Cytoreduction and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis of colorectal origin

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Chapter ten

General discussion and further analysis
In the past decade, a number of groups have reported on results of cytoreduction with some form of intraperitoneal chemotherapy. Most reports showed results similar to those found in this thesis.

In the USA, the Sugarbaker-group has been the most productive. They published a paper on 385 patients affected by appendiceal malignancies in 1999. They found a five-year survival rate of 30%. This report provides only data on patients affected by carcinomatosis of appendiceal origin, which is known to have a better prognosis than carcinomatosis of colorectal origin. Another important North American study was conducted by Loggie et al. They 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. The overall survival of the entire studied population was 14 months. This report was followed by a similar study conducted by Shen et al, showing an improved survival after complete cytoreduction. The three-year survival rate was 68% for those who underwent a complete cytoreduction versus 21% for the others.

The European counterparts produced also several series since 1997. In Germany, Piso et al found 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%. Despite these good results, they concluded that only patients with WHO 0 – 1 performance status and patients with minimal disease benefit from cytoreduction and hyperthermic intraperitoneal chemotherapy. The precise patient selection criteria are not stated in this paper. Elias and co-workers concluded from their experience in Paris that a 50% two-year survival could be reached. At the end of their report, they state that the efficacy of such an intense and toxic treatment definitely needs to be proven. The Lyon group of Beaujard found a median survival of 16 months in patients who underwent a successful cytoreduction. They reserve cytoreduction followed by intraperitoneal hyperthermic chemotherapy for stage I and II disease. Cavaliere et al found in the Roman study a two-year survival of 61%. They claim that the patients suitable for this treatment are those who do not respond to any other therapy. This contrasts with the stage I and II selection criterion of the French study.

With the increasing number of studies, the total population of patients enlarged over the recent years, but this did not result in a change of the level of evidence of its effectiveness. All these studies are subject to a selection bias. The studies give the results of patients in whom cytoreduction followed by intraperitoneal chemotherapy has proven to be feasible. From these reports, it can be concluded that the ideal patient would be someone with minimal disease, or at least someone in whom the disease is easily resectable.

The analyses in this thesis show that patients affected by peritoneal carcinomatosis of colorectal origin have a median life-span of 22 months following cytoreduction with intraperitoneal chemotherapy. This is almost a year longer than after conservative surgery and systemic chemotherapy. Patients who have a limited number of regions involved survive even longer. Although cytoreduction with intraperitoneal chemotherapy is associated with considerable toxicity, the complication rate is reasonable in patients with limited disease. In the follow-up, most recurrences can be
found by medical history, physical examination and tumor marker testing. If the disease recurs, the life-span can be extended by further treatment in patients who have a long disease-free interval.

Sadeghi et al performed a large multi-center study to determine the results of standard treatment in patients affected by peritoneal carcinomatosis. They found a median survival of only six months in patients with carcinomatosis from colorectal cancer. Jayne et al found similar results as the Sadeghi group. In the last update of the control arm in our randomized trial, the median survival was 14 months. The three-year survival was 22% in this group.

A number of explanations can be given for the better than expected survival of our patients treated by conventional surgery and systemic chemotherapy. Perhaps the most likely explanation is that patients in The Netherlands Cancer Institute are treated following a study protocol in which an active management is advocated. Within the study, patients received chemotherapy to treat their carcinomatosis and various treatment options were considered even for intra-abdominal and systemic recurrences. This is in contrast to the nihilistic approach of carcinomatosis management, which is common in medical practice. Another explanation for our results could be a selection bias. The Netherlands Cancer Institute is a third-line referring center. Although there is no official threshold, the patient population does not reflect the average carcinomatosis patient of the Netherlands. The most severe patients were probably not referred at all.

Stamou et al reported recently survival data of carcinomatosis patients treated in various ways. In their report a subset of patients were treated by a cytoreduction, including a peritonectomy, without intraperitoneal chemotherapy. These patients had a worse survival rate compared to those treated by cytoreduction plus intraperitoneal chemotherapy. But the patients treated by cytoreduction without hyperthermic intraperitoneal chemotherapy had a better survival rate than the survival rate of patients in the analysis of Sadeghi and Jayne, whom did not underwent any cytoreduction. In our analysis of the control arm, the suggestion is made that a resection of affected intraperitoneal areas correlates with a better survival. The patients in whom a complete resection was performed were probably the patients with minimal disease at onset. Thus, these patients' characteristics match those of patients who are the ideal candidates for cytoreduction and hyperthermic intraperitoneal chemotherapy.

Our randomized trial showed a positive effect of cytoreduction and hyperthermic intraperitoneal chemotherapy on survival time. Through this randomized trial, the level of evidence of effectiveness of cytoreduction and hyperthermic intraperitoneal chemotherapy improved from level V to level II. Although this level of evidence is seldom reached in surgical treatment, there is still a need for confirming this result in other studies. Unfortunately, our study did not answer detailed questions on patient selection with the same level of evidence.

Since the start of the project a number of changes were made in the procedure. Most changes were made for practical reasons and do not interfere with the concept of the treatment. The first treatments were done with a "Sugarbaker-like" system. The open carrousel method was used in all patients during the entire study period. The perfusion circuit consisted of a centrally placed inflow catheter, three outflow catheters placed in the pelvis and below left and right diaphragm, tub-
ing, a roller pump, a reservoir and a heat exchanger. Four temperature probes were placed in the abdomen close to in- and out-flow catheters. 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 and to prevent hot spots. Three liters of perfusate were used at an inflow temperature of 41-42 °C. As soon as the temperature in the abdomen was stable above 40 °C, Mitomycin C was added in three fractions with a 30-minute interval (⅓, ¼, ⅔ of the total dose respectively).

Sugarbaker used the Tenckhof catheter for the inflow. The essential element of the inflow catheter is that the perfusate flows in the abdominal cavity without spurt. In the first papers on the technique it was suggested that the perfusate is sprayed into the abdomen. It is not likely that this really happens. The spray effect is hampered by nearby bowel parts and surrounding fluid, and therefore is limited to a few centimeters. This means that any inflow catheter can be used. To prevent high pressure in the circuit and to prevent a jet effect at the tip, a large diameter, ordinary silicone drain is suitable.

A considerable effort has been made to create an optimal open carousel. The most practical way is shown in figures 1 and 2. Towel clamps (Bakhause-clamps) are attached to the wound and pulled with tie-raps to the Bookwalter retractor. The retractor is positioned approximately 20 centimeters

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**Figure 1.** Open carousel, suspension system to retractor

**Figure 2.** Open carousel, central aperture

**Figure 3.** Covering hood of the open carousel
above the abdomen. This system is easy to set up and provides a wide access to the abdomen. The system is covered with a “hat” connected to a suction device (figure 3).

With increasing experience, details of the technique of cytoreduction were changed along the way. The peritonectomies are done by electro-coagulation. The Erbe electro-coagulation device with a built-in smoke suction system is used to prevent spread of smoke and micro-particles. This unit has extension ability without the loss of smoke suction efficacy. The ligasure (Tyco) was used to dissect the omentum from the stomach and to divide the mesentery for bowel resections. The left upper part of the abdomen is often cleared of tumor by a splenectomy. This procedure often causes injury to the pancreas tail. In many of the early patients, this resulted in a mild to severe pancreatitis. In later patients, the pancreas tail was resected using an automatic stapler (Ethicon) when this region was heavily involved. This reduced the number of pancreatic complications.

Pre-operatively, a complete bowel lavage is done to reduce stool spill during the operation and to make bowel handling easier. Unfortunately, bowel lavage leads to inadequate nutrition during the last 36 hours before the procedure. Recent literature advocates pre-operative feeding. To achieve this, we started to give low-fiber nutridrinks (Nutricia) during the day before the operation.

Selecting the patients for cytoreduction and hyperthermic intraperitoneal chemotherapy is difficult. Although it is obvious that the key issue is to select patients in whom it is feasible to reach a complete cytoreduction, it is hard to identify these patients without doing an explorative laparotomy. The best information to select patients is gathered during the laparotomy in which the diagnosis peritoneal carcinomatosis is made. This information is too often poorly presented. The majority of the general surgeons, and even the surgical oncologists, are unaware of the importance of proper staging of an abdomen affected by peritoneal carcinomatosis. This probably reflects their nihilistic ideas on further treatment of this disease. 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 chapter nine.

The theoretical side of the selection is even more complex. Patients without either a complete or near-complete resection have a median life expectancy of less than half a year. For such a short median survival time, the risks accompanying an intensive treatment like cytoreduction followed by hyperthermic intraperitoneal chemotherapy are not acceptable. It would be of interest to know whether cytoreduction with hyperthermic intraperitoneal chemotherapy prolongs the symptom-free interval even in these extensively affected patients, and whether this reduces the number of subsequent laparotomies during the last months of life.

At the other end of the spectrum, things are even less clear. Patients with limited disease do well when treated by cytoreduction and hyperthermic intraperitoneal chemotherapy. There is also an indication that patients in whom the tumor load is minimized do reasonably well with standard treatment.

Thus, patients with minimal disease will do well with any serious treatment and patients with ex-
tensive disease will suffer from fast progression whatever treatment regime is used. It is therefore likely that a patient with moderate extension of disease benefits most from cytoreduction followed by hyperthermic intraperitoneal chemotherapy.

Unfortunately, the implementation of the above-mentioned selection criterion is not without hazards. The level of evidence of this selection criterion is low because no comparative study has been performed within each stage of disease. This is due to lack of information on tumor load in patients treated by conventional surgery and systemic chemotherapy. The way to overcome this problem would be a detailed staging in all patients, whether randomized for conventional treatment or experimental treatment. Such a staging requires a full exploration of the abdomen.

At the current level of evidence, it would be best to exclude only patients in whom disease is too extensive. This means that after exploration of the abdomen the decision has to be made whether to proceed with a full resection and cytoreduction with intraperitoneal chemotherapy, or to do a palliative resection with minimal risk of complications. In this way, these latter patients could be spared the toxicity because they do not have a chance of extending their life span.

In general, it is said that there is 10% improvement of survival only because a patient is treated within the framework of a trial protocol. We found a 50% increased survival time in the standard arm compared to other publications.\textsuperscript{13-15} This raises the question whether the standard arm of the randomized trial represents the common medical practice. All patients in this study, whether treated by hyperthermic intraperitoneal chemotherapy or by systemic chemotherapy only, were managed pro-actively. This meant that during the follow-up every recurrence was dealt with in the most active way. The "gold standard" in the treatment of peritoneal carcinomatosis has not yet been established. In practice, most of these patients face a therapeutic nihilism, and do not undergo major treatments. In this perspective, a novel therapy like cytoreduction with hyperthermic intraperitoneal chemotherapy should be compared to this nihilistic regime, as being the "standard".

The question remains which part of the procedure "cytoreduction and hyperthermic intraperitoneal chemotherapy" is effective. None of the current analyses exclude the possibility that only the cytoreduction part of the treatment was responsible for the result. The data derived from the control arm of our study suggests that cytoreduction is at least responsible for an important part of the effect.\textsuperscript{15}

In addition to the analyses performed in the former chapters, we analyzed the influence of the result of the operation before randomization on the survival time in the patients in the trial. The diagnostic operation before randomization was either only diagnostic without resection, or therapeutic with resection of the affected tissues. After this operation, the patients were randomized to the standard arm or to cytoreduction followed by hyperthermic intraperitoneal chemotherapy. This allotment resulted in four subgroups (1) no resection before randomization and allocated in the standard arm, (2) resection before randomization and allocated in the standard arm, (3) no resection before randomization and allocated in the experimental arm and (4) resection before randomization and allocated in the experimental arm. The survival curves of all groups are displayed in figure 4. Groups 2, 3 and 4 underwent a resection of the affected tissue, either before randomization or thereafter. The median survival of patients who had a resection was 20 months and this was
eight months in those without resection. This difference was significant when tested with the log-rank test \( p=0.0024 \). It is obvious that this analysis can only be suggestive, as it is not built on randomized, or standardized data. The reason for not performing a resection before the randomization is presumably strongly related to the tumor load. This analysis suggests that hyperthermic intraperitoneal chemotherapy has no major impact on survival in patients in whom the tumor is resectable by conventional surgery. It also suggests that cytoreduction followed by hyperthermic intraperitoneal chemotherapy does improve survival if a conventional resection has not yet been done. Both suggestions indicate that clearing the abdominal cavity from tumor is the most important part of the treatment.

A randomized study in which one arm consists of cytoreduction and the other arm of cytoreduction and hyperthermic intraperitoneal chemotherapy would answer many important questions. Such a study could solve the selection problem, as detailed information of both arms would be available. The suggested study would also resolve the issue whether the cytoreduction alone or the additional hyperthermic intraperitoneal chemotherapy provides the benefit. The null hypothesis of this study would be that survival in the two arms is different. This would be a non-inferiority study, which would need a large number of patients. Such study also allows proper staging of all patients because both arms undergo a complete exploration of the abdominal cavity. A possible outcome could be that a minimal tumor load can be managed by cytoreduction alone, whereas an extensive

Figure 4. Survival of 105 patients affected by peritoneal carcinomatosis of colorectal origin, subanalysis by resection before randomization and cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC)
tumor load cannot be managed by any treatment. This would leave only the in-between patients with a nearly complete resection to benefit from hyperthermic intraperitoneal chemotherapy. This study would require 400 to 500 patients. To reach such a number, multiple centers need to participate. Preparations for such protocol are being made at The Netherlands Cancer Institute.

At the writing of this thesis, there are only a limited number of institutions treating patients by cytoreduction and hyperthermic intraperitoneal chemotherapy.23 Most institutions will see 20 to 40 new patients a year. The number of patients who could benefit from cytoreduction and hyperthermic intraperitoneal chemotherapy exceeds these numbers. Efforts are being made to encourage other institutes to start this treatment.

The randomized trial was initiated to prove the effectiveness of the approach. The underlying goal of this study was to find official recognition by the Dutch government for this treatment and therefore it was supported by the “College voor Zorgvoorzieningen”, an organization that approves new treatments for standard care. This recognition enables other institutes to start this therapy as regular management for peritoneal carcinomatosis. Unfortunately, The Netherlands Cancer Institute is still the only Dutch center providing this treatment.

Table 1 Major institutes performing hyperthermic intraperitoneal chemotherapy

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<tr>
<th>Abbreviation</th>
<th>Full text</th>
<th>Institution</th>
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<tr>
<td>HIPEC</td>
<td>Hyperthermic IntraPEritoneal Chemotherapy</td>
<td>Ghent University Hospital, Belgium</td>
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<td></td>
<td>University Hospital Mannheim, Germany</td>
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<td></td>
<td></td>
<td>Washington Cancer Institute, USA</td>
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<td></td>
<td></td>
<td>Centre Hospitalo-Universitair Lyon Sud, France</td>
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<td></td>
<td></td>
<td>The Netherlands Cancer Institute, the Netherlands</td>
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<tr>
<td>IPHC</td>
<td>Intra Peritoneal Hyperthermic Chemotherapy</td>
<td>Wake Forest University School of Medicine</td>
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<td></td>
<td></td>
<td>Centre Hospitalo-Universitair Lyon Sud, France</td>
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<tr>
<td>HIIP</td>
<td>Hyperthermic Intraoperative Intraperitoneal Chemotherapy</td>
<td>Washington Cancer Institute, USA</td>
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<td>University of North Dakota School of Medicine and Health Sciences, USA</td>
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<td>Universita' di Padova, Italy</td>
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<tr>
<td>IPHP</td>
<td>Intra Peritoneal Hyperthermic Perfusion</td>
<td>National Cancer Institute of Milan, Italy</td>
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<tr>
<td>IPCH</td>
<td>Intra-operative intraPeritoneal Chemo-Hyperthermia</td>
<td>Institut Gustave Roussy Comprehensive Cancer Center, France</td>
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A number of different names and abbreviations are used to refer to hyperthermic intraperitoneal chemotherapy. Table 1 lists these names and the major institutes treating patients by this procedure. Although no official hyperthermic intraperitoneal chemotherapy organization exists, a group of institutes involved in this treatment is developing. Part of this group meets once every two years in a master class session. In recent years, sub-meetings within surgical oncology conferences have been held to discuss intraperitoneal chemotherapy and related protocols. The idea of a North American study was launched at the annual meeting of the Society of Surgical Oncology in Denver (2002). At the writing of this thesis, a protocol was sent out to potential participants. A consensus meeting was held during the congress of the European Society of Surgical Research in Ghent, Belgium (2003). The study, comparing cytoreduction to cytoreduction combined with hyperthermic intraperitoneal chemotherapy, as mentioned above, was initiated at this meeting.

In conclusion:

Peritoneal carcinomatosis of colorectal origin is stadium of colorectal cancer which is historically under treated. Cytoreduction combined with hyperthermic intraperitoneal chemotherapy has shown to give chance to survival this illness in selected patients. Therefore should this treatment be considered in every patient affected by peritoneal carcinomatosis of colorectal origin when there is no evidence of systemic metastasis.

References


