Cytoreduction and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis of colorectal origin

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Chapter seven

Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment and outcome

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Background: After treatment of peritoneal carcinomatosis of colorectal origin by cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC), recurrences develop in approximately 80\% of patients. This study evaluates the outcome of such recurrences after initial treatment by cytoreduction and HIPEC.

Methods: Between November 1995 and May 2003, 106 patients underwent cytoreduction and HIPEC. The progression-free interval, the location of the recurrence, and its treatment were recorded. Factors potentially related to survival after recurrences were studied.

Results: Sixty-nine patients had a recurrence within the study period. For patients who had undergone a gross incomplete initial cytoreduction, the median duration of survival after recurrence was 3.7 months (SE 0.3). If a complete cytoreduction had been accomplished initially, the median duration of survival after the recurrence was 11.1 months (SE 0.9). A shorter interval between HIPEC and recurrence was associated with shorter survival after treatment of recurrence (Hazard ratio 0.94; SE 0.02). After effective initial treatment, a second surgical debulking for recurrent disease resulted in a median survival duration of 10.3 months (SE 1.9), and after treatment with chemotherapy it was 8.5 months (SE 1.6). The survival was 11.2 months (SE 0.5) for patients who received radiotherapy for recurrent disease. Patients who did not receive further treatment survived 1.9 months (SE 0.3).

Conclusions: Treatment of recurrence after cytoreduction and HIPEC is often feasible and seems worthwhile in selected patients. Selection should be based mainly on the completeness of initial cytoreduction and the interval between HIPEC and recurrence.

Recurrence

Introduction

Peritoneal carcinomatosis is a manifestation of colorectal cancer in which intraperitoneal seeding of tumor cells occurs. After implantation on the peritoneal surfaces, the malignant cells may form tumor nodules throughout the abdominal cavity, which can cause bowel obstructions. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a novel treatment for this disease. In recent years, several phase II studies and one phase III study have shown that this therapy improves survival to a median of two years and that up to 20% of patients live longer than five years and are probably cured.\(^{1-6}\) A common feature of all these studies is that the outcome was determined mainly by the completeness of the cytoreduction.\(^{7-9}\) After a macroscopically complete debulking, patients have a reasonable chance of surviving.

Recurrent disease after cytoreduction and HIPEC develops in approximately 80% of patients. These recurrences can occur within the abdomen as well as at distant sites. A local recurrence is likely to cause bowel obstruction, which needs surgical treatment. Radiotherapy may be indicated if the local recurrence cannot be removed surgically with free margins. Systemic chemotherapy is the treatment of choice for patients who have distant metastases. Systemic therapy is also given in cases of multiple intra-abdominal recurrences.

Although the above-mentioned general guidelines are common policy,\(^{10,11}\) there is no good documentation on the effects of third-line treatment of recurrent peritoneal carcinomatosis after cytoreduction followed by HIPEC. Most patients have a strong desire to be treated for recurrence. Patients who survive the “HIPEC struggle” tend to agree to any possible means of increase their life span, no matter what the associated morbidity and mortality might be.

The objectives of the study were to determine the patterns of recurrence and the survival after third-line and even fourth-line treatment of patients with peritoneal carcinomatosis of colorectal origin managed by cytoreduction and HIPEC.

Patients and methods

Between November 1995 and May 2003, 106 patients were treated for peritoneal carcinomatosis of colorectal origin at The Netherlands Cancer Institute. The first 35 patients were enrolled in phase I and II studies. The next 49 patients were enrolled in a randomized phase III study, and the remaining 22 patients were treated afterward. The protocols were approved by the local ethics committee. The protocols were open for patients with proven peritoneal metastases of colorectal origin or cytologically positive ascites. Patients with radiological evidence of distant metastases were excluded. Patients had to be younger than 71 years and fit to undergo major surgery (with normal bone marrow indices and normal renal and liver function). All patients were treated in accordance to the phase III study protocol,\(^5\) and their data were prospectively collected.

The treatment is described in detail elsewhere.\(^12\) In brief, it consisted of two elements: aggressive surgical cytoreduction and HIPEC. Mitomycin C was used as intraperitoneal chemotherapy at a temperature of 40°C to 41°C for 90 minutes.
During laparotomy, we collected data on the tumor distribution. Before cytoreduction, we recorded the presence of macroscopic tumor deposits 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. After 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; if it was larger than 2.5 mm, the cytoreductive surgery was scored as R-2b.

After discharge and recovery, 5-fluorouracil/leucovorin was given as adjuvant therapy in a weekly, slightly modified Laufman regimen for 26 weeks\(^\text{13}\). Irinotecan was used in 3-week intervals if 5-fluorouracil/leucovorin had been given within one year before the HIPEC treatment.

The protocol required patients to visit the outpatient clinic every three months for two years and at 6-month intervals thereafter. The follow-up visit included a recording of history, physical examination, and determination of serum CEA and CA 19.9 values, with the addition of computed tomography (CT) scanning of the abdomen every other visit. If symptoms arose, CT-scan or endoscopy was performed as required to determine their cause. Positron emission tomography (PET) was performed in cases involving a tumor marker rise or inconclusive CT-scan findings.

A local recurrence was defined as any new lesion revealed by physical examination or CT in comparison with the first examination findings after the HIPEC procedure. When a lesion was found on endoscopy, a recurrence was diagnosed only if histological proof was obtained. If a tumor marker value doubled, attempts were made to confirm the presence of a recurrence. If the tumor marker value kept rising, the patient was considered to have recurrent disease even if this could not be demonstrated with an extensive search. Systemic metastases were defined as any lesion evident on a CT-scan or chest radiograph that was not seen at a previous examination. The location of a recurrence was classified in one of five groups: intra-abdominal, liver, lung, both systemic and intra-abdominal and unknown.

Recurrences were treated according to the following general guidelines. Surgical treatment was always considered as the first option. Surgery with curative intent was performed in cases involving one intra-abdominal lesion if this lesion could be removed with a free margin. After operative treatment, patients did not receive systemic chemotherapy as adjuvant therapy. In cases involving predictably questionable margins, radiotherapy with curative intent was given. The radiation schedule was determined on the basis of the patient’s general condition and the extent of the recurrence. In the patient’s condition was reasonably good and the tumor was of limited size, a total of 39 Gy was given in 13 fractions. If resection or radiotherapy could not possibly be curative for all recurred lesions, systemic chemotherapy was given. Typically, patients who underwent systemic chemotherapy had multiple intra-abdominal locations of metastasis. Second- or third-line chemotherapy was also offered for distant metastases, with or without local recurrence.

When an abdominal emergency occurred, mostly due to bowel obstruction, the first objective was to restore bowel function conservatively. Laparotomy was performed if this approach failed. The aims were then to relieve the obstruction and to make a second attempt to debulk. No second hyperthermic intraperitoneal chemotherapy procedures were done.
The patients were grouped in the original category of completeness of cytoreduction after the HIPEC procedure: no macroscopic residual tumor (R-1), minimal residual disease (maximum thickness of 2.5 mm, R-2a), or gross residual disease (R-2b).

The Kaplan-Meier method was used to determine overall survival, progression-free interval, and survival after recurrence. The progression-free interval was calculated from the moment of the HIPEC procedure to the date of proven recurrence. Survival after recurrence was determined from the date this recurrence was diagnosed.

The log rank test was used for univariate analysis and the Cox proportional hazard method was used for multivariate analysis.

**Results**

Cytoreduction as initial treatment for peritoneal carcinomatosis was macroscopically complete (R-1) in 54 patients (51%), nearly complete (R-2a) in 37 patients (35%), and grossly incomplete (R-2b) in 15 patients (14%). Tumor characteristics of the primary colorectal cancer and the extent of the peritoneal carcinomatosis are given in table 1. After a median follow-up of 47.5 months (range 1.3 to 88.3 months), 69 of the 106 patients had had a recurrence. The time to recurrence was related mainly to the completeness of the cytoreduction in the initial treatment for carcinomatosis (table 2).

Most of the recurrences after an R-1 or R-2a resection occurred in the abdominal cavity. Distant metastases as first recurrences were predominantly located in the liver (table 3). In one patient the tumor marker value rose but the location of the recurrence was unknown. The time to liver metastases and recurrence at unknown locations was shorter than for other sites.

Patients who had undergone R-1 and R-2a resections had a median survival of 11.1 months (SE 0.9) and 5.9 months (SE 0.8) after recurrence, respectively. When there was gross residual tumor (R-2b resection) at the initial cytoreduction site, median survival was a mere 3.7 months (SE 0.3). A shorter interval between the initial treatment of carcinomatosis and recurrence was related to shorter survival after recurrence (Hazard ratio 0.94; 95% confidence interval [CI] 0.91–0.98). Signet cell carcinoma and older age were also significant risk factors for a shorter survival (Hazard ratios, 3.5 and 1.0; SE’s 1.6 and 0.02, respectively). Gender, location of the primary tumor, synchronous or metachronic carcinomatosis, and malignancy grade had no prognostic value.

Twelve patients did not receive any treatment for their recurrence, mostly because of a poor performance state. They survived for a median period of 1.9 months (SE 0.3). Twenty-eight patients underwent surgery, which for six patients consisted of an explorative laparotomy only. Twenty patients received systemic chemotherapy, and nine patients, radiotherapy. Only six of 11 patients with an initial R-2b resection underwent further treatment.

Fifty-eight patients who had an effective initial cytoreduction (R-1 and R-2a) were further analyzed. Seven of them received no treatment at all, whereas five patients underwent an explorative laparotomy only. Among six patients who underwent bypass surgery for recurrence, the median
Table 1. Characteristics of 106 patients with peritoneal carcinomatosis treated by cytoreduction and HIPEC divided by results of initial cytoreduction

<table>
<thead>
<tr>
<th></th>
<th>R-1</th>
<th>R-2a</th>
<th>R-2b</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>54</td>
<td>37</td>
<td>15</td>
<td>106</td>
</tr>
<tr>
<td>Median age</td>
<td>55.5</td>
<td>52.0</td>
<td>48.0</td>
<td>53.4</td>
</tr>
<tr>
<td>Female / Male</td>
<td>24 / 30</td>
<td>17 / 20</td>
<td>5 / 10</td>
<td>46 / 60</td>
</tr>
<tr>
<td>Location CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Colon</td>
<td>44</td>
<td>29</td>
<td>9</td>
<td>82</td>
</tr>
<tr>
<td>Rectum</td>
<td>3</td>
<td>-</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>NS</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Differentiation CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Moderate</td>
<td>30</td>
<td>24</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>Poor</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Histology^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>41</td>
<td>25</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>Mucinous cancer</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Signet cell cancer</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Number regions PC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 5</td>
<td>51</td>
<td>24</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>6 – 7</td>
<td>3</td>
<td>13</td>
<td>10</td>
<td>26</td>
</tr>
</tbody>
</table>

R-1: no residual tumor, R-2a: residual tumor ≤ 2.5 mm, R-2b: residual tumor > 2.5 mm
CRC: colorectal cancer, NS: not specified, PC: peritoneal carcinomatosis
^data of 6 patients missing, ^data of 2 patients missing

Table 2. Time to recurrence in 69 patients with recurrence after cytoreduction and HIPEC by initial cytoreduction result

<table>
<thead>
<tr>
<th></th>
<th>Number of patients at risk</th>
<th>Number of recurrences</th>
<th>Median time to recurrence (months)</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-1</td>
<td>54</td>
<td>25</td>
<td>13.7</td>
<td>1.0</td>
</tr>
<tr>
<td>R-2a</td>
<td>37</td>
<td>33</td>
<td>10.8</td>
<td>1.7</td>
</tr>
<tr>
<td>R-2b</td>
<td>15</td>
<td>11</td>
<td>4.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

R-1: no residual tumor, R-2a: residual tumor ≤ 2.5 mm, R-2b: residual tumor > 2.5 mm
Recurrence

The median survival of the 15 patients who underwent a second surgical debulking was 10.3 months (SE 1.9). The 16 patients who received systemic chemotherapy for recurrence survived a median of 8.5 months (SE 1.6). Most of those patients were treated with irinotecan; three patients one patient received radiotherapy for a metastasis in an abdominal wound. Five patients received radiotherapy for which the intent was a long-term palliative effect, and their survival was 11.2 months (SE 0.5). Survival was 8.7 months (SE 1.1) among the four patients who underwent short-term palliative radiotherapy.

### Table 3. Location of recurrences after treatment by cytoreduction and HIPEC

<table>
<thead>
<tr>
<th>Initial cytoreduction</th>
<th>R-1 N= 54</th>
<th>R-2a n = 37</th>
<th>Disease-free interval (SE) (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal</td>
<td>13</td>
<td>26</td>
<td>12.7 (1.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>8</td>
<td>2</td>
<td>9.0 (0.6)</td>
</tr>
<tr>
<td>Lung</td>
<td>-</td>
<td>1</td>
<td>14.7</td>
</tr>
<tr>
<td>Intra-abdominal and</td>
<td>3</td>
<td>4</td>
<td>13.7 (1.1)</td>
</tr>
<tr>
<td>systemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown location</td>
<td>1</td>
<td>-</td>
<td>3.9</td>
</tr>
<tr>
<td>All</td>
<td>25</td>
<td>33</td>
<td>12.3 (2.1)</td>
</tr>
</tbody>
</table>

R-1: no residual tumor, R-2a: max residual tumor 2.5 mm

### Discussion

There is growing evidence that patients affected by peritoneal carcinomatosis of colorectal origin benefit from cytoreduction and some form of intraperitoneal chemotherapy. Although this treatment may improve survival, the majority of patients will have recurrent disease within the first three years. These recurrences most often occur intra-abdominally, even if the abdomen is assumed to be free of tumor nodules after the initial cytoreduction and HIPEC (R-1 and R-2a). This contrasts with the natural history of colon cancer; in one-half of patients with colon cancer, the first site of recurrence is the liver. The pattern corresponds more to findings in rectal cancer, where local recurrence occurs more often.

The tendency for intra-abdominal recurrences instead of hematogenic metastases can be explained in two ways: either a biological mechanism makes cancer cells more adherent to the peritoneum and encourages local seeding rather than hematogenic spread or else intraabdominal recurrence occurs long before systemic metastases develop. The latter argument is unlikely because the median time for the development of liver metastases in this study was less than for intra-abdominal
recurrences.

The survival time after recurrence in our series depended on the interval between the initial treatment of carcinomatosis and the appearance of recurrent disease. This kind of relationship is also seen in other forms of recurrence in colon cancer. Goldberg et al.\textsuperscript{18} concluded that the treatment of a recurrence within the first year after the initial treatment for colon cancer resulted in a limited 5-year survival rate, in contrast with recurrences treated after three years. It seems likely that this reflects slow growth characteristics of the tumor involved. This feature of the tumor determines the odds of survival after second-line and third-line treatment.

Patients in whom initial treatment of peritoneal carcinomatosis failed (R-2b resections) not only had early progression of disease but often failed third-line treatment as well. This seems logical, because a less aggressive treatment is unlikely to benefit these patients when a more aggressive treatment, e.g., cytoreduction followed by HIPEC, fails to cure the initial carcinomatosis. These patients should therefore be spared the morbidity risk of a third-line treatment.

There have been only a few reports on the results of treatment of recurrence after cytoreduction and HIPEC. Portilla et al.\textsuperscript{8} noted long-term survival after cytoreduction was repeated. The value of these third-line treatments, however, is difficult to assess in terms of morbidity and mortality.

In the presented analysis patients were treated with one of the three treatment options. The analysis shows that systemic chemotherapy has its value as a single-treatment modality. This suggests that systemic chemotherapy should be considered in addition to a secondary cytoreduction, because this procedure will probably leave macroscopic or microscopic disease behind.

The current evaluation of various treatments for recurrences pertains to a subgroup analysis and gives only level III evidence. From these data it is not possible to determine which treatment modality is optimal, because surgery, chemotherapy, and radiotherapy were given for different volumes of recurrent disease. A randomized trial on third-line treatments in this patient group is not feasible because patterns of recurrent disease vary and the number of patients is limited.

In conclusion, most recurrences after cytoreduction and HIPEC are intra-abdominal. The median survival of patients who underwent effective treatment of their initial peritoneal carcinomatosis was approximately one year. Treatment of recurrence of peritoneal carcinomatosis of colorectal origin is feasible and seems worthwhile for selected patients. Selection should be based mainly on the success of cytoreduction and HIPEC and on a long interval between this treatment and the occurrence of recurrent disease. In addition, younger age and the absence of pathologic signet cells favor outcome.

References


