Cytoreduction and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis of colorectal origin
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Chapter nine

Long-term survival of patients with peritoneal carcinomatosis of colorectal origin

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Introduction: Peritoneal carcinomatosis of colorectal cancer is probably best treated by cytoreduction and hyperthermic intraperitoneal chemotherapy. In The Netherlands Cancer Institute this treatment is performed since 1995. The long tradition of this treatment enabled us to study long-term survival in detail.

Patients and method: Between 1995 and 2003 117 patients affected by peritoneal carcinomatosis of colorectal origin were treated by cytoreduction combined with hyperthermic intraperitoneal chemotherapy. The aim of the cytoreduction was to remove all visible tumor. Mitomycin C (35 mg/m²) was given intraperitoneally at a temperature of 40 to 41 °C during 90 minutes. Overall survival was calculated by the Kaplan Meier method. Survival was also analyzed for the following subgroups: patients with no residual tumor, with residual tumor ≤ 2.5 mm and with residual tumor > 2.5 mm. Hazard ratios for each of the 7 abdominal regions were calculated to determine the influence on survival.

Results: The median survival of peritoneal carcinomatosis of colorectal cancer once treated by cytoreduction and hyperthermic intraperitoneal chemotherapy was 21.8 months. The 1-year, 3-year and 5-year survival rate were 75%, 28%, 19% respectively. The Kaplan Meier curve shows a consistent survival rate after 54 months of 18%. In 59 patients a complete cytoreduction was achieved, and in 41 patients there was minimal residual disease. The median survival of these patients groups was 42.9 and 17.4 months respectively. When gross macroscopic tumor was left behind, which was the case in 17 patients, the median survival was five months. Involvement of the small bowel prior to the cytoreduction was associated with poorer outcome.

Conclusion: Cytoreduction followed by intraperitoneal chemotherapy showed a median survival of 21 months. From three year on a consistent group of 18% stays alive.

Submitted
Long-term survival

Introduction

Peritoneal carcinomatosis is a manifestation of colorectal cancer in which tumor cells float through the abdominal cavity and reseed in peritoneal surface. After implantation on the peritoneal surfaces, the malignant cells may form tumor nodules throughout the abdominal cavity. Peritoneal carcinomatosis is present in approximately 10% of patients with colorectal cancer at the time of first diagnosis and in approximately 25% of patients with recurrent disease. Although peritoneal carcinomatosis is frequently found in combination with distant metastases, it appears to be the only site of disease in about 25% - 35% of the patients, even after an extensive diagnostic work-up.

The treatment of peritoneal carcinomatosis of colorectal origin is shifting from a nihilistic approach to a very active management. Cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is the most pro-active way of dealing with peritoneal carcinomatosis. This treatment has been established by a number of phase II studies and even a phase III study. In the phase III study a significant better survival was found when this treatment is compared to palliative surgery and systemic chemotherapy.

This potential improvement in survival has to be balanced against the side effects of this intensive treatment. A number of studies report complication rates as high as 30%. Although most complications are surgery related, hyperthermic intraperitoneal chemotherapy probably increases the impact of the complications.

The above-mentioned complication rates are only acceptable if a long-term survival can be expected. In The Netherlands Cancer Institute this treatment is performed since 1995. The long tradition of this treatment enables to study long-term survival.

Patients and methods

Between November 1995 and August 2003, 117 patients with peritoneal carcinomatosis of colorectal origin were treated with cytoreduction and HIPEC at The Netherlands Cancer Institute. Sixty-four patients were male and 53 women with a median age of 53 years. The first 36 patients were entered in phase I and II studies. The following 48 patients were entered in a randomized phase III study and the remaining 33 patients were treated after this study.

Patients with histologically proven peritoneal carcinomatosis of colorectal origin without evidence of liver or lung metastases, up to 70 years of age and fit to undergo major surgery were eligible for this therapy. Both synchronic and metachronic carcinomatosis was included. Written informed consent was required for patients who participated in the trials.

Treatment schedule

The entire treatment consisted of surgical cytoreduction plus intraperitoneal chemotherapy, followed by adjuvant systemic chemotherapy.

The objective of cytoreduction was to leave no macroscopic tumor behind. If this was not feasible, the aim was reframed to "no thicker than 2.5 mm", as this is the maximum penetration depth.
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at which a dose advantage of intraperitoneal Mitomycin C can be expected.

Maximum exposure was obtained by opening the abdominal cavity from xyphoid to pubis and dividing all adhesions. Resection of the peritoneum was carried out as described by Sugarbaker.\textsuperscript{16} Infiltrated viscera were (partly) resected. Restrictions were made on the extent of surgery as far as it was compatible with sufficient post-operative function.

The perfusion method used for the hyperthermic intraperitoneal chemotherapy is described in detail elsewhere by Witkamp et al\textsuperscript{17}. The inflow temperature of the perfusate was 41-42° C. As soon as this temperature was reached, Mitomycin C was added in three fractions with a 30-minute interval (\(\frac{1}{2}, \frac{1}{4}, \frac{1}{4}\) of the total dose respectively). For patients in the phase II study, the dose of Mitomycin C was increased step-wise from 25 mg/m\textsuperscript{2} to 40 mg/m\textsuperscript{2}. All other patients were treated with 35 mg/m\textsuperscript{2} Mitomycin C. After completion of 90 minutes perfusion, the fluid was drained from the abdomen.

The continuity of the gastro-intestinal tract was restored after finishing the perfusion. Single-layer hand-sutured anastomoses were used. A colostomy was routinely made in case of a rectum resection. A gastrostomy was used to allow the stomach to drain, and a trans-gastric jejunal feeding tube was placed for enteral nutrition.

Patients stayed in the intensive care unit until they were stable with respect to cardiac and pulmonary function. Close watch was kept for any sign of abdominal sepsis, which was an indication for relaparotomy at an early stage.

Systemic adjuvant chemotherapy was given for six months, using the modified Laufman regimen (5-Fluorouracil 400 mg/m\textsuperscript{2} and Leucovorin 80 mg/m\textsuperscript{2}, weekly).\textsuperscript{18} If patients had been treated with 5-Fluorouracil within a year prior to hyperthermic intraperitoneal chemotherapy, they were treated with Irinotecan (350 mg/m\textsuperscript{2}, three-weekly) instead of 5-Fluorouracil.\textsuperscript{19,20}

Grading tumor amount

The spread and thickness of tumor was measured in seven regions of the abdomen: pelvis, right lower abdomen, omentum / transverse colon, small bowel / mesentery, subhepatic space / stomach, right subphrenic space and left subphrenic space. For each region a semi-quantitative score was allocated by measuring maximum thickness of the largest nodules (none = 0; < 20 mm = 1; 20-50 mm = 2; >50 mm = 3). In case of confluent nodules the maximum thickness of the resulting plaque was used.

The result of cytoreduction was determined according to maximum thickness of tumor nodules left behind at any place in the abdomen. No residual macroscopic tumor was graded as an R-1 resection, residual macroscopic tumor ≤ 2.5 mm was recorded as R-2a resection and if more disease was left behind as R-2b resection.

Statistical analyses

Survival was measured from the date of cytoreduction and hyperthermic intraperitoneal chemotherapy until death or date of last follow-up in censored cases. The median survival as well as the one-, two-, three-, four- and five-years survival rates were determined for the entire patients population and for each cytoreduction category. The survival differences between categories were tested
using the log rank test. Potential prognostic factors were analyzed for their impact on survival by using the log rank test. The relation between affected region and survival was analyzed by using the Cox regression analysis.

Results

Data on 117 consecutive patients were analyzed with a median follow-up of 46 months. The distribution of the follow-up is shown in figure 1. The colorectal cancer was in ninety-five patients located in the colon. Thirty-three patients had a right-sided colon cancer, 15 patients had a left-sided colon cancer and in 47 patients the tumor was located in the sigmoid. In 15 patients the carcinomatosis was based on an appendix cancer and in five patients on rectal cancer. The location of the primary tumor was not known in two patients. Sixty-seven patients had synchronous carcinomatosis and 50 had carcinomatosis metachronic with the colorectal cancer.

The TNM classification of the primary tumor showed a T4 tumor in 61 patients and in 52 patients had a T3 tumor. In two patients the primary tumor was T2. In 24 patients the primary tumor was graded as N0, in 34 patients as N1 and in 12 patients as N2. In the remaining 47 patients the N-status could not be determined.

Table 1. Percentage of affection with peritoneal carcinomatosis per region before and after cytoreduction and percentage of clearance per region in 117 patients treated by cytoreduction plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis

<table>
<thead>
<tr>
<th>Percentage affected</th>
<th>Before</th>
<th>After</th>
<th>Percentage cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>90.6</td>
<td>15.4</td>
<td>83.0</td>
</tr>
<tr>
<td>Ileocecal</td>
<td>67.5</td>
<td>6.0</td>
<td>91.1</td>
</tr>
<tr>
<td>Omentum / transverse colon</td>
<td>83.8</td>
<td>12.0</td>
<td>85.7</td>
</tr>
<tr>
<td>Small bowel / mesentery</td>
<td>78.6</td>
<td>40.2</td>
<td>48.9</td>
</tr>
<tr>
<td>Subhepatic space</td>
<td>34.2</td>
<td>19.7</td>
<td>42.5</td>
</tr>
<tr>
<td>Subphrenic space left</td>
<td>23.1</td>
<td>9.4</td>
<td>59.3</td>
</tr>
<tr>
<td>Subphrenic space right</td>
<td>34.2</td>
<td>18.0</td>
<td>47.5</td>
</tr>
</tbody>
</table>
Table 1 shows the percentage in which a region is affected before and after the cytoreduction. The pelvis and the omentum were affected in almost all patients. The ileocecal region was cleared in most patients. If tumor deposits had to be left behind, this was in the subhepatic space, on the mesentery of the small bowel and in the right subphrenic space.

A large number of organs were resected. Omentum and ovaries were resected in female patients. The rectum was resected in 51.3% of the patients, parts of the colon were resected in 41% patients and ileocecal resections were done in 58% of the patients. Forty-eight percent of the patients needed a colostomy. In the upper abdomen, partial stomach resections were performed in 10% of the patients and 56% needed one or more small bowel resections. A splenectomy was performed in 9% patients.

The cytoreductions were in 59 patients macroscopically complete (R-1), in 44 patients there was minimal residual tumor left behind (R-2a) and in 14 patients there was gross macroscopic tumor left behind (R-2b).

Of the 117 treated patients, seven (6%) died of treatment related causes. Three of these patients had gross incomplete resections (R-2b), the other four had minimal residual disease.

The median survival of the entire study population was 21.8 months (CI 19.0 – 25.5). The one-year, three-year and five-year survival probability was 0.75 (CI 0.65 – 0.82), 0.28 (CI 0.18 – 0.38) and 0.19 (CI 0.10 – 0.29) respectively.

Figure 2. Kaplan Meier curve by result of cytoreduction of 117 treated for peritoneal carcinomatosis of colorectal origin by cytoreduction plus hyperthermic intraperitoneal chemotherapy
Patients in whom six or all seven regions were affected had a median survival time of only 11.2 months (CI 5.0 – 20.8), while this was 25.5 months (CI 19.7 – 33.4) when less regions were affected.

The survival was also strongly correlated with the degree of completeness of the cytoreduction (figure 2). In patients in whom the cytoreduction was macroscopically complete the median survival was 42.9 months (CI 22.8 – not reached). In this group the one-year, three-year and five-year survival probability was 0.94 (CI 0.83 – 0.98), 0.56 (CI 0.38 – 0.71) and 0.43 (CI 0.25 – 0.60) respectively. When there was residual tumor left behind, which was not thicker than 2.5 mm the median survival was 17.4 months (CI 12.0 – 20.8). The one-year and three-year survival was 0.66

<table>
<thead>
<tr>
<th>Table 2. Hazard ratios for survival per affected region in 117 patients treated by complete cytoreduction plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
</tr>
<tr>
<td>Pelvis</td>
</tr>
<tr>
<td>Ileocecal</td>
</tr>
<tr>
<td>Omentum / transverse colon</td>
</tr>
<tr>
<td>Small bowel / mesentery</td>
</tr>
<tr>
<td>Subhepatic space</td>
</tr>
<tr>
<td>Subphrenic space left</td>
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<tr>
<td>Subphrenic space right</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Hazard ratios for survival per region with residual tumor in 117 patients after treatment by cytoreduction plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis</th>
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</thead>
<tbody>
<tr>
<td>Region</td>
</tr>
<tr>
<td>Pelvis</td>
</tr>
<tr>
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<td>Subphrenic space right</td>
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</table>
(CI 0.49 – 0.79) and 0.09 (CI 0.02 – 0.20). Only one patient survived more than five years. One patient, who had a gross incomplete cytoreduction survived three years. The median survival was only 5.0 months (CI 2.7 – 9.5) in patients in whom the cytoreduction gross was incomplete.

In patients in whom a complete cytoreduction was reached involvement of the small bowel prior to the cytoreduction was related to decreased survival. Hazard ratios per region of patients with complete cytoreduction are shown in table 2. On the other hand, if tumor was left behind in the abdomen, no specific region dominates the effect on survival. Table 3 provides the hazard ratios for regions with residual disease.

Discussion

In the past decade, a number of groups have reported on results of cytoreduction with some form of intraperitoneal chemotherapy. The Sugarbaker-group has been the most productive. They published a paper on 385 patients affected by appendiceal malignancies showing a five-year survival rate of 30% in 1999. In a similar study Loggie et al made a clear distinction between patients who had a complete cytoreduction and patients who had an incomplete cytoreduction. Patients with a complete cytoreduction had a median survival of 28 months and those who had an incomplete cytoreduction survived median 10 months. A comparable result was found by Shen et al, showing an improved survival after complete cytoreduction. The three-year survival rate in their study was 68% for those who underwent a complete cytoreduction versus 21% for the others. In Europe, Piso et al found a remarkable four-year survival rate of 75%. Even in incomplete cytoreduced patients the four-year survival rate was 40%, whereas after complete cytoreduction this was 90%. Elias and co-workers concluded from their experience in Paris that a 50% two-year survival could be reached and the group of Beaujard in Lyon found a median survival of 16 months in patients who underwent a successful cytoreduction. The Roman study of Cavaliere et al showed a two-year survival of 61%. At The Netherlands Cancer Institute a median survival of 22 months was found in a randomized trial comparing cytoreduction plus hyperthermic intraperitoneal chemotherapy followed by systemic adjuvant chemotherapy to palliative surgery and systemic chemotherapy. In the presented study a median survival of 42.9 months and a five-year survival rate of 43% was found in patients in whom a complete cytoreduction could be reached.

Selecting patients for cytoreduction and hyperthermic intraperitoneal chemotherapy is difficult. In prospective to survival and to complication rates, it is obvious that the key issue is to select patients in whom it is feasible to reach a complete cytoreduction. The best information to select these patients is gathered during the laparotomy in which the diagnosis peritoneal carcinomatosis is made. It is therefore, of utmost importance that the operative notes provide full details of the procedure during which the carcinomatosis is found. This means that a description of the findings should be accompanied by an explanation of the attempts made to reach every part of the abdomen. A standardized form on which operative findings can be reported would be of help. An example of such a form is displayed in figure 3.

Cytoreduction plus hyperthermic intraperitoneal chemotherapy is combined treatment modality.
Although surgical groups conduct most studies, the studies provide full data on the hyperthermic intraperitoneal chemotherapy itself, while data on the surgery done to reach the cytoreduction is often poorly presented. In the current study, the extent of surgery is given. Unfortunately, we did not record the extent of the peritoneal stripping. Our data indicate that small bowel and its mesentery is the limiting factor for survival. Once it has been affected and cleared from tumor, it still remains the region, which indicates poor outcome.

It is obvious that the large number of resected organs does not only result in high complication rates, but will also have impact on the remaining function. McQuellon et al studied quality of life after cytoreduction plus hyperthermic intraperitoneal chemotherapy.\textsuperscript{25,26} They found, however, no long lasting impairment of the quality of life after cytoreduction plus hyperthermic intraperitoneal chemotherapy. This probably means that the remaining abdominal function is adequate for a

Figure 3. Registration form

<table>
<thead>
<tr>
<th>Number affected regions:</th>
<th>No tumor</th>
<th>&lt; 2 cm</th>
<th>2 – 5 cm</th>
<th>&gt; 5 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pelvis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Ileo-colic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Omentum / Transverse colon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Small bowel / Mesentery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Subhepatic / Subgastric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Subphrenic left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Subphrenic right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Procedures done: Exploration only / Bypass / Ostomy / Debulking [ complete / incomplete ]

Resections:
- Stomach
- Small bowel
- Ileo-colic
- Large bowel
- Rectum
- Peritoneum
- Ovaries
- Uterus

Remarks:..............................................................................
“normal” well-being.

The question remains which part of the combination treatment “cytoreduction plus hyperthermic intraperitoneal chemotherapy” is effective. From the presented analysis it is clear that a macroscopic complete resection (R-1) is a basic necessity for good outcome. Nevertheless, this does not exclude that hyperthermic intraperitoneal chemotherapy is the condition making an R-1 resection worthwhile. A randomized study in which one arm consists of cytoreduction and the other arm of cytoreduction and hyperthermic intraperitoneal chemotherapy would answer the question if an element of the treatment can be left out.

References


