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# Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin

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**Abstract**

Peritoneal seeding from colorectal cancer has a very poor prognosis and is relatively resistant to systemic chemotherapy. We performed a phase I/II trial to investigate the feasibility and effectiveness of extensive cytoreductive surgery in combination with intra-operative hyperthermic intraperitoneal chemotherapy (HIPEC) in these patients. 29 patients with peritoneal carcinomatosis of colorectal origin without evidence of distant metastases underwent cytoreductive surgery and intra-operative HIPEC with mitomycin-C (MMC), followed by systemic chemotherapy with 5-fluorouracil (5-FU)/leucovorin. Surgical complications occurred in 11 patients (38%). One patient died directly related to the treatment, resulting in a mortality rate of 3%. MMC toxicity existed mainly of leucocytopenia (in 15 patients; 52%). After a median follow-up of 38 months (range 26–52 months) we found a 2- and 3-year survival rate (Kaplan–Meier) of 45 and 23%, respectively. Extensive cytoreductive surgery and HIPEC is feasible in patients with peritoneal seeding of colorectal cancer. First results suggest that a higher median survival could be achieved compared with conventional palliative surgery and systemic chemotherapy, therefore a randomised phase III study is now being conducted. 

*Keywords:* Peritoneal carcinomatosis; Colorectal cancer; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

## 1. Introduction

Despite advances in adjuvant therapy for colorectal cancer, the peritoneal surface still remains an important failure site for patients with recurrence of disease. Peritoneal seeding may also be observed at the time of diagnosis or surgical treatment of the primary tumour. The peritoneal failure rate among patients who present with recurrence after colon cancer resection is approximately 25–35% [1]. The high incidence of tumour implantation on the peritoneal surface in the operative management of colorectal cancer might be due to free intraperitoneal tumour emboli as a result of serosal penetration. Other causes might be leakage of malignant cells from the lymphatics, dissemination from trauma to the cancer as a result of dissection, fibrin entrapment of intra-abdominal cancer cells and tumour promotion of the entrapped cells by the wound healing process [2]. When treated with intravenous (i.v.) administration of 5-fluorouracil (5-FU) and palliative surgery, the median survival of patients with metastatic colorectal cancer is approximately one year [3]. Despite the use of new chemotherapeutic agents, alone or in combination, the results remain disappointing with response rates of approximately 25% and only a limited impact of chemotherapy on survival [3,4]. Two-year survival rates after palliative surgery and systemic chemotherapy for metastatic colorectal cancer are reported to be 10–20% [5]. Colorectal carcinoma cells are relatively resistant to chemotherapy, although

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higher dosages seem to be associated with increased response rates [4]. However, dose intensification of i.v. administered 5-FU is associated with intolerable systemic side-effects [2].

Theoretically, intraperitoneal chemotherapy can increase local drug exposure with less systemic toxicity when compared with conventional chemotherapy [6]. Intraperitoneal chemotherapy began with the simple instillation of the drug in the peritoneal cavity, but inadequate distribution of the drug to the entire seroperitoneal surface resulted in a high recurrence rate [7]. Intra-operative intraperitoneal perfusion chemotherapy results in a more uniform distribution of the cytotoxic drug throughout the abdominal cavity. Additionally, it can be performed under hyperthermic conditions. Hyperthermia has a direct cytotoxic effect and enhances the activity and the penetration depth of many cytotoxic drugs [8,9]. Extensive cytoreductive surgery always has to precede the hyperthermic intraperitoneal chemotherapy (HIPEC) during the same procedure, since the penetration depth of this thermochemotherapy is estimated to be limited to a few millimetres only [10,11]. Most experience of HIPEC procedures is gained in peritoneal carcinomatosis secondary to gastric cancer and for pseudomyxoma peritonei [12,13].

Promising results regarding survival benefit have been reported in these studies. The experience of this regional cancer treatment in peritoneal seeding from colorectal origin, however, is still limited [14–17].

At the Netherlands Cancer Institute, we conducted a phase I/II trial to investigate the feasibility of this multimodality treatment with extensive cytoreductive surgery and HIPEC with mitomycin-C (MMC), followed by systemic chemotherapy with 5-FU and leucovorin, in patients with peritoneal dissemination of colorectal carcinoma. End-points were treatment-related morbidity, mortality and survival.

## 2. Patients and methods

### 2.1. Patient selection

Patients with peritoneal carcinomatosis of colorectal origin without evidence of extra-abdominal or parenchymal liver metastases were entered into a phase I/II study looking at extensive cytoreductive surgery with hyperthermic intra-operative intraperitoneal chemotherapy with MMC, followed by systemic chemotherapy. The protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

Inclusion criteria were as follows: peritoneal seeding of colorectal carcinoma proven by biopsy during laparotomy or laparoscopy or by cytology of radiological suspected areas or ascites; no signs of distant metastases on abdominal and chest computed tomography (CT scan); the primary tumour and/or recurrence must be technically resectable while, in general, infiltration of adjacent organs is not considered a reason for inoperability; normal laboratory blood examinations, including blood cell count and renal and liver function tests; the patient must be considered medically fit to undergo this aggressive locoregional treatment.

### 2.2. Surgical aspects

The abdomen was approached through a median incision from xyphoid process to the pubic symphysis. Comprehensive adhesiolysis was performed. The primary tumour, if still present, and/or recurrences were excised and all visceral or parietal peritoneal surface tumour deposits were removed as completely as possible. The tumour distribution was recorded according to the presence of tumour deposits in seven abdominal areas defined as follows: left and right subdiaphragmatic, subhepatic, omentum/transverse colon, small intestine/mesenterium, ileocoecal and pelvic regions. The objective of optimal cytoreductive surgery was to leave no macroscopic tumour behind or, when this could not been achieved, only tumour deposits of less than 2.5 mm in size. If a deposit was infiltrating deeply into an organ and it was impossible to peel the malignancy from its surface, the involved organ or a segment of it was excised. After bowel resections, anastomoses were postponed until after the intraperitoneal MMC perfusion to prevent suture line seeding. When parietal peritoneal surfaces were significantly involved, peritonectomy procedures, as described by Sugarbaker [18], were performed. When left and/or right upper quadrant peritonectomy had been performed, thoracic drains were placed to drain the expected postoperative pleural effusion.

### 2.3. Perfusion

A Tenckhoff inflow catheter (Curl Cath$^{TM}$, Quinton, Bothell, WA, USA) was introduced centrally into the abdominal cavity through the laparotomy wound and three silicone outflow drainage tubes (Dura-Sil, Biometrix Ltd, Jerusalem, Israel) were placed through separate stab wounds subphrenically on both sides and in the small pelvis. Temperature sensors (Mon-a-therm$^{TM}$, Mallinckrodt Medical Inc., St Louis, MO, USA) were attached to the inflow and outflow catheters and Yellow Spring Instruments sensors to the pump system. The catheters were connected through connection tubes containing filters (blood transfusion filters, Pall Corporation, East Hills, NY, USA) to a reservoir with filter (Safe II Filtered Cardiotomy Reservoir, Polystan, Copenhagen, Denmark) and to the roller pump (Polystan, Copenhagen, Denmark) and heat

exchanger (Baxter, Uden, The Netherlands) back to the patient (Fig. 1). The skin surrounding the laparotomy was sutured to a retractor ring placed above the anterior surface of the abdomen, causing an elevated rim around the abdominal cavity. In this way, peritoneal cavity expansion was achieved, resulting in better exposure of the peritoneal surface to the perfusate. Simultaneously, a strong piece of plastic was sutured to cover the laparotomy wound to prevent spillage of the perfusate and to limit heat loss (Fig. 2). Centrally in the plastic cover a hole was made just large enough to allow entrance of the surgeon's hand for stirring in the abdominal cavity. The closed perfusion system was filled with 3 to 4 l of isotonic dialysis fluid (Dianeal® PD1, Baxter, Uden, The Netherlands). The perfusate circulated at approximately 1 l/min with an inflow temperature of 43°C. When the intraperitoneal temperature reached 40°C the MMC was added in three divided doses with a 30 min interval to the perfusate. The first dose contained 50% and the following administrations 25% of the total dose. Initially, in a dose finding study, 15–40 mg/m$^2$ of MMC was given. In the majority of patients and in all cases after completing the latter study, 35 mg/m$^2$ of MMC was administrated. Frequently, at standard time intervals after the start of the perfusion chemotherapy, samples were taken of perfusion fluid, plasma and urine to determine concentrations of MMC for pharmacokinetic studies. The intraperitoneal temperature was maintained between 40 and 41°C and the duration of the perfusion was 90 min. To achieve uniform temperature and drug distribution throughout the abdominal cavity, the perfusate and the bowel loops were gently stirred by the hand of the surgeon and, if necessary, the position of the inflow catheter was altered. The core temperature, measured in the pharynx, was kept below 39.5°C. After completion of the abdominal perfusion, the Tenckhoff catheter and temperature probes were removed and the excess fluid was drained from the abdominal cavity. The outflow drains were left in place for postoperative drainage. The bowel anastomoses and, if needed, a colostomy was made in the usual way. Because of the expected long gastric pareses, a gastrostomy was performed for gastric decompression. Through the gastrostomy, stomach and duodenum, the distal end of a feeding tube was positioned in the proximal jejunum for early postoperative enteral nutrition. The abdominal wall was closed in the usual way by a continuous polydioxanon suture (PDS).

Surgical complications and toxicity attributed to MMC, according to the World Health Authority (WHO) grading for chemotherapy toxicity, were recorded. Duration of admission to hospital was also noted. Six to 12 weeks after discharge weekly adjuvant systemic chemotherapy with a bolus injection of 400 mg/m$^2$ 5-FU and 80 mg/m$^2$ leucovorin in a 1 h infusion was started to treat potential systemic micrometastases. The duration of this chemotherapy was 6 months. Treatment was discontinued when progression of the disease was observed or intolerable toxicity occurred. Six weeks and 3 months after discharge and afterwards at 3 month intervals, patients were seen and laboratory examination, including determining carcinoembryonic antigen (CEA), blood cell count and renal and liver function

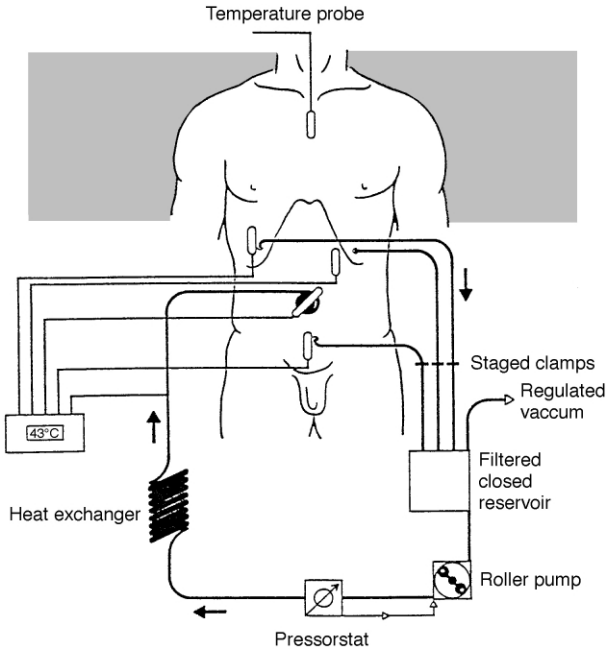


Fig. 1. The perfusion system model.

Fig. 2. The skin surrounding the laparotomy is sutured to a retractor ring. A piece of plastic is sutured to cover the wound to prevent spillage of perfusate and to limit heat loss. A hole made centrally in the plastic cover allows entrance of the surgeon's hand for stirring in the abdominal cavity.

tests, were performed. CT scans of chest and abdomen were made 3 months after discharge and at 6 month intervals thereafter. Supplementary diagnostic tests, such as ultrasound, magnetic resonance imaging (MRI) or positron emission tomography (PET) scan, were only performed on indication. Time to recurrence, local or distant, and survival were recorded. The Pearson two-tailed test was used to correlate survival with prognostic factors (completeness of cytoreduction and histology grade).

## 3. Results

From November 1995 to December 1997, 29 patients were included in this study. In 3 (10%) patients, the primary tumour was located in the appendix, in 22 (76%) in the colon and in 4 (14%) in the rectum. Peritoneal carcinomatosis was diagnosed as recurrence in 21 patients (72%), usually diagnosed at laparotomy for intestinal obstruction, while in 8 cases (28%) it was found during treatment of the primary tumour. 2 patients (7%) had low-grade malignancy, 12 (41%) high-grade and in another 15 cases (52%) had an intermediate malignancy. All patients underwent prior abdominal surgery with a mean of 1.5 laparotomies (range 1–4, S.D. 1.1). There were 14 females (48%) and 15 (52%) males, ranging in age from 29 to 74 years (mean 49 years, S.D. 10.2). In 4 patients (14%), the tumour deposits were limited to one abdominal region, while in 16 patients (55%) tumour was found in 2–4 regions. In the remaining 9 patients (31%) tumour was spread over five or more regions. Optimal cytoreduction, leaving tumour deposits of less than 2.5 mm behind, could be achieved in 26 patients (90%). An average of 2 (range 0–5, S.D. 1.3) bowel anastomoses was needed per patient. Mean duration of operation was 8.25 h (range 6.25–11.5 h, S.D. 2.0), while the mean total estimated blood loss was 4.7 l (range 1–11 l, S.D. 2.7).

Surgical complications occurred in 11 patients, resulting in a morbidity rate of 38%. 6 patients (21%) developed a grade 1 or 2, while in 9 patients (31%) a grade 3 leucopenia was observed. Major complications that were observed were postoperative bleeding (1 patient; 3%), bowel perforation (1; 3%), urinary bladder perforation (1; 3%), hydronephrosis treated by nephrostomy (2; 7%), wound dehiscence (1; 3%), subclavian vein thrombosis (1; 3%), prolonged chylus leakage treated by placement of a Denver shunt (1; 3%) and peripheral neuropathy due to pressure during prolonged anaesthesia (3; 10%). 5 patients (17%) had to be re-operated upon for postoperative complications. One patient died of sepsis caused by intestinal leakage in combination with grade 3 leucopenia after HIPEC with the highest dose of 40 mg/m$^2$ MMC, resulting in a treatment-related mortality rate of 3%. Gastric pareses

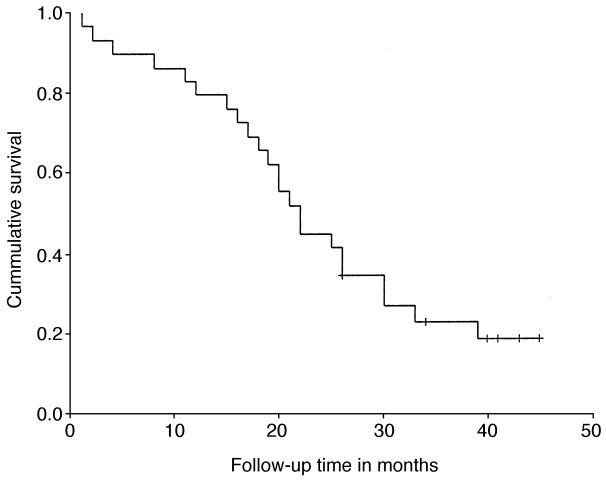


Fig. 3. Actuarial survival (Kaplan–Meier) after a median follow-up of 38 months (+ means censored).

delayed oral intake until the 5th to 25th postoperative day (mean 14th). Mean hospital stay was 23 days (range 17–67, S.D. 10.1). There was no long-term toxicity or morbidity related to HIPEC registered. 21 patients (72%) received systemic chemotherapy with 5-FU/leucovorin postoperatively. In 5 cases (17%) the latter treatment was discontinued because of intolerable toxicity (2) or progressive disease (3).

After a median follow-up of 38 months (range 26–52 months, S.D. 8.0), 7 patients are still alive. 2 of them have proven distant metastases. 21 patients died of recurrent disease. 8 patients had locoregional recurrence, 8 both locoregional and distant metastases and 5 presented with distant metastases alone. Therefore, the locoregional recurrence rate was 57%. Distant disease included lung, liver, bone and cerebellum metastases. Survival was positively correlated to completeness of cytoreduction ($P < 0.05$). There was no correlation found between survival and histological tumour grade. Mean and median time to recurrence were 12 and 11 months, respectively (range 3–29). The actuarial 1- (95% CI: 69–96%), 2- (95% CI: 27–63%) and 3-year (95% CI: 7–39%) survival rates (Kaplan–Meier) are 82, 45 and 23%, respectively (Fig. 3).

## 4. Discussion

HIPEC is a relatively new regional combination treatment for primary and secondary peritoneal malignancy. The first clinical report on this treatment modality was published in 1980. Spratt and colleagues [19] had performed this treatment successfully in a patient with pseudomyxoma peritonei. Especially during the last decade, more attention has been paid to this treatment modality and more clinical experience has been gained. Application of this approach in patients with pseudomyxoma peritonei, malignant peritoneal meso-

thelioma and peritoneal dissemination of gastric carcinoma have demonstrated promising results regarding survival benefits in non-randomised studies [13,20–22]. In cases of gastric carcinoma with serosal invasion in the absence of peritoneal dissemination, HIPEC has been performed successfully as an adjuvant treatment to primary resection [23]. However, there is less experience with HIPEC for peritoneal carcinomatosis of colorectal origin [15–17,24].

The HIPEC procedure has not yet been standardised with regard to indications, duration and temperature of the perfusion, abdominal closure during perfusion, open or closed perfusion models or type and dosage of chemotherapeutic agents used. To optimise exposure of the surface of the abdominal organs and the parietal peritoneum to the perfusate, peritoneal expansion is applied in some centres. This may be achieved by different methods [20,25,26]. We used a technique of peritoneal cavity expansion by elevation of the skin of the laparotomy wound using a retractor ring placed above the abdomen (Fig. 2), similar to the technique used by Sugarbaker and associates [20]. The abdominal cavity is maintained open allowing the surgeon's hand to stir the abdominal content, resulting in better exposure of the seroperitoneal surfaces and a more uniform distribution of heated drug through the entire abdominal cavity.

MMC was chosen as chemotherapeutic agent because of its known activity in colorectal cancer [27], its direct cytotoxic effect, the thermal enhancement of its activity [8] and penetration depth [28] and its favourable pharmacokinetics in HIPEC procedures. The latter has been demonstrated in our and other pharmacokinetic studies [29–31]. 5-FU is not suitable for this application because the exposure duration is too short for this anti-metabolite to be effective; in HIPEC procedures a direct-acting cell cycle independent cytotoxic agent is needed.

This aggressive regional treatment is associated with significant morbidity, probably mainly associated with the extensive surgery needed. In our series, 1 patient died directly related to treatment of sepsis after intestinal leakage in combination with grade 3 leucopenia, resulting in fulminant peritonitis and a mortality rate of 3%. The mortality rate in our HIPEC series is comparable to that reported by others, varying from 0 to 14%, regardless of the technique and indication used [24,26,32–34]. In the few series with HIPEC for peritoneal seeding from a colorectal origin, morbidity and mortality rates of 7–35 and 0–5% have been reported, respectively [15]. Mortality seems to be related to higher age and higher intra-abdominal temperature ($>41.5^{\circ}C$) [24]. Major complications from different techniques have been reported in up to 35% of cases and include anastomotic leakage, bowel perforations, bile leakage, pancreatitis, intra-abdominal bleeding, wound dehiscence, pulmonary embolism, renal failure and grade 3 and 4 haematological toxicity [24,31,34]. The latter is a result of the intra-operative chemotherapy and dose-related, while renal failure is probably due to temporarily low renal perfusion state intra-operatively in combination with absorption of nephrotoxic cytotoxic agents used like cisplatin and MMC [31]. Most complications, however, are attributed to the extensive surgery performed, especially when the patient had undergone multiple operations before [21]. Although in experimental models healing of intestinal anastomotic suture lines is impaired when exposed to intraperitoneal chemotherapy [35], clinical randomised control studies have failed to demonstrate this [23]. After low anterior resection of the rectosigmoid with extensive pelvic surgery, we tend to make a colostoma. This is justified by a study in which integrity of a low colorectal anastomosis was compromised by HIPEC when extensive resection had been performed [36]. The other major enteral complication after HIPEC remains bowel perforation, which is probably caused by surgical trauma to the bowel surface combined with thermal and chemotherapeutic damage [24]. Prolonged gastric paresis is another common postoperative complication. Thoracic complications occur frequently, but are usually minor and include bilateral basilar atelectasis (76% of cases) and pleural effusion (64%) [37]. To avoid problems caused by pleural effusion, we routinely place thoracic drains intra-operatively after right- and left-upper quadrant peritonectomy. These percentages and also the type of complications are similar to those after HIPEC for other indications.

Patients who presented with extra-abdominal metastases were excluded from our study. They should not undergo this treatment, since they will be exposed to the significant morbidity associated with this aggressive regional treatment with little or no systemic therapeutic benefit. Patients with small-volume peritoneal seeding from colorectal cancer are probably the best candidates for cytoreductive surgery and HIPEC. Other favourable prognostic factors are: optimal cytoreduction, leaving tumour residue smaller than 2.5 mm behind, involvement of a small number of abdominopelvic regions, absence of lymph node metastases, low grade and intestinal histological type [38]. In our (limited) group of patients, we only found a positive correlation between completion of cytoreduction and survival.

Our 2- and 3-year survival rates of 45 and 23%, respectively, are comparable to those previously reported by others [14–17,38] and seem to be better than what can be achieved by systemic chemotherapy alone. Two-year survival rates after palliative surgery and systemic chemotherapy for metastatic colorectal cancer are reported to be 10–20% [5]. Our results suggest that HIPEC may contribute especially to long-term survival. However, a survival benefit can not be proven by a phase II study. Therefore we are now conducting a

randomised phase III trial. In this trial, we compare extensive cytoreductive surgery in combination with HIPEC with MMC in addition to 5-FU/leucovorin, with palliative surgery and systemic 5-FU/leucovorin alone. Endpoints of this study are survival, quality of life and costs.

## References


1. Minsky BD, Mies C, Rich TA, Recht A, Chaffey JT. Potentially curative surgery of colon cancer: patterns of failure and survival. *J Clin Oncol* 1988, **6**, 106–118.
2. Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. *Dis Colon Rectum* 1994, **37**, 115–122.
3. Machover DA. A comprehensive review of 5-fluoracil and leucovorin in patients with metastatic colorectal carcinoma. *Cancer* 1997, **80**, 1179–1187.
4. Midgley R, Kerr D. Colorectal cancer. *Lancet* 1999, **353**, 391–399.
5. Benson 3rd AB. Therapy for advanced colorectal cancer. *Sem Oncol* 1998, **25**, 2–11.
6. Markman M. Intraperitoneal chemotherapy. *Sem Oncol* 1991, **18**, 248–254.
7. Zoetmulder FAN, Sugarbaker PH. Patterns of failure following treatment of pseudomyxoma peritonei of appendicceal origin. *Eur J Cancer* 1996, **32A**, 1727–1733.
8. Storm FK. Clinical hyperthermia and chemotherapy. *Radiol Clin N America* 1989, **27**, 621–627.
9. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. *Cancer Chemother Pharmacol* 1998, **41**, 147–154.
10. Fujimoto S, Takahashi M, Kobayashi K, *et al*. Relation between clinical and histologic outcome of intraperitoneal hyperthermic perfusion for patients with gastric cancer and peritoneal metastasis. *Oncology* 1993, **50**, 338–343.
11. van de Vaart PJM, Van der Vange N, Zoetmulder FAN, *et al*. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin–DNA adduct formation in patients and ovarian cancer cell lines. *Eur J Cancer* 1998, **34**, 148–154.
12. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999, **6**, 727–731.
13. 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.
14. Fujimoto S, Takahashi M, Endoh F, *et al*. A clinical pilot study combining surgery with intraoperative pelvic hyperthermochemotherapy to prevent the local recurrence of rectal cancer. *Ann Surg* 1991, **213**, 43–47.
15. Yamaguchi A, Tsukioka Y, Fushida S, *et al*. Intraperitoneal Hyperthermic treatment for peritoneal dissemination of colorectal cancers. *Dis Colon Rectum* 1992, **35**, 964–968.
16. Nishimura G, Fushida S, Fujimura T, Yonemura Y, Miwa K, Miyazaki I. Intraperitoneal treatment for peritoneal dissemination of colorectal cancer. *Reg Cancer Treat* 1996, **9**, 60–62.
17. Schneebaum S, Arnold MW, Staubus A, Young DC, Dumond D, Martin Jr EW. Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996, **3**, 44–50.
18. Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995, **221**, 29–42.
19. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. *Cancer Res* 1980, **40**, 256–260.
20. Sugarbaker PH, Ronnet B, Archer A, *et al*. Pseudomyxoma peritonei syndrome. *Adv Surg* 1996, **30**, 233–280.
21. Sayag-Beuajard AC, Francois Y, Glehen O, *et al*. Intraperitoneal chemohyperthermia with mitomycin C for gastric cancer patients with peritoneal carcinomatosis. *Anticancer Res* 1999, **19**, 1375–1382.
22. de Bree E, Christodoulakis M, Tsiftis D. Malignant peritoneal mesothelioma treated by continuous hyperthermic peritoneal perfusion chemotherapy. *Ann Oncol* 2000, **11**(6), 753–756.
23. Fujimura T, Yonemura Y, Muraoka K, *et al*. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. *World J Surg* 1994, **18**, 150–155.
24. Jacquet P, Stephens AD, Averbach AM, *et al*. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer* 1996, **77**, 2622–2629.
25. Fujimura T, Yonemura Y, Fushida S, *et al*. Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. *Cancer* 1990, **65**, 65–71.
26. Tsiftis D, de Bree E, Romanos J, *et al*. Peritoneal expansion by artificially produced ascites during perfusion chemotherapy. *Arch Surg* 1999, **134**, 545–549.
27. Haller DG. Chemotherapy in gastrointestinal malignancies. *Sem Oncol* 1988, **15**, 50–64.
28. Panteix G, Guillaumont M, Cherpin L, *et al*. Study of the pharmakokinetics of mitomycin C in humans during intraperitoneal chemothermia with special mention of the concentration in local tissues. *Oncology* 1993, **50**, 366–370.
29. Fujimoto S, Shrestha RD, Kokobun M, *et al*. Pharmacokinetic analysis of mitomycin C for intraperitoneal hyperthermic perfusion in patients with far-advanced or recurrent gastric cancer. *Reg Cancer Treat* 1989, **2**, 198–202.
30. Jacquet P, Averbach A, Stephens AD, Stuart OA, Chang D, Sugarbaker PH. Heated intraoperative intraperitoneal mitomycin C and early postoperative intraperitoneal 5-fluorouracil: pharmacokinetic studies. *Oncology* 1998, **55**, 130–138.
31. Loggie BW, Fleming RA. Complications of heated intraperitoneal chemotherapy and strategies for prevention. *Cancer Treat Res* 1996, **82**, 221–233.
32. Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin-C. *Cancer* 1988, **61**, 232–237.
33. Yonemura Y, Ninomiya I, Kaji M, *et al*. Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. *World J Surg* 1995, **19**, 450–455.
34. Stephens AD, Alderman R, Chang D, *et al*. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* 1999, **6**, 790–796.
35. Fumagalli U, Trabucchi E, Soligo M, *et al*. Effects of intraperitoneal chemotherapy on anastomotic healing in the rat. *J Surg Res* 1991, **50**, 82–87.
36. Averbach AM, Chang D, Koslowe P, Sugarbaker PH. Anastomotic leak after double-stapled low colorectal resection. *Dis Colon Rectum* 1996, **39**, 780–787.
37. Chen MYM, Chiles C, Loggie BW, Choplin RH, Perini MA, Fleming RA. Thoracic complications in patients undergoing intraperitoneal heated chemotherapy with mitomycin following cytoreductive surgery. *J Surg Oncol* 1997, **66**, 19–23.
38. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* 1995, **221**, 124–132.