Cytoreduction and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomastosis of colorectal origin

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Chapter five

Peritoneal carcinomatosis without distant metastasis of colorectal origin:
Results of conventional surgery and systemic chemotherapy

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Background: Cytoreduction combined with intraperitoneal chemotherapy enhances survival in patients with isolated peritoneal carcinomatosis. However, little is known about the results of the conventional approach, which consists of conventional surgery and systemic chemotherapy.

Method: Fifty patients with proven peritoneal carcinomatosis of colorectal origin were treated with conventional surgery and 5-fluorouracil (400mg/m²) and leucovorin (80mg/m²) once weekly, or irinotecan (350mg/m²) every three weeks in patients treated by 5-fluorouracil within 12 months prior to entry. Survival and progression-free survival were studied by using the Kaplan Meier method. Prognostic factors were analyzed.

Results: The median survival time of these patients was 12.8 months. The median time to progression was 7.6 months. Location of primary tumor and result of conventional surgery were prognostic factors related to survival.

Conclusion: The survival time of patients with peritoneal carcinomatosis of colorectal origin is short when treated by conventional surgery and systemic chemotherapy. Patients do better after adequate surgical debulking.

Submitted
Introduction

A growing number of non-randomized studies are being published on cyto-reductive surgery combined with some form of hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal origin.1-6 These papers emphasize encouraging results compared to the poor results of standard management.7 This increasing number of publications is in contrast to the limited knowledge of the results of conventional surgery and systemic chemotherapy. The latter approach is at this moment more or less standard in most western countries.

In many studies published on the effects of chemotherapy in advanced colorectal cancer, patients with carcinomatosis have been lumped together with patients with systemic metastases.8-9 Studies focusing on carcinomatosis often combine results of patients with and without distant metastases.9,10 They also describe the results in patients treated in a variety of ways or not treated at all. Therefore, it is not possible to determine whether the particular characteristics that distinguish peritoneal carcinomatosis from metastases at other sites have implications for survival.11 Nor is it possible to compare these results with outcomes of phase II studies dealing with cytoreductive surgery and intraperitoneal chemotherapy.

Recent editorials call for randomized trials examining the potential benefit of cytoreduction followed by hyperthermic intraperitoneal chemotherapy.12,13 However, there is still much to be learned from the results of the standard treatment of peritoneal carcinomatosis.

Patients with isolated peritoneal carcinomatosis of colorectal origin have been treated at The Netherlands Cancer Institute within a trial comparing standard therapy to cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy. The first analysis of this trial has been performed in 2002 with a median follow-up of 21.6 months.14 The prospective database of this trial is continuously updated. The present study concerns the patients treated by palliative surgery and systemic chemotherapy, with a current median follow-up of 42 months.

Patients and methods

Between April 1997 and August 2001, 105 patients were treated in a single-institution randomized trial comparing conventional surgery and systemic chemotherapy to cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy. Within this trial, 51 patients were randomized to standard therapy. Two of these patients rejected the result of the randomization and were treated by cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy. In the experimental arm, one patient refused experimental therapy shortly after entering the study and was treated by standard therapy. Thus, 50 patients were treated according to the control arm of the protocol, 25 were female and 25 were male with median age of 55 years (range 29-70 years). All these patients remained in follow-up until the writing of this report and their data were prospectively collected.

Entry criteria were proven peritoneal carcinomatosis of colorectal origin without distant metasta-
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ses, age 70 years or younger, fit to undergo major surgery and written informed consent. The study was open for both patients with synchronous and metachronic peritoneal carcinomatosis.

Time between first diagnosis of colorectal cancer and the diagnosis of peritoneal carcinomatosis, location of the primary tumor, malignancy grade, histological type, presentation with or without obstruction or perforation, type of initial surgery and extent of peritoneal carcinomatosis were recorded as pre-study data.

Systemic chemotherapy, often given in the referring hospital, was started as soon as possible after entering the study using the slightly modified Laufman regimen.\textsuperscript{16} This consisted of a one-hour intravenous infusion of leucovorin (80 mg/m\textsuperscript{2}) followed by an intravenous push dose of 5-fluorouracil (400 mg/m\textsuperscript{2}) in a weekly schedule for 26 weeks or till progression or intolerable toxicity. Patients who had been treated with 5-fluorouracil within 12 months prior to entering the protocol were treated with irinotecan, 350 mg/m\textsuperscript{2} for nine cycles.\textsuperscript{31}

Data on type of chemotherapy, number of courses and reasons for stopping were registered. Any second-line therapy was allowed after progression of the disease. This could include both surgical procedures to overcome obstruction or other cancer related problems and second-line or third-line chemotherapy. Follow-up consisted of medical history and physical examination with CEA and CA19.9 measurements every three months. Every six months, a CT of the abdomen and a chest X-ray were made. Progressive disease was defined as 25\% growth of CT- or palpable findings, appearance of new lesions or rise of tumor markers above normal values.

Time to progression and overall survival were taken from the moment of entering. The number of hospital admissions and the number of operations during follow-up were also registered.

Parameters were tested for a possible effect on survival by using the Log rank test, in which \(P<0.05\) was considered to be significant.

<table>
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<th>Synchronous</th>
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Table 1. Peritoneal carcinomatosis of colorectal cancer by location of origin in 50 patients
Table 2. Extent of peritoneal carcinomatosis of colorectal origin in 50 patients (largest distance from primary tumor)

<table>
<thead>
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<td>Sub-hepatic space</td>
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Table 3. Operations performed in 50 patients with peritoneal carcinomatosis of colorectal origin

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</tr>
<tr>
<td>Radical resection</td>
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</table>

Figure 1. Kaplan Meier curves for survival and progression-free survival in 50 patients affected by peritoneal carcinomatosis of colorectal origin
Chapter 5

Results

Twenty-eight of the 50 patients had peritoneal carcinomatosis synchronous with the colorectal cancer and in 22 patients this was metachronic. The median time between the primary carcinoma and the carcinomatosis was 36 months (range 15-107 months) for patients with metachronic disease. The location of the original colorectal tumor is shown in Table 1. In two female patients the location of the primary tumor was not clear. They had an immuno-histological marker pattern consistent with colorectal cancer and were classified accordingly.

Of the 28 synchronous patients, three (11%) presented with tumor perforation and eighteen (63%) with bowel obstruction. Four of the 22 patients (17%) with metachronic carcinomatosis had previous a perforation and four (17%) had an obstruction.

The diagnosis of peritoneal carcinomatosis was made during laparotomy in all patients. In 27 patients (54%), it was found during surgery for an abdominal emergency, mostly obstruction. In 20

| Table 4. Median survival after recurrence of colorectal peritoneal carcinomatosis in 50 patients |
|---------------------------------|-----------------|-----------------|------------------|
|                                | Number of patients | Median survival (SE) | P value¹ |
| All                            | 50               | 12.8 (2.6)        |       |
| Gender                         |                  |                  | 0.05   |
|                               | female           | 25               | 17.7 (1.2) |
|                               | male             | 25               | 10.1 (1.7)  |
| Presentation                   |                  |                  | 0.85   |
|                               | synchronous      | 28               | 12.8 (1.9) |
|                               | metachronic      | 22               | 12.6 (2.3) |
| Location primary tumor         |                  |                  | <0.01  |
|                               | appendix         | 7                | 21.7 (0.8) |
|                               | colon            | 36               | 12.8 (1.9) |
|                               | rectum           | 5                | 16.3 (2.1) |
|                               | ns               | 2                | 0.8     |
| Malignancy grade               |                  |                  | 0.09   |
|                               | good / moderate  | 24               | 16.3 (1.5) |
|                               | poor             | 13               | 9.7 (1.2)  |
| Site of PC                     |                  |                  | 0.25   |
|                               | local            | 20               | 14.2 (0.5) |
|                               | ovarian          | 10               | 17.6 (2.9) |
|                               | extensive        | 20               | 10.1 (0.8) |
| Resection                      |                  |                  | <0.01  |
|                               | no               | 21               | 8.3 (0.2)  |
|                               | palliative       | 22               | 17.7 (2.1) |
|                               | radical          | 7                | 16.3 (1.1) |

¹ Log rank test, ns: not specified, PC: peritoneal carcinomatosis

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patients (40%), peritoneal carcinomatosis occurred near the location of the primary colorectal tumor. The extent of the tumor spread is listed in table 2. Table 3 describes the surgical procedures performed at the laparotomy during which the carcinomatosis was found. Because most of these procedures were undertaken in the referring hospital, the reason why a particular procedure was performed could not always be ascertained.

Four of the 50 patients (8%) never started the chemotherapy they were scheduled to receive. One refused systemic treatment after entering the study and two deteriorated rapidly and died of progressive disease. In the remaining patient, the reason why systemic chemotherapy was not given remained unknown.

Twenty-five patients (50%) completed the full 26-week schedule. Fifteen patients (33%) had progression during the 26 weeks and, consequently, the treatment was stopped. In three patients (6%) the treatment was stopped because of toxicity and three other patients refused further treatment as they found the impact on their quality of life unacceptable.

The median follow-up was 43 months (range 21-64 months) and was completed in all patients until June 2003. Forty-six patients had progression of disease within the follow-up period. Progression was located only intraperitoneally in 38 patients, in the liver in four patients and both intraperitoneally and hepatic or distant in four patients. The median time to progression was 7.6 months (SE 0.7).

Twelve patients were still alive at the last follow-up update. The median survival time was 12.8 months (SE 2.6). Figure 1 shows overall and progression-free survival. The two patients with carcinomatosis of unknown colorectal location had a poor survival (0.3 and 2.5 months). Table 4 shows the impact of patient-, tumor- and treatment-related factors on survival. In patients in whom it was possible to perform either a radical or a palliative resection, the median survival was 16.3 months (SE 1.1) and 17.7 months (SE 2.1) respectively. The median survival of the four patients who did not start systemic chemotherapy was 0.8 months (SE 0.1). In patients who did receive chemotherapy survival was 14.8 months (SE 1.9) and 8.3 months (SE 0.9) for 5-fluorouracil / leucovorin and irinotecan respectively.

The majority of the patients developed serious medical problems during follow-up. The average number of hospital admissions was 1.4 (range 0-7). They spent on average 15.2 days in the hospital, up to 93 days. One out of every two patients had to undergo further surgery, usually because of recurrent bowel obstruction.

**Discussion**

This study shows a longer survival of patients with peritoneal carcinomatosis of colorectal origin after conventional surgery and systemic chemotherapy than is reported by other investigators, but the median survival is still limited to 12.6 months. The observed difference is probably due to a positive selection of patients entering this study, e.g. no distant metastases, fit to undergo major surgery and potential resectable disease.
Sadeghi et al showed a lower overall survival of only 5.2 months.\textsuperscript{11} In their study, patients with less extensive regional disease and without distant metastases were not distinguished and these patients in particular are subjected to the new therapeutic strategies.\textsuperscript{18,19} Therefore, a comparison between phase II studies of the novel therapeutic strategies and the Sadeghi study is inappropriate.

The present study shows interesting basic characteristics of peritoneal carcinomatosis. It confirms the earlier observation that peritoneal carcinomatosis originates more often in appendiceal cancer and right-sided colon cancer compared to left colon cancer and rectal cancer.\textsuperscript{20,21} A substantial number of patients presented with either tumor perforation or bowel obstruction initially, suggesting that these events can stimulate the spread of tumor cells to the peritoneal surface.

Survival time in this study varies widely and appears to be related to multiple factors. A poor differentiation grade of the primary tumor results in a shorter survival. Ovarian metastases have a relatively good prognosis, while extensive involvement of the bowel mesentery translates to a short survival. These differences are not significant, probably due to the small numbers. Female patients have a better survival. This may be related to the observed relatively good prognosis of ovarian metastases.\textsuperscript{22} Patients who underwent resection of the involved lesions fared significantly better than those who had a by-pass procedure only or were just opened and closed. Marcus et al did similar observations.\textsuperscript{12} It is difficult to determine the value of this observation into clinical practice. We are not informed about the reasons why in some patients a choice for resection was made, while in others a bypass was performed. Clearly this decision was partly dictated by the extent of tumor involvement. Limited peritoneal seeding adjacent to the colorectal tumor or ovarian metastases will tempt most surgeons to resect. Patients with extensive mesenteric involvement, on the other hand, will almost always have an explorative laparotomy only. Preferences of the surgeon may also play a role. The accuracy of the operative notes describing the situation found at laparotomy often leaves much to be desired. Comparing operative notes of previous laparotomies with the observations during a second laparotomy showed unexplained discrepancies. For this reason, a multivariate analysis including these factors was not performed. The survival benefit of resection of all macroscopic tumors suggests that this is the best option, even in regionally disseminated disease.

The impact of systemic chemotherapy is difficult to determine. Imaging response to chemotherapy by CT or ultrasonography is often unreliable in peritoneal carcinomatosis, leaving serum markers (CEA and CA 19.9) as tool for response measurement,\textsuperscript{23} a clinical situation not different from management of stage III ovarian cancer. The value of this latter tool is also limited as only 60% of patients with metastatic colorectal cancer have increased serum marker levels.

The time to progression in this series is barely seven months. The abdomen remains in the vast majority of patients the main site of tumor activity. In most patients, this leads to recurrent bowel obstruction and half of all patients underwent an additional laparotomy to overcome this problem. It is clear that peritoneal carcinomatosis patients lay a major claim on health care resources.

In conclusion, this study confirms the poor outcome of patients with peritoneal carcinomatosis of colorectal origin treated with conventional surgery and systemic chemotherapy. The response of peritoneal carcinomatosis to systemic chemotherapy seems to be limited. At present no data are available on newer schedules such as oxaliplatin - 5-fluorouracil - leucovorin or irinotecan - 5-
fluorouracil - leucovorin. In selected patients with this grave disease cytoreduction combined with hyperthermic intraperitoneal chemotherapy is a promising treatment option.15

References

Chapter 5


