# Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

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_Purpose:_  To confirm the findings from uncontrolled studies that aggressive cytoreduction in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) is superior to standard treatment in patients with peritoneal carcinomatosis of colorectal cancer origin.

_Patients and Methods:_  Between February 1998 and August 2001, 105 patients were randomly assigned to receive either standard treatment consisting of systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery, or experimental therapy consisting of aggressive cytoreduction with HIPEC, followed by the same systemic chemotherapy regime. The primary end point was survival.

_Results:_  After a median follow-up period of 21.6 months, the median survival was 12.6 months in the standard therapy arm and 22.3 months in the experimental therapy arm (log-rank test, _P_ = .032). The treatment-related mortality in the aggressive therapy group was 8%. Most complications from HIPEC were related to bowel leakage. Subgroup analysis of the HIPEC group showed that patients with 0 to 5 of the 7 regions of the abdominal cavity involved by tumor at the time of the cytoreduction had a significantly better survival than patients with 6 or 7 affected regions (log-rank test, _P_ < .0001). If the cytoreduction was macroscopically complete (R-1), the median survival was also significantly better than in patients with limited (R-2a), or extensive residual disease (R-2b; log-rank test, _P_ < .0001).

_Conclusion:_  Cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin. However, patients with involvement of six or more regions of the abdominal cavity, or grossly incomplete cytoreduction, had still a grave prognosis.

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PERITONEAL CARCINOMATOSIS (PC) of colorectal origin is common and is the second-most frequent cause of death in colorectal cancer after metastatic disease to the liver. In an estimated 25% of patients, no other tumor locations can be found, even when a detailed diagnostic work-up is performed.[1-3] Sugarbaker[4,5] has suggested that PC of colorectal origin should probably not be equated with generalized disease, but can be a first step of dissemination, not unlike the situation with liver metastases of colorectal origin.

Based on this concept, attempts have been made to achieve long-term survival in patients with PC by combining surgery and intraperitoneal chemotherapy to eradicate microscopic residual disease. Advances in surgical techniques and improved anesthesiology have made it possible to remove most or all macroscopic tumor in PC.[6] In theory, intraperitoneal chemotherapy could eradicate limited residual tumor, and should have an optimal chance to succeed if it would immediately follow surgery (to avoid regrowth of tumor cells), and if exposure of the peritoneal surface at risk could be guaranteed. To achieve these goals, peritoneal lavage, as part of the surgical procedure, has been developed.[7] Others and our group have shown that peritoneal lavage containing mitomycin C (MMC) results in a drug exposure to the peritoneal surface that is 20 times higher than elsewhere in the body.[8,9] This degree of pharmacokinetic advantage is thought to result in optimal circumstances for tumor cell kill. In addition, enhancement of MMC cytotoxicity at temperatures higher than 39°C has been demonstrated in animals and in vitro models.[10,11] The addition of intraperitoneal hyperthermia has been shown to be technically feasible in the surgical setting.[12,13]

This approach of aggressive cytoreduction in combination with intraperitoneal chemotherapy, often employing MMC and hyperthermia, has been studied in 11 phase II studies on patients with PC of colorectal origin.[12,14-23] The results of these studies show a strikingly long median survival and, more importantly, a 20% to 30% long-term (5-year) survival rate, reminiscent of that of surgery for isolated liver metastases. It has been advocated that these favorable results justify such an aggressive treatment, particularly since long-term survival is hardly ever seen after systemic chemotherapy alone.

It remains to be shown that these encouraging results of uncontrolled studies are not the result of patient selection. The

need for a controlled study was recently re-emphasized in an editorial in the *Journal of Clinical Oncology* by Sugarbaker,[24] who originally pioneered the approach. This need is particularly urgent because HIPEC is associated with significant morbidity and treatment-related mortality. In this article, we report the results of a randomized single-institution phase III study, and present data that may aid in better selection of patients for aggressive treatment of peritoneal carcinomatosis.

## PATIENTS AND METHODS

### Patient Selection and Study Design

Patients with histologically proven peritoneal metastases of colorectal adenocarcinoma (CRC) or positive cytology of ascites, who were diagnosed either at first presentation or at recurrence of CRC, were eligible. No signs of distant metastases (liver, lung) on computed tomography (CT) scan of abdomen and chest x-ray were allowed. Patients had to be younger than 71 years and fit for major surgery (normal bone marrow indices, and normal renal and liver functions). Initially, patients who had received fluorouracil (FU) within 12 months before random assignment were excluded. In the first year of the study, an amendment to the protocol was made to allow inclusion of these patients.

Patients were randomly allocated to either standard treatment or to the experimental treatment. The randomization was performed centrally by computer, and stratified for presentation (primary or recurrence) and site (appendix, colon, or rectum).

The medical ethical committee of the Netherlands Cancer Institute approved the study, and written informed consent was obtained from all patients.

### Standard Treatment

Surgery was only performed in cases of symptoms of intestinal obstruction, and consisted of either bypass or stoma surgery. Often, this type of surgery had already been performed before referral for random assignment. Patients started chemotherapy immediately after random assignment or after recovery from surgery. Chemotherapy was given in the local setting, usually by the patients' own medical oncologist, and consisted of FU (intravenous [IV] push-dose of 400 mg/m$^2$) and leucovorin (IV 80 mg/m$^2$) on an outpatient basis (modified Laufman regimen[25]). Treatment was given weekly for 26 weeks, or until progression, death, or unacceptable toxicity. Patients who had already been treated with FU within 12 months before random assignment were treated with irinotecan (350 mg/m$^2$) at 3 weekly intervals for 6 months or until progression or intolerable toxicity.

### Experimental Treatment

*Cytoreductive surgery.* All procedures were carried out in the Netherlands Cancer Institute. Laparotomy under general anesthesia was performed from xyphoid to pubis. After opening the abdomen, the presence of macroscopic tumor deposits was recorded in seven abdominal regions: pelvis and sigmoid; right lower abdomen; small bowel and mesentery; omentum and transverse colon; subhepatic space and stomach; right subphrenic space; and left subphrenic space. The maximal tumor size was recorded in each region as: none, less than 1 cm, 1 to 5 cm, or more than 5 cm.

The objective of cytoreduction was to leave no macroscopic tumor behind, or at least to have limited residual tumor (<2.5 mm in thickness). To achieve this, the stripping of the parietal peritoneum was carried out as described by Sugarbaker et al.[26] Infiltrated viscera were resected if this was compatible with retaining function. Most often this concerned the rectum, parts of small bowel and colon, the gall bladder, parts of the stomach, and the spleen. The greater omentum was routinely removed. Reconstruction of gastrointestinal continuity was postponed until after the lavage, to prevent entrapment of tumor cells in suture lines. At completion of cytoreduction, the absence of residual tumor was recorded as R-1. If the largest residual tumor was smaller than 2.5 mm, it was regarded as an R-2a resection. In cases of residual tumor

larger than 2.5 mm, cytoreductive surgery was scored as R-2b. The total length of the operation, and blood loss were also recorded.

*Hyperthermic intraperitoneal chemotherapy (HIPEC).* To increase the volume of the abdominal cavity and to prevent spillage of lavage fluid, the skin of the laparotomy wound was pulled up against a retractor. A plastic sheet covered the laparotomy opening to reduce heat loss and to avoid drug spilling. A central aperture was made to allow manipulation to achieve optimal drug and heat distribution. The perfusion circuit consisted of a centrally placed inflow catheter, outflow catheters, placement in the pelvis below left and right diaphragm, a roller pump, and a heat exchanger. Temperature probes were attached to inflow and outflow catheters. Perfusion was started with a minimum of 3 L of isotonic dialysis fluid, at 1 to 2 L/min, and an inflow temperature of 41°C to 42°C. As soon as the temperature in the abdomen was stable above 40°C, MMC was added to the perfusate at a dose of 17.5 mg/m$^2$ followed by 8.8 mg/m$^2$ every 30 minutes. The total dose was limited to 70 mg at maximum. If the core temperature exceeded 39°C, the inflow temperature was reduced. After 90 minutes, the perfusion fluid was drained from the abdomen, and bowel continuity was restored. A temporary colostomy was made in most cases if the rectum was resected. A draining gastrostomy and transgastric jejunal feeding tube were inserted. The outflow catheters were used for postoperative drainage of the abdomen cavity.

### Postoperative Care

Patients stayed in the intensive care unit for 3 days. In cases of abdominal sepsis (faecal flora in drain fluid, high fever, sepsis), a laparotomy was performed to correct bowel leakage at an early stage.

Jejunal tube feeding was begun on day 1. Parenteral nutrition was given until jejunal feeding could cover all nutritional needs. Oral fluid and food intake was resumed as soon as the gastrostomy production dropped below 500 mL per 24 hours.

### Adjuvant Chemotherapy

Systemic chemotherapy was intended to start after 6 weeks beyond cytoreduction followed by HIPEC, and before 3 months after cytoreduction followed by HIPEC. The regimens as described in the standard therapy arm were used.

### Toxicity/Complications

Chemotherapy-related toxicity was recorded using the World Health Organization (WHO) scale. All postoperative complications were noted, and were graded as toxicity according to the WHO scale.

### Follow-Up

All patients were seen at the outpatient clinic once every 3 months for 2 years, and every 6 months thereafter. The follow-up consisted of physical examination and serum CEA every 3 months and an abdominal CT scan of the abdomen every 6 months, starting 3 months after randomization in the standard arm and 3 months after cytoreduction followed by HIPEC in the experimental arm.

### Statistical Analysis

The main end point was survival, measured as time from randomization to death from any cause. Patients alive at the time of analysis were censored at their last follow-up examination. The survival was estimated by the Kaplan-Meier method and tested with the log-rank test following the intention-to-treat principle. The analysis was planned at a median follow-up of 2 years to have 80% power to detect a 20% absolute difference in survival. To detect this difference, with $P < .05$ (two-tailed test), at least 100 patients had to be entered.

To improve patient selection in the future, additional exploratory analyses were performed to identify potential prognostic factors. Presentation (primary $v$ recurrence), site (appendix $v$ colon $v$ rectum), number of regions involved (<5 regions $v$ >5 regions), and completeness of cytoreduction (R-1 $v$ R-2a $v$ R-2b) were included in a Cox proportional hazards regression model

Randomization
105 patients

Standard treatment
51 patients

Started chemotherapy
44 patients

Experimental arm
54 patients

Treated by HIPEC
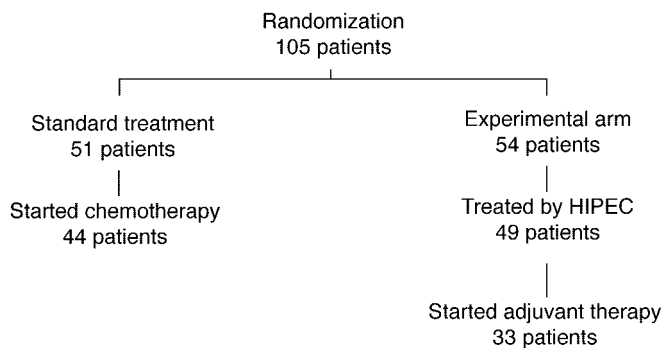49 patients

Started adjuvant therapy
33 patients

**Fig 1.** Trial profile of all 105 randomly assigned patients. HIPEC, hyperthermic intraperitoneal chemotherapy.

in order to obtain hazard ratios and 95% confidence intervals. All *P* values are two-sided.

## RESULTS

Between January 1998 and August 2001, 105 patients were randomly assigned in this study—51 to standard therapy and 54 patients to experimental therapy. Two patients proved ineligible—one patient with pseudomyxoma peritonei in the standard arm and one with peritoneal mesothelioma in the experimental

arm. Figure 1 shows the trial profile. All patients, including the ineligible ones, were included in the intention-to-treat analysis. The patient group included 58 men and 47 women, with a median age of 54 years (range, 28 to 70 years). Fifty-eight patients had PC at their primary presentation, and 47 patients had the disease at recurrence. The primary sites were appendix in 18 patients, colon in 75, and rectum in 12. The patient and tumor characteristics were well balanced within both arms, except for a nonsignificant overrepresentation of males in the "HIPEC" arm (63% *v* 47%; *P* = .11). Tumor size and differentiation grade were equally distributed in both arms. The majority of the patients (95.8% standard arm; 98.0% HIPEC arm) had large tumors (T3 and T4). All patients with small tumors (3.1%; T1 and T 2) were patients with PC at recurrence of CRC. (Table 1).

### Standard Arm

Seven patients never started systemic chemotherapy: five patients withdrew their consent; two patients had severe progressive disease before they could start, and deteriorated rapidly. Thirty-eight patients started with FU-leucovorin, of whom 21 received treatment for at least 5.4 months (median, 5.8 months; range, 5.4 to 6.7); 12 stopped because of progression of disease; two stopped because of toxicity; and three were still on treat-

**Table 1.** Patient Characteristics of the 105 Patients Randomly Assigned Onto the Trial

| | Arm | | | | Total | |
| | Standard | | HIPEC | | | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
|---|---|---|---|---|---|---|
| All patients | 51 | 100.0 | 54 | 100.0 | 105 | 100.0 |
| Sex | | | | | | |
| Male | 24 | 47.1 | 34 | 63.0 | 58 | 55.2 |
| Female | 27 | 52.9 | 20 | 37.0 | 47 | 44.8 |
| Age, years | | | | | | |
| Median | 55 | | 53 | | 54 | |
| Range | 29-70 | | 28-69 | | 28-70 | |
| Performance status | | | | | | |
| Not recorded | 19 | 37.3 | 15 | 27.8 | 34 | 32.4 |
| 0 | 23 | 45.1 | 30 | 55.6 | 53 | 50.5 |
| 1 | 7 | 13.7 | 9 | 16.7 | 16 | 15.2 |
| 2 | 2 | 3.9 | — | — | 2 | 1.9 |
| Presentation at random assignment | | | | | | |
| Carcinosis as primary presentation | 28 | 54.9 | 30 | 55.6 | 58 | 55.2 |
| Carcinosis as recurrence | 23 | 45.1 | 24 | 44.4 | 47 | 44.8 |
| Primary tumor | | | | | | |
| Appendix | 11 | 21.6 | 7 | 13.0 | 18 | 17.1 |
| Colon | 34 | 66.7 | 41 | 75.9 | 75 | 71.4 |
| Rectum | 6 | 11.8 | 6 | 11.1 | 12 | 11.4 |
| Differentiation grade* | | | | | | |
| Good | 3 | 6.3 | 5 | 9.43 | 8 | 7.9 |
| Moderate | 27 | 56.3 | 33 | 62.3 | 60 | 59.4 |
| Poor | 18 | 37.5 | 15 | 28.3 | 33 | 32.7 |
| T status of primary tumor† | | | | | | |
| T1 | 1 | 2.1 | — | — | 1 | 1.0 |
| T2 | 1 | 2.1 | 1 | 2.0 | 2 | 2.1 |
| T3 | 17 | 35.4 | 19 | 38.8 | 36 | 37.1 |
| T4 | 29 | 60.4 | 29 | 59.2 | 29 | 60.0 |

Abbreviation: HIPEC, hyperthermic intraperitoneal chemotherapy.
*Data from four patients are missing.
†Data of eight patients are not available.

**Table 2.** Major Toxicity and Complications of 48 Patients With Peritoneal Carcinomatosis Treated by Cytoreduction Followed by HIPEC

| | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Fever | 3 | 6 | — | — |
| Leukopenia | 7 | 15 | 1 | 2 |
| Thrombocytopenia | 2 | 4 | — | — |
| Neuropathy (paresis) | 2 | 4 | — | — |
| Pleural effusion | 1 | 2 | — | — |
| Pulmonary embolus (within 3 months after surgery) | — | — | 2 | 4 |
| Pneumonia | 1 | 2 | — | — |
| Renal obstruction | 2 | 4 | — | — |
| Anuria (acute tubular necrosis) | — | — | 3 | 6 |
| Cardiac arrhythmia | — | — | 1 | 2 |
| Heart failure | 4 | 8 | 2 | 4 |
| GI fistula | — | — | 7 | 15 |
| Pancreatitis | 1 | 2 | — | — |
| Catheter infections | 3 | 6 | — | — |
| Haemorrhage | 3 | 6 | 4 | 8 |
| Psychological disorders | 3 | 6 | 2 | 4 |

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; GI, gastrointestinal.

ment. Six patients started with irinotecan, of whom two completed treatment.

*Experimental Arm*

Five patients did not undergo cytoreduction followed by HIPEC treatment. While waiting for surgery, one died due to rapid tumor progression; two patients developed lung and liver metastases, for which they were treated with palliative chemotherapy; and in one patient, a primary lung cancer was detected shortly after randomization. This patient died shortly after randomization. One patient withdrew consent. The median time between randomization and surgery was 6 weeks (range, 6 days to 14 weeks). The median hospital stay of the 49 patients operated on was 29 days (range, 6 to 166 days). The median duration of the cytoreduction and HIPEC was 485 minutes (range, 315 to 765 minutes), while the median blood loss was 3.9 L (range, 0.5 to 30.0 L; for seven patients, data were not available). Of the seven possible affected regions, six or seven were involved in 16 patients. Those patients had a median operation time of 585 minutes (range, 440 to 765 minutes) and a median blood loss of 6.0 L (range, 3.5 to 30.0 L). In two patients, no macroscopic tumor was found at all, and peritoneal metastases had been resected at a previous laparotomy. Both received HIPEC without cytoreduction. The median hospital admission duration was 23 days (range, 13 to 90 days) for zero to five affected regions, and 38 days (range, 6 to 166 days) for six to seven regions.

An average of 1.8 visceral resections were performed per patient. Most often, parts of small bowel (45 patients) and rectum (25 patients) were resected. Twenty-four patients needed a colostomy. The median number of bowel anastomoses was two (range, zero to seven anastomoses). In 18 patients, no macroscopic residual disease was left behind (R-1); in 21, the residual deposits were smaller than 2.5 mm (R-2a); and in 10 cases, residual deposits were ≥ 2.5 mm (R-2b).

Grade 3 and 4 toxicity, as well as complications, are shown in Table 2. The surgical complications are recorded as toxicity, as described in the WHO criteria. Only bone marrow toxicity (14% grade 3, and 5% grade 4) is definitely attributable to MMC. The nadir was between 10 and 12 days. All other toxicity is most likely due to surgery or to an interaction between MMC and major surgery. The most important complications were small bowel leakage and abdominal sepsis. Four patients (8%) died as a result of the treatment. Two patients (4%) died of abdominal sepsis within 30 days after cytoreduction followed by HIPEC. Two other patients (4%) never recovered and died of a complicated postoperative course.

Fourteen patients never started adjuvant chemotherapy after cytoreduction followed by HIPEC. This was because of early progression (eight patients) or refusal (three patients). All 33 patients who started chemotherapy received FU-leucovorin. Nineteen completed 6 months of therapy, four stopped early because of disease progression, two stopped because of toxicity, and one withdrew consent. At the time of closing the database, seven patients were still receiving the treatment.

*Survival*

One patient was lost during follow-up after 7 months, while the follow-up was complete for all other patients. After a median follow-up of 21.6 months, 20 patients were still alive in the standard treatment group, compared with 30 patients in the HIPEC group. Cytoreduction followed by HIPEC significantly reduced the risk of dying (hazard ratio, 0.55; 95% CI, 0.32 to 0.95; log-rank $P = .032$). Median survival in the standard arm was 12.6 months, compared with 22.4 months in the HIPEC arm ($P = .032$; Fig 2). Exploratory subgroup analysis did not reveal any particular subgroup in which the effect of cytoreduction followed by HIPEC was better or worse compared with standard treatment (Fig 3). When the data of the patients who underwent cytoreduction followed by HIPEC were further analyzed, they
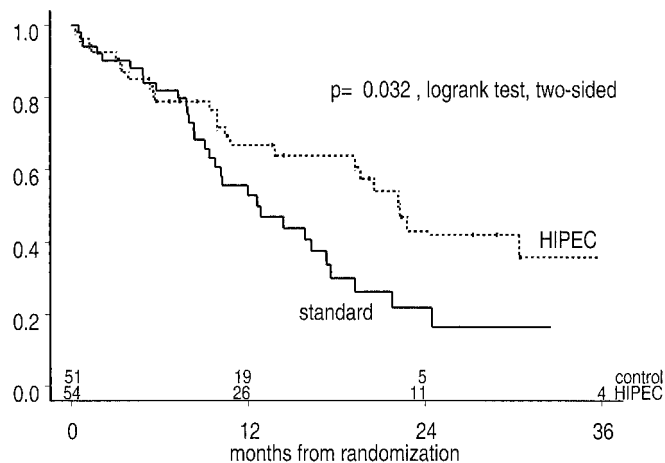
Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).



Fig 4. Kaplan-Meier survival curve of 49 patients with peritoneal Carcinomatosis (PC) treated by cytoreduction followed by hyperthermic intraperitoneal chemotherapy, comparing the number of regions affected with PC.

showed that patients with six to seven regions still had a very poor survival (median, 5.4 months) compared with those with zero to five regions involved (median, > 29 months; Fig 4; $P <$ .0001). The success of the surgical procedure also had prognostic value. After complete resection (R-1), only one of 18 patients died. Fourteen of the 21 patients with limited residual disease (R-1a) died, compared with seven of the 10 patients with extensive residual disease (R-2b) ($P <$ .0001). The median times to death in the latter two groups were 20 and 5 months, respectively (Fig 5).

## DISCUSSION

This study was designed to answer the question of whether the addition of aggressive cytoreduction and HIPEC with MMC improves survival in patients with PC of colorectal origin. In this analysis, the results of all 105 randomly assigned patients are reported. The median follow-up at the time of analysis was 21.6 months, which is more than twice the median survival in the standard arm. At the time of this writing, an event (either recurrence or death) had occurred in 61% of the patients—almost two-thirds of what had been experienced in the standard arm. Follow-up, therefore, is long enough to demonstrate any impact of this new therapy on survival. The analysis was carried out according to the intention-to-treat principle, irrespective of the actual treatment received. Protocol violations, including ineligibility of enrolled patients and treatment alterations, should have a negative impact on the experimental arm. Nevertheless, Kaplan-Meier survival analysis showed a statistically significant survival benefit for the experimental therapy. The effect is of a remarkable size. The median duration of survival almost doubled, while the 2-year survival was even more than twice as high. The difference between the patient groups withstands selection bias, as in the control arm, life expectancy exceeded 6 months known from literature.[27,28] Nevertheless, these relative good results suggest positive selection before random assignment.

Although the longest survivor is at present only 4 years after randomization, the Kaplan-Meier survival curve suggests a 5-year survival rate in the order of 20%, which is comparable to
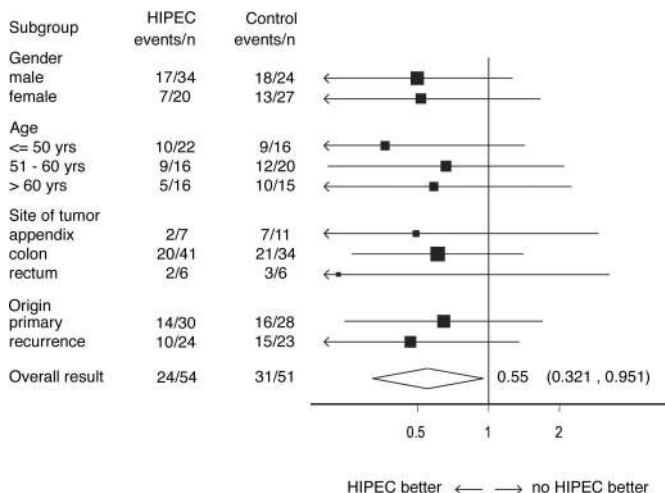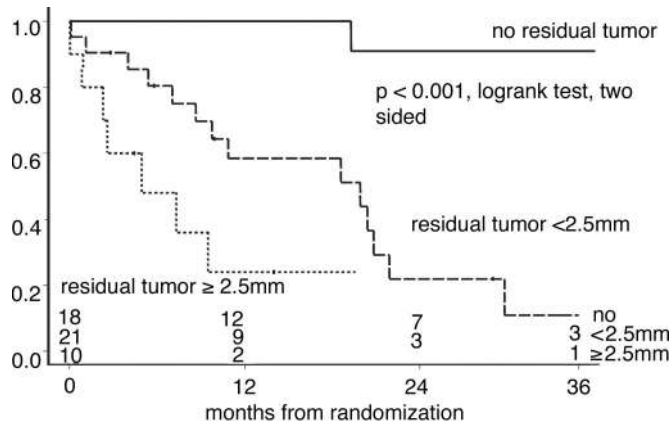


Fig 3. Explorative subgroup analysis on survival of all 105 patients randomized. This Forest plot shows the hazard ratio (odds of death) for various subgroups of patients. The size of the squares represent the number of patients, the horizontal lines through the squares indicate the 99% CIs. The diamond (◇) indicating the overall result corresponds with the 95% CI. HIPEC, hyperthermic intraperitoneal chemotherapy.
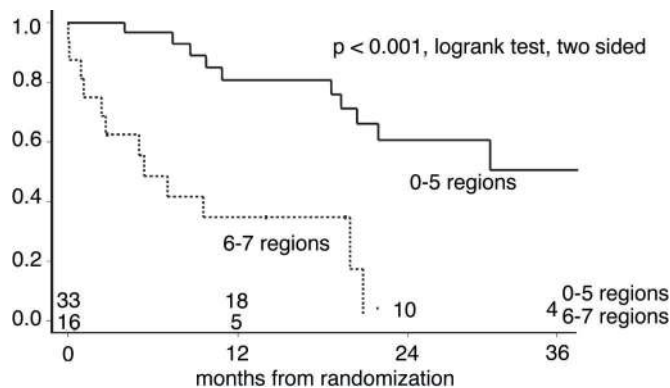


Fig 5. Kaplan-Meier survival curve of 49 patients with peritoneal carcinomatosis treated by cytoreduction followed by HIPEC, comparing the number of regions with residual tumor.

Table 3. Literature Review of Nonrandomized Data on Patients With Peritoneal Carcinomatosis Treated by Cytoreduction and Intraoperative Hyperthermic Chemotherapy

| Study | Year | No. of Patients | Median Survival (months) | Survival | |
|---|---|---|---|---|---|
| | | | | Duration (years) | % of Patients |
| Shen et al[21]* | 2002 | 109 | 16 | 3 | 33 |
| Piso et al[18] | 2001 | 17 | 39 | 4 | 75 |
| Elias et al[16] | 2001 | 64 | 36 | 5 | 27 |
| Witkamp et al[23] | 2001 | 29 | NA | 2 | 45 |
| Beaujard et al[14] | 2000 | 21 | 12 | 1 | 50 |
| Cavaliere et al[15] | 2000 | 14 | NR | 2 | 64 |
| | 2000 | 22† | 31 | 2 | 52 |
| Loggie et al[17] | | 38‡ | 15 | 2 | 39 |
| Rey et al[19] | 2000 | 26 | NA | 2 | 12 |
| Sugarbaker and Chang[22] | 1999 | 161 | NA | 5 | 30 |
| Fujimara et al[12] | 1999 | 14 | 10 | 2 | 21 |
| Schneebaum et al[20] | 1996 | 15 | 6 | NA | |

Abbreviations: NA, not available; NR, not reached.
*Mixed patient group.
†Appendiceal cancer.
‡Colorectal cancer.

survival found in phase II studies. Together with the results of published phase II studies[12,14-23] (Table 3), our results provide compelling evidence of the effectiveness of aggressive cytoreduction and HIPEC.

This effect was associated with considerable morbidity and mortality (8%), which is similar to that reported by others.[21] Most of the serious complications seem to be related to the extent of surgery, and may be related to the extent of peritoneal involvement, rather than to the HIPEC procedure. The median blood loss of almost 4 L is high. The most extreme blood loss measurements were found in patients with six and seven regions involved. Characteristically, these patients would undergo a partial gastrectomy, splenectomy, resection of the tail of the pancreas, omentectomy, multiple small bowel resections, ileocecal resection, rectosigmoid resection, and uterus with adnex extirpation combined with multiple peritonectomy procedures, leaving an enormous intra-abdominal wound bed. Exhaustion of coagulations factors, though replaced with fresh frozen plasma and thrombocytes if measurably low, has probably contributed to the blood loss.

It is noteworthy that in the first 6 months, the period in which the treatment-related deaths occurred, survival was identical in both treatment arms. This emphasizes one of the problems of this study—the inclusion of many patients with extensive peritoneal disease. This was due partly to our lack of understanding of the impact of extent of the disease on morbidity and survival, which meant that we did not exclude any patients based on the extent of the disease. Even if we had designed the study to exclude patients with extensive disease (six or seven regions), we would not have been very successful in predicting the extent of the disease based on preoperative findings. CT scans failed because typical PC is a like a coating that projects as a thin line on a cross-section. More modern positron emission tomography scans are based on tumor density per volume unit, which is low in these circumstances. The only trustworthy moment of predicting outcome occurs after exploration of the abdomen.

The analysis of prognostic factors in the HIPEC arm shows that patients with cancer deposits in six or seven regions of the abdomen do poorly, both in respect to direct postoperative complications and long-term survival. Eighty percent of all incidences of grade 4 toxicity (postoperative complications included) and all treatment-related deaths were in this patient group. These are the same patients in whom we failed to obtain a complete cytoreduction. These patients have clearly not benefited from cytoreduction and HIPEC. Both Sugarbaker et al,[26] and Elias and Ouellet[29] have reported very similar findings. Patients in whom six or seven regions were affected by tumor also had poor survival (median, 5.4 months). Patients with a high tumor load could be spared unnecessary toxicity since there is little chance of improved survival. Such patients should be identified before surgery by standardization of explorations in every patient affected by PC.

Many questions remain unanswered. The experimental arm of this study combined two treatment elements: aggressive cytoreduction and HIPEC. Whether the combination of these treatment modalities was required for the survival benefit is unclear. Complete or nearly complete resection seems to be a prerequisite for a favorable outcome. This is consistent with our understanding that intraperitoneal chemotherapy only leads to drug delivery advantages to the superficial layers below the peritoneal surface, and can therefore only be effective in minimal-residue disease. Nevertheless, it cannot be excluded that the observed effect was exclusively or mainly caused by the aggressive cytoreduction alone.

In this study, a moderately dosed regimen of FU-leucovorin was used, as this is a convenient outpatient regimen with only minimal gastrointestinal toxicity or other toxicity.[25] Recently, somewhat more aggressive schedules of combination chemotherapy have been introduced in advanced colorectal cancer, which may be associated with a small survival benefit.[30,31] It is possible that the use of these contemporary chemotherapy schedules would have slightly prolonged survival in both treatment arms. However, it seems unlikely that it would have had any influence on the survival differences found in this study. The

combination of cytoreduction and HIPEC with continuous FU-leucovorin, irinotecan, and/or oxaliplatin seems certainly promising for further outcome improvement.

Questions concerning other aspects of HIPEC, for instance, the role of hyperthermia and the best choice of drug or dosage for intraperitoneal therapy, remain completely open. Other drugs such as oxaliplatin[32] and floxuridine[33] have been studied and may be incorporated alone or in novel combinations.

In this study, the open coliseum technique is used. This open system presents the possibility to maintain optimal distribution by manual stirring. Recently, this system has been tested for safety by operating room personnel.[34] In this study, MMC was found neither in the operating room air, nor in the urine of the surgeon or perfusionist, and is therefore safe.

This study shows that the therapeutic nihilism that has dominated the care for patients with PC for such a long time may not be appropriate. Limited PC may represent a situation analogous to that of isolated liver metastases, in which long-term survival can be achieved in some patients by the surgical removal of macroscopic disease and by systemic treatment to deal with microscopic residual disease. With the appropriate patient selection and a determined locoregional treatment effort, PC of colorectal origin may even be a potentially curable disease in patients with limited peritoneal involvement.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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