when the PCI was less than 16. Pestiau and Sugarbaker reported for 104 patients with carcinomatosis of colorectal origin, a 5-year survival rate of 50% when PCI was less than 10, 20% with a PCI of 11-20 and 0% with a PCI >20.²⁹ These authors suggested that carcinomatosis from colon cancer with PCI > 20 should only be treated with palliative intent and IPCH is seldom indicated. Portilla et al. also showed that the PCI could be used to predict long-term survival in patients with carcinomatosis from colon cancer having a second cytoreduction.²⁸

The survival results reported by many authors also demonstrated the importance of residual tumour volume after the cytoreductive surgery. With a median follow-up of more than 4 years, Elias et al.¹² who treated 56 patients with

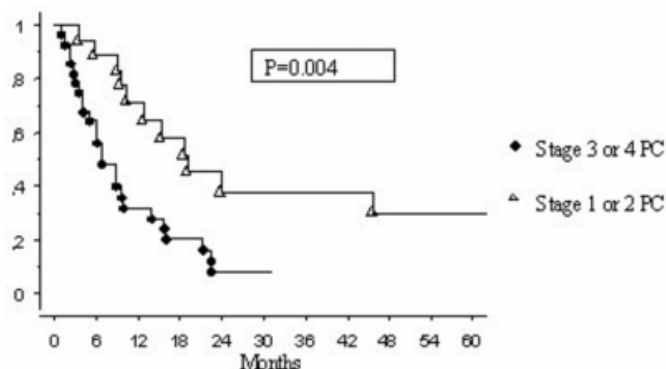
complete cytoreductive surgery followed by early postoperative intraperitoneal chemotherapy or IPCH, reported 3-year and 5-year survival rates of 47 and 27%, respectively. All phase II studies reported median survival of more than 2 years for patients treated with complete macroscopic cytoreductive surgery or with residual tumour nodules less than 5 mm following cytoreduction.^{10, 11, 29, 30} The results of the randomised Dutch trial comparing IPCH with mitomycin C and cytoreductive surgery to intravenous chemotherapy alone (5-fluorouracil, leucovorin) for the treatment of carcinomatosis from colorectal origin, were recently reported.⁶⁰ The benefit of this combined procedure was clearly demonstrated (2-year survival rate of 43% in the IPCH group versus 16% in the control: $p=0.014$) and the trial stopped for ethical reasons.

GASTRIC CANCER

We also recently updated our experience.³¹ From January 1989 to February 2000, 48 patients with gastric carcinomatosis were treated by IPCH with mitomycin C in Lyon-Sud. In 17 patients, IPCH was performed following extensive cytoreductive surgery. At the end of the surgical procedure, only 5 patients were considered to have undergone a CCR-0 resection, 20 patients a CCR-1 and 24 patients a CCR-2. With a median follow up of 99 months, the overall median survival was 10.3 months. By multivariate analysis, the presence of preoperative ascitis and the completeness of cytoreductive surgery were the only two independent predictors of survival ($p=0.04$ and $p<0.001$, respectively). For resectable gastric cancer with stage 1 and 2 PC, the 1-year, 2-year and 5-year survival rates were 71.3%, 37.8% and 30.2% respectively with a median survival of 19 months, while for stage 3 and 4, the 1-year and 2-year survival rates were 32% and 8% respectively with a median survival of 6.6 months ($p=0.004$) (Figure 3). For CCR-0 or CCR-1 patients the 1-year, 2-year and 5-year survival rates were 74.8%, 36.8% and 29.4% respectively with a median survival of 21.3 months, while for CCR-2 patients, the 1-year survival rate was 15.8% with nobody alive at 2 years and a median survival of 6.6 months ($p<0.0001$).

Figure 4

Figure 3: Actuarial survival of 49 patients with gastric carcinomatosis treated by surgery and IPCH, according to the carcinomatosis extent, with the Kaplan Meier method



The principal studies reporting the treatment of carcinomatosis from gastric origin are Japanese.^{24, 32, 33} Western studies are small and the median survival rates do not exceed 1 year.^{6, 10} In a large study of 85 patients, Yonemura et al.²⁴ reported a median survival of more than 1 year for patients treated with complete cytoreductive surgery and 5 five-year survivors. In a smaller study with shorter follow-up, Fujimoto et al.³² also observed promising survival results. However, the prognosis of gastric carcinomatosis treated with the combined therapeutic approach (cytoreductive surgery plus IPCH) seems to be worse than for colorectal carcinomatosis.

As for colorectal carcinomatosis, the most important prognostic indicator seems to be the completeness of cytoreduction. IPCH appears to be most effective when cytoreduction achieves a complete or nearly complete resection, with the intent to cure. The same observations have been reported by other peritoneal surface malignancy centers, for peritoneal carcinomatosis arising from gastric cancer (5-year survival rates in patients treated by complete cytoreduction and IPCH ranging between 11% and 31%^{24, 33}). Similar results for carcinomatosis arising from other origins have been reported.^{8, 10} An aggressive attempt at complete resection including surgical excision of all sites of macroscopic disease may add to the efficacy of IPCH. When the cytoreductive surgery does not allow a sufficient downstaging, the survival benefit of IPCH remains extremely low, and the median survival does not exceed 6 to 8 months.^{24, 32} In the light of the risk of postoperative complications, IPCH may be not indicated in patients for with a CCR-2 resection score. These patients will be excluded from our further studies.

For many Korean and Japanese authors, IPCH has been performed for prophylactically or in an adjuvant setting.^{34,35,36,37} They report encouraging survival results in pT3 gastric adenocarcinoma. Yonemura et al. recently conducted a randomized controlled study on 139 patients with T3 or T4 gastric tumor, allocated in 3 groups :IPCH + surgery, intraperitoneal normothermic chemotherapy + surgery and surgery alone.³⁶ After a median follow-up greater than 5 years, the 5-year survival rate of patients treated by the combination of IPCH with surgery was significantly higher at 60% than those of the two other groups, with similar morbidity rates. But these promising results were not confirmed by all Japanese studies.³⁷ In Western countries, only one German study reported the use of IPCH for the prevention of carcinomatosis recurrence in advanced gastric cancer.³⁸ Nine patients were included in the study with a high postoperative morbidity rate (66%). Prospective randomized studies are needed in Europe to demonstrate the benefit of IPCH in earlier stages of carcinomatosis disease. Positive peritoneal cytology is a risk-factor for the development of peritoneal carcinomatosis and may be indicative of poor prognosis. We are currently conducting a prospective multicentre study, EVOCAPE 2, to evaluate if patients with positive peritoneal cytology are at risk for PC disease. This study could define a group of patient at risk for peritoneal carcinomatosis development for whom IPCH would be indicated.

CONCLUSION

In conclusion, our results confirm that IPCH combined with cytoreductive surgery may improve survival results in digestive cancer with carcinomatosis and may result in some long-term survivors among highly selected patients. This combined and loco-regional therapeutic strategy offer a chance for cure or palliation in this condition with few alternative treatment options. Further collaboration of other peritoneal surface malignancy treatment centers are needed in order to standardize indications, IPCH and peritonectomy techniques.

CORRESPONDENCE TO

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