

# Results of Systematic Second-look Surgery Plus HIPEC in Asymptomatic Patients Presenting a High Risk of Developing Colorectal Peritoneal Carcinomatosis

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**Purpose:** To analyze the impact of systematic second-look surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) performed 1 year after resection of the primary tumor in asymptomatic patients at high risk of developing peritoneal carcinomatosis (PC).

**Patients and Methods:** From 1999 to 2009, 41 patients without any sign of recurrence on imaging studies underwent second-look surgery aimed at treating limited PC earlier and more easily. They were selected based on 3 primary tumor-associated criteria: resected minimal synchronous macroscopic PC (n = 25), synchronous ovarian metastases (n = 8), and perforation (n = 8).

**Results:** PC was found and treated with complete surgery plus HIPEC in 23 of the 41 (56%) patients. The other patients underwent complete abdominal exploration plus systematic HIPEC. Median follow-up was 30 (9–109) months. One patient died postoperatively at day 69. Grade 3–4 morbidity was low (9.7%). The 5-year overall survival rate was 90% and the 5-year disease-free survival rate was 44%. Peritoneal recurrences occurred in 7 patients (17%), 6 of whom had macroscopic PC discovered during the second-look (26%), and one patient had no macroscopic PC (6%). In the univariate analysis, the presence of PC at second-look surgery was a significant risk factor for recurrence ( $P = 0.006$ ).

**Conclusion:** Selection criteria for high-risk patients appear to be accurate. In these patients, the second-look strategy treated peritoneal carcinomatosis preventively or at an early stage, yielding promising results. This study has allowed us to design a multicentric randomized trial (comparing the second-look + HIPEC approach versus standard follow-up alone), which is beginning.

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Stage IV colorectal cancer is a very morbid disease, with a 5-year overall survival rate of 10% and a median survival of 14.4 months. The prognosis is significantly worsened when there is peritoneal carcinomatosis (PC), with a median survival of 6.7 months versus 18.1 months when it is absent ( $P < 0.01$ ).<sup>1</sup> During the last 10 years a new approach combining complete cytoreductive surgery (CCRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has yielded encouraging results.<sup>2,3</sup> The purpose of surgery is to treat all the macroscopic, ie, visible disease and the aim of HIPEC is to

treat the microscopic, ie, occult residual disease.<sup>4</sup> In selected patients presenting with macroscopic colorectal PC who received this combined treatment, the results of a phase 3 study demonstrated that the survival rate was 3-fold higher in the experimental arm compared to the systemic chemotherapy arm.<sup>5</sup> The 5-year overall survival rate in a recent multicentric retrospective study of 523 patients submitted to CCRS with intraperitoneal chemotherapy was 30%<sup>6</sup> and could exceed 40% in specialized centers.<sup>7–9</sup>

The extension of peritoneal disease is one of the major prognostic factors: long-term survival results and postoperative morbidity are far better when PC is more limited in extent.<sup>5–10</sup> This is a strong argument in favor of attempting to detect and treat PC at an early stage. Unfortunately, detecting PC at an early stage is not currently possible because of the absence of symptoms and the poor accuracy of imaging for the diagnosis of peritoneal carcinomatosis. Exploration of the peritoneal cavity during a laparotomy (second-look surgery) has therefore been developed to circumvent these obstacles.<sup>11</sup> In a previous study, we demonstrated that PC was present and diagnosed during second-look surgery in 55% of patients considered at high risk of developing PC.<sup>11</sup>

The aim of this study was to analyze the potential benefit of systematic second-look surgery plus HIPEC, even in the absence of macroscopic PC, in patients at high risk of developing peritoneal carcinomatosis.

## MATERIALS AND METHODS

This was a prospective study, and all the patients were systematically informed of the aim of the study before the second-look procedure and gave their consent. The study was approved by the local Ethics Committee.

### Patient Inclusion Criteria

1. Patients curatively (R0-1 resection) treated for their primary colorectal tumor, but who at the time had presented with: (i) either minimal PC which was macroscopically visible, completely resected at the same time as the primary, and histologically examined, (ii) or ovarian metastasis (also resected), synchronous with the primary (iii) or a perforated primary tumor inside the peritoneal cavity. Patients presenting with an initial PC associated with a perforated tumor or with ovarian metastases were classified in the initial PC group.
2. Patients who had no sign of recurrence (clinical, biological or radiological) 1 month before second-look surgery. The month preceding second-look surgery, imaging studies including a CT scan of the abdomen and the pelvis with oral and intravenous contrast agent, and a thoracic CT scan were reviewed by 2 experienced radiologists. FDG-PET was not systematically performed.
3. Patients with a good general status (WHO performance status < 2), able to undergo CCRS combined with HIPEC.

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## Design of the Study

1. After surgical resection of the primary tumor, these “high-risk PC” patients received adjuvant 5-FU plus oxaliplatin- or irinotecan-based chemotherapy regimens over 6 months.
2. Six months after the end of the adjuvant chemotherapy, if the complete work-up was negative (no clinical symptoms, nor any CT scan abnormality nor blood tumor marker elevation), second-look surgery was proposed to the patients and was performed during the following month.
3. Laparotomy was performed to reopen the dissection planes of the first operation and to palpate the tissues. A median xypho-pubic incision was systematically used and the abdominal cavity was completely explored.
4. HIPEC was systemically performed, after resection of all macroscopic lesions in patients who had macroscopic PC (PC+), or just systemically in patients without macroscopic PC (PC0).

## CCRS with HIPEC

At laparotomy, the peritoneal extent of peritoneal seeding was calculated for each with the peritoneal cancer index (PCI) which ranges from 1 to 39.<sup>7,12</sup> The macroscopically detectable peritoneal disease had to be completely resected before administering HIPEC. Oxaliplatin was administered alone intraperitoneally in an open abdominal cavity (Coliseum technique) at a dose of 460 mg/m<sup>2</sup> in 2 L/m<sup>2</sup> of iso-osmotic 5% dextrose,<sup>13</sup> or at a dose of 300 to 360 mg/m<sup>2</sup> when associated with irinotecan at a dose of 200 mg/m<sup>2</sup>.<sup>12,13</sup> The intraperitoneal temperature was homogeneous at 43°C (range: 42–44°C) for 30 minutes. Patients received an intravenous perfusion of 5-fluorouracil (5-FU) (400 mg/m<sup>2</sup>) with leucovorin (20 mg/m<sup>2</sup>) just before starting HIPEC.<sup>14,15</sup>

## Complications

Complications were graded according to the Dindo-Clavien classification.<sup>16,17</sup> A significant postoperative complication was defined as exceeding grade 2.

## Follow-Up of Patients After Second-Look Surgery and Long-Term Results

Patients were followed up after the second-look procedure with a clinical examination, imaging studies and blood tumor marker determination every 3 months for the first 2 years and every 6 months for the next 3 years.

## Statistics

Categorical variables were compared within groups using the Chi-squared and Fisher's Exact test, when appropriate. The survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test including the postoperative death. All statistical analyses were performed using Statistica computer software (StatSoft Inc. Tulsa, Oklahoma, USA). Data were expressed as means ± the standard error of the mean (SEM), unless otherwise stated. A *P* value of less than 0.05 was considered significant.

## RESULTS

Between April 1999 and November 2009, 41 patients underwent second-look surgery, approximately 1 year after the first surgical procedure for curative treatment of a primary tumor presenting a “high-risk of giving rise to PC.”

### Three Subgroups of Patients According to Their High-Risk Factor for PC

Patient distribution in the groups considered at high risk of developing PC was as follows: the initial PC group (n = 25), the ovarian

group (n = 8) and the perforated group (n = 8). All patients received adjuvant systemic chemotherapy over 6 months. The characteristics of the primary tumors, their main risk factors for PC, and adjuvant chemotherapy are reported in Table 1.

### Peritoneal Carcinomatosis at Second-Look Surgery

Macroscopic PC was discovered in 23 of 41 (56%; group PC+) of these asymptomatic patients during the second-look procedure. The incidence of macroscopically visible PC was 62% in the ovarian group, 60% in the initial PC group and 37% in the perforated group. The interval between resection of the primary and second-look surgery was 11.1 ± 7.1 months, and was not statistically different between PC+ and PC0 patients, respectively 12.6 ± 8.7 and 9.2 ± 3.7 (*P* = 0.366). The mean PCI for the extent of peritoneal seeding was respectively 9 ± 6, 7 ± 5 and 5 ± 2 for the initial PC, ovarian and perforated groups.

In the univariate analysis, neither gender, tumor location, subgroups of high-risk tumors (perforated tumor, ovarian metastasis, initial PC), nor the T or N status of the primary was predictive of finding macroscopic PC during second-look surgery.

HIPEC was performed at the end of surgery in all PC+ patients (n = 23) and in all PC0 patients (n = 18). The mean duration of surgery was longer in the PC+ group (422 ± 109 minutes, [240–660]) than in the PC0 group (316 ± 76 minutes, [105–560]) (*P* = 0.028). The mean blood loss was higher in the PC+ group (710 ± 633 mL, [100–3000]) than in the PC0 group (342 ± 271 mL, [100–1000]), nearly reaching statistical significance (*P* = 0.065).

### Mortality and Morbidity

One patient (2%) died of multiple organ failure after the combined treatment. This was a 58-year-old woman operated on for a rectal adenocarcinoma with synchronous and limited pelvic carcinomatosis. She received 6 months of adjuvant chemotherapy. The patient's general condition was poor, and the decision to perform second-look procedure was validated as we considered it would not be a major resection. During the operation, the peritoneal index proved to be higher than expected (PCI = 13) and the surgical procedure was difficult and long (570 minutes). The patient was reoperated on at day 6 for anastomotic leakage from a colorectal anastomosis. Subsequently, many complications (pulmonary infection, bleeding, etc.) occurred and the patient died of multiple organ failure at day 69.

Overall severe morbidity (grade > 2) was 9.7% (4/41 patients), and was respectively 11.1% (2/18) in the PC0 group, and 8.6% (2/23) in the PC+ group (*P* = 1.000). The postoperative course was uneventful in more than half of the patients (53.6%).

The overall mean hospital stay was 21 ± 10 days [13–69]. It was not different between the 2 groups of patients, 20 ± 7 days [14–42] in the PC0 group and 21 ± 11 days [13–69] in the PC+ group (*P* = 0.816).

### Follow-Up and Survival

Median follow-up after second-look surgery was 30 [9–109] months (mean: 40 ± 27 months). No patient was lost to follow-up.

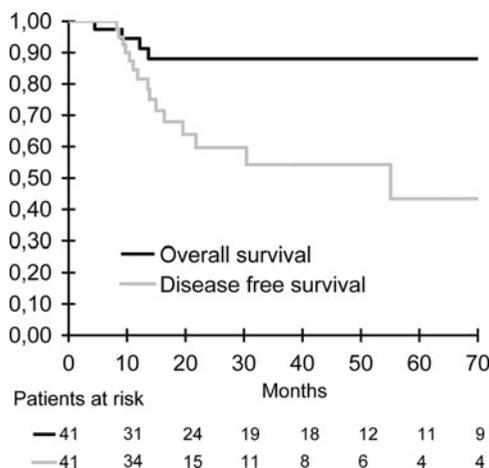
Overall and disease-free survival rates of the 41 patients who received HIPEC are reported in Figure 1. The 5-year overall survival rate was 90%, and 5-year disease-free survival rate was 44%. Median survival has not yet been reached for these 41 patients. In the univariate analysis of prognostic factors (gender, tumor location, subgroup of high-risk tumors, T status, N status, histological differentiation, presence or not of macroscopic PC during the second-look), none of them exerted a significant impact on overall or disease-free survival rates after second-look surgery + HIPEC.

In the PC+ group, 12 of 23 patients (52%) relapsed and 3 (13%) have died. Recurrences were situated in the peritoneum

**TABLE 1.** Patients' Demographic and Primary Tumor Characteristics

Variables	Total (N = 41)	Synchronous Minimal PC (n = 25)	Ovarian Metastase (n = 8)	Perforated Tumor (n = 8)
Male/female ratio				
Male	15	11	0	4
Female	26	14	8	4
Median age (year)	49 ± 12	49 ± 13	53 ± 7	44 ± 12
Primary tumor location				
Colon	40	24	8	8
Rectum	1	1	0	0
ASA score				
1	5	1	1	3
2	32	21	6	5
3	4	3	1	0
Primary tumor stage				
T2	1	0	1	0
T3	15	10	2	3
T4	22	13	4	5
N0	9	5	1	3
N1	15	10	3	2
N2	11	7	1	3
Nx	2	1	1	0
Unknown	3	2	2	0

PC indicates peritoneal carcinomatosis.

**FIGURE 1.** Overall and disease-free survival of the 41 patients who underwent systematic second-look surgery plus HIPEC.

(n = 1), in the peritoneum + liver + lung (n = 5), and were diffuse but not present in the peritoneum (n = 6). In the PC0 group, 2 of 18 relapsed (11%) and all of these patients are alive. Recurrences were situated in the peritoneum (n = 1) and in the colon (second cancer: Lynch syndrome n = 1). In all, 7 of the 41 patients (17%) relapsed in the peritoneum, 1 patient in the PC0 group (6%) and 6 in the PC + group (26%;  $P = 0.006$ ).

## DISCUSSION

This second-look policy in colorectal patients at high risk of developing PC, without any apparent clinical or imaging abnormality, effectively led to the discovery of macroscopic PC in 56% of the patients and allowed early and optimal curative therapy with CCRS plus HIPEC. These results confirm those observed in the previous study in which fewer patients were included.<sup>11</sup> Also, this is the first

study to evaluate the strategy of systematic HIPEC in patients at high risk of developing PC of colorectal origin.

The availability of an effective therapy (ie, HIPEC) for treating colorectal PC, allowing more than 40% of the patients to be alive at 5 years,<sup>7-9</sup> and the fact that the results are far better when PC is limited in extent<sup>5,6,10</sup> are very strong arguments in favor of attempting to detect and treat PC at an early stage. Because modern noninvasive diagnostic tools are ineffective to diagnose early PC (in our study, the false negative rate was higher than 50%), we had to design a new approach. The concept of second look-surgery was first used by Wangenstein<sup>18</sup> in 1948. The principles are based on the systematic use of planned reoperation in asymptomatic patients with malignant disease who are theoretically at risk for developing recurrent or metastatic disease despite initial curative surgery. As in past studies,<sup>19,20</sup> we decided to use laparotomy as a diagnostic tool. However, as early PC is only detectable by laparotomy and as second-look surgery plus HIPEC is an aggressive and costly treatment, it must be restricted to patients presenting a high risk of developing PC. This study confirms the accuracy of our selection criteria for high-risk patients. Half of them exhibited visible PC at the time of the second-look procedure. The risk of carcinomatosis was higher among patients with ovarian metastases, and lower in patients initially operated on for a perforated tumor. None of the patients in the perforated tumor group were initially treated in our center (they were referred to us for the second-look procedure). Whether the exact cause of perforation was tumor related or diastatic was not clear in half of them. In the near future, diastatic perforation will probably not be considered an indication for the second-look strategy, whereas awaiting more precise data on the real risk of developing PC. Iatrogenic perforation of the tumor by a stent or during surgery should be considered as a perforated tumor. In contrast, for the time being, we feel that data are not sufficiently clear to consider that pT4 primary tumors (invading neighboring structures), occlusive tumors, or positive peritoneal cytology should be treated with this new approach.<sup>21-24</sup> The patients in the initial PC group had a high risk of peritoneal recurrence (60%) and could have received HIPEC immediately, during the first operation. But, achieving HIPEC during the first operation is quite difficult, because either HIPEC is not available (most common in this study,

patients had been operated for the primary tumor in another hospital) or because the patient has not been informed in advance and has not signed consent.

As in our preliminary work, the PC index ascertained 1 year after surgical removal of the primary tumor was low and lower than indexes reported when the diagnosis of PC is based on a clinical or radiological abnormality.<sup>6</sup> It has been clearly demonstrated that morbidity and mortality after CCRS + HIPEC are correlated with the spread of peritoneal disease and the extent of the surgical resection. However, 1 patient died. With the benefit of hindsight, if the diagnosis of macroscopic PC had been known preoperatively, CCRS + HIPEC would not have been scheduled in this fragile patient. The decision to undertake the second-look procedure was made because of a high probability of finding limited carcinomatosis that would have been easily amenable to a complete resection. During the operation, we should have stopped the procedure and treated the patient with systemic palliative chemotherapy alone but we did not do so. This highlights the difficulty of canceling a decision during surgery when complete resection is technically possible, but the risk of postoperative morbidity is high. Furthermore, this case shows that there may be fairly extensive carcinomatosis even in the absence of morphological abnormalities. However, the overall morbidity rate was low and the postoperative course was uneventful when there was no macroscopic peritoneal disease, and thus no visceral resection. This could be an argument in favor of proposing this second-look approach earlier than 1 year after resection of the primary.

Among the 41 patients treated with HIPEC, only 7 (17%) relapsed in the peritoneum, which is usually the most frequent site of recurrences in these high-risk patients. Indeed, in the literature, peritoneal recurrences occur in 14% to 58% of cases with perforated tumors<sup>22,25,26</sup>, in 27% to 56% of cases with ovarian metastases<sup>27,28</sup> and in 64% to 91% of cases with resected minimal PC.<sup>29,30</sup> The risk of peritoneal recurrence is correlated with the PCI and with the completeness of resection, which is confirmed by this study, because the index was low and resection was complete in all the patients. The univariate analysis of risk factors for recurrence identified macroscopically visible PC at the time of second-look surgery as the only statistically significant factor. A number of plausible explanations could account for this finding. It could reflect a tumor subtype with a higher response to chemotherapy in the PC0 group (all patients received 6 months of adjuvant chemotherapy) which could explain the better response to systemic therapy. Another possible explanation is the systemic response induced by the surgical trauma (including immunosuppression and the release of growth factors) which is far greater in case of complete cytoreduction and which could promote a tumor recurrence. Another explanation could be the presence in PC0 patients of a “naturally” less aggressive tumor subtype but this point is highly debatable. The diagnosis of real PC0, ie, no residual disease at second-look surgery is difficult and in our previous study, the peritoneal recurrence rate among patients without PC who did not receive HIPEC was 75%, reason why we started the systematic HIPEC policy further on. In this study, the recurrence rate dropped to 6% in the group without PC. This fact strongly argues in favor of the first 2 explanations because without treatment, the tumor “naturally” evolved toward a recurrence in most cases. The other point, which comforted us in this systematic HIPEC policy is that in at least 1 patient of our study, a PC0 classification was made, confirmed by frozen section but the final histological results showed residual disease. For these reasons, and until we have a better tool to diagnosed microscopic disease, we deliberately chose to treat all patient to be sure not to miss any recurrence.

However, the presence (or not) of visible PC at second-look surgery did not significantly influence the overall survival rate, which means that CCRS + HIPEC appears to be effective in this prophyl-

actic setting. Also, a possible explanation for this lack of statistical significance is the combination of a very high overall survival rate, the presence of extra-peritoneal relapses and the small number of patients resulting in an underpowered statistical analysis. Although this early optimal treatment yielded a 5-year overall survival rate of 90%, the rate of extra-peritoneal recurrences (liver, lung) remains high since the 5-year disease-free survival rate was only 44%. Optimal systemic treatment, including targeted therapies and more and more personalized treatment should ultimately also reduce the rate of extra-peritoneal recurrences.

No solid comparison is currently possible because of the lack of studies in the literature focusing on the survival rate of these high-risk patients treated with only 6 months of adjuvant systemic chemotherapy without second-look surgery. Only a randomized multicentric trial comparing monitoring, the standard attitude to second-look surgery + systematic HIPEC, the experimental one would be able to demonstrate whether this approach is beneficial. Such a trial is currently beginning in France. Its design is as follows: all patients at risk will receive the gold standard adjuvant systemic chemotherapy over 6 months (currently the FOLFOX regimen). At the end of chemotherapy, a complete work-up will be performed. If it is negative, the patient will be randomized (after a signed consent) between the 2 arms.

In conclusion, for selected high-risk patients, peritoneal recurrence occurs in more than 50% after curative resection, even with a complete adjuvant therapy. Systematic second-look surgery helped to diagnose and optimally treat limited peritoneal carcinomatosis in more than half of the patients. Systematic second-look surgery + HIPEC in these high-risk patients allows a 90% 5-year overall survival. even in the absence of PC seems to decrease the risk of peritoneal recurrence. If the results of the randomized trial comparing this strategy to standard management are in favor of second-look surgery + HIPEC, the next step will be to assess immediate and systematic HIPEC at diagnosis or just after surgical resection of the primary in these high-risk patients.

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