Long-Term Results of Cytoreduction and HIPEC Followed by Systemic Chemotherapy

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Abstract: Cytoreduction followed by hyperthermic intraperitoneal chemotherapy is a treatment option for peritoneal surface malignancies in The Netherlands. This treatment has been available for more than 10 years. Therefore, long-term results on survival and quality of life can now be studied. With these results, the true long-term benefits of this new management strategy can be determined.

Key Words: peritoneal surface malignancies, cytoreduction, hyperthermic intra peritoneal chemotherapy, survival and quality of life

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Peritoneal carcinomatosis has been treated by the cytoreductive plus hyperthermic intraperitoneal chemotherapy (HIPEC) procedure for the last 20 years. In the early years of this treatment, it was debated whether the good results were related to patient selection or positive effects of the combined treatment. It was also questioned whether the long-term quality of life benefits were balanced with the efforts for both patients and resources. As a result of continued clinical and laboratory research in the beginning of the 21st century in The Netherlands, the HIPEC procedure became an established treatment for peritoneal carcinomatosis of colorectal origin and pseudomyxoma peritonei. Nowadays, the indication for the HIPEC procedure is extended to other peritoneal surface malignancies such as peritoneal mesothelioma and ovarian cancer. Currently, these other malignancies are treated with the HIPEC procedure in trial protocols.

In the early days of this complex treatment, there were still many shortcomings in the technique and patient management. Now, as a result of many conferences, international workshops and side by side intraoperative teaching, this treatment has been brought to a high level of care. Standardized protocols are available that allow for greater availability of the benefits. Also, there has been a shift in patient selection. In the 1990s, the HIPEC procedure was offered to patients who were at the end stage of their disease having been previously treated with multiple lines of systemic chemotherapy. Today more patients receive the HIPEC procedure upfront. Nowadays, a discussion on prophylactic treatment with the HIPEC procedure for T4 carcinomas is to prevent the progression of carcinomatosis.

DUTCH ORGANIZATION

The first randomized trial on the HIPEC procedure was conducted in The Netherlands. Perhaps it is not surprising that after the early results of this trial became available in 2003, the waiting list soon go out of hand. To overcome the extremely long-waiting list, new HIPEC centers were setup throughout the country. All the new centers were trained by the "founding" center, The Netherlands Cancer Institute. This training included side by side intraoperative teaching in the new centers. Meanwhile, a national group was founded to discuss HIPEC matters both on patient level and on organizational level.

Currently, the results of the procedures and the adverse outcomes are presented biannually in the Dutch HIPEC group meeting. Also discussed are possible new indications and new trials. The group also provides a base for any new center to start. As a result of proper training and education, new centers can start at a high level of knowledge and performance. In this way, the learning curve has been greatly reduced. The results of the HIPEC procedure of the Dutch groups are presented in Figure 1. In France, a similar organization was set up, and the results were reported by the peritoneal surface workshop meeting in Lyon, France in 2008.

DATA ON LONG-TERM RESULTS OF CYTOREDUCTION AND HIPEC

Long-term results of cytoreduction followed by HIPEC were published in 2005. The first publication of long-term results had a median follow-up of 46 months.[1] In this publication, there was a median survival of 42.9 months for those patients who underwent a complete cytoreduction. This publication shows the results of the patients treated in the early days of the HIPEC era. The interpretation of the results of this publication was difficult because of possible selection bias and nonstandardized technique.

In 2003, the randomized trial comparing standard chemotherapy with cytoreduction followed by HIPEC and adjuvant therapy was published.[2] In this publication of a prospective randomized trial, the group of patients treated by the HIPEC procedure were not preselected. This study showed that cytoreduction followed by HIPEC had a significant better survival than systemic chemotherapy alone. In the intention to treat analysis, the results of the study showed median survival of 12.5 months in the standard arm and 22.3 months in the experimental arm.

This study was updated in 2008.[3] This update was based on the original 105 patients. The randomized trial protocol stated that patients who progressed should be treated with the best available at that time. As such, patients randomized to the standard treatment who had an intra-abdominal recurrence were offered treatment with the HIPEC procedure after the randomized trial was published in 2003.

To overcome a cross-over problem from the standard arm to the HIPEC arm, the patients were censored at the moment of the cross over. Although this may have presented a major issue in data evaluation, it was only the case in 2 patients.

In the update of the original trial, the follow-up was complete in all patients until August 2007. At that moment, there was a median follow-up of 94 months (range from 72 to 115 months). In Figure 2, the Kaplan-Meier survival curve is shown. Patients of the standard arm had

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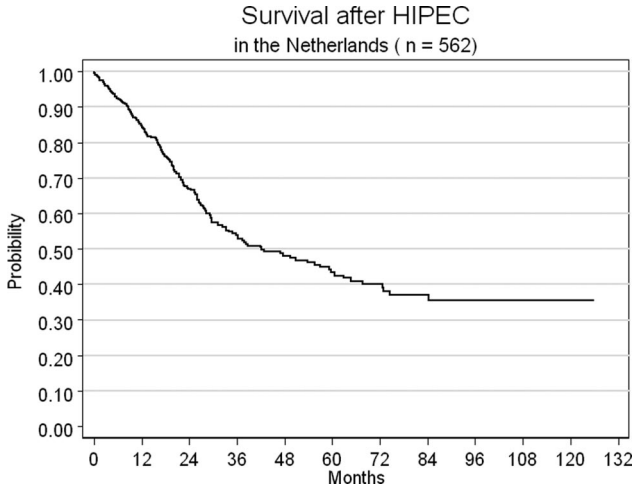

FIGURE 1. Dutch multicenter data showing the survival of patients with colorectal carcinomatosis treated by cytoreductive surgery plus heated intraperitoneal chemotherapy.

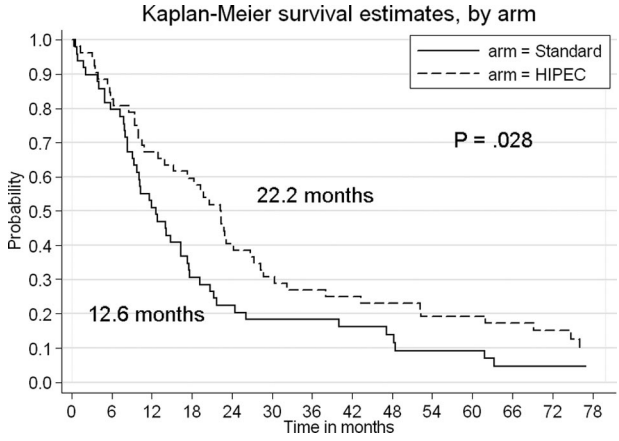

FIGURE 2. Kaplan-Meier survival estimates, by arm in patients with colorectal carcinomatosis (modified from *Ann Surg Oncol.* 2008;15:2426–2432).

a median survival of 12.6 months. The median survival of patients from the experimental arm was 22.2 months. This difference was significant with a *P* value of 0.028. The 6-year survival was only 5% in the standard arm and 20% in the experimental arm. It is still important to bear in mind that this analysis was by intention to treat.

Figure 3 shows details of the survival in the experimental arm. From this graph, it is obvious that the requirement for success is the completeness of the cytoreduction. The 5-year survival rate in those patients who had a complete cytoreduction was 45%. In those patients in whom the attempt for a complete cytoreduction was fruitless, the survival was still very poor. The median survival was less than 1 year.

In the randomized trial, bias from patient selection was ruled out by randomizing all patients referred for peritoneal carcinomatosis of colorectal origin. At that time, there was little data to support any rational patient selection. After the randomized trial, important selection criteria became available. Data on prognostic factors pointed out the patients most likely to benefit.[4,5] Data on toxicity pointed to be considered ineligible for treatment.[6,7] All the publications taken together summarized all options available for these patients. In this way, eligible for this extensive treatment became standardized.[8]

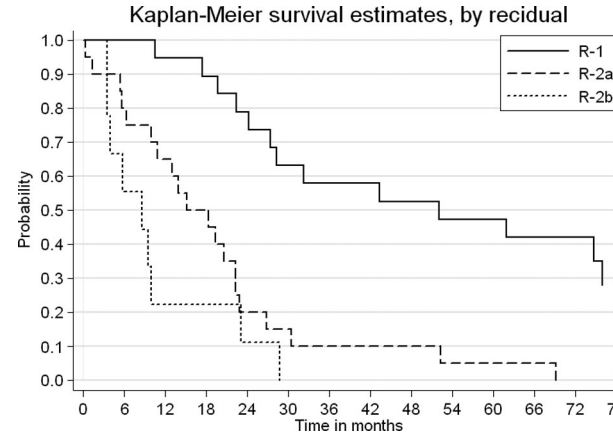

FIGURE 3. Kaplan-Meier survival estimates by residual in patients with colorectal carcinomatosis R-1 = no remaining macroscopic tumor, R-2a = residual tumor smaller than 2.5mm, and R-2b = residual tumors greater than 2.5 mm (modified form *Ann Surg Oncol.* 2008;15:2426–2432).

DATA REGARDING THE LEARNING CURVE

The learning curve of cytoreduction followed by HIPEC has been extensively studied.[9] In the publication by Smeenk et al, an increase of the median survival was seen from a survival probability at 24 months increased from 59.7% in 1996–1998 to 61.9% in 1999–2002 and 71.7% in 2003–2006. The survival rate at 24 months was 49.0% for peritoneal carcinomatosis and 83.1% for pseudomyxoma peritonei.

Besides the effect on survival, there has been also a decrease in toxicity. Not only the toxicity itself decreased but also the outcome of complications improved.[10] It is important to emphasize that the learning curve of an institute reflects not only the capability of that institute but also the world's knowledge at that moment on a disease or its treatment. The lack of general knowledge of peritoneal carcinomatosis and the HIPEC procedure in the 1990s led to slow learning curves. Now that we understand the disease and its treatment more completely and now that education programs are available for institutes introducing this treatment, learning curves will be much shorter. This phenomenon is called the "world learning curve."

Accepting the possibility that the learning curve has now come to its maximum, and knowing that the results for those patients treated on the slope of the learning curve had a 5-year survival of 45%, one can predict that the median survival of those patients treated today will be beyond 5 year.

LONG-TERM RESULTS OF ALTERNATIVES

Stage IV colorectal cancer is general described as any metastasized colorectal cancer. Peritoneal carcinomatosis is one of the different subcategories of stage IV colorectal cancer. In general, Medical Oncologists treat all stage IV colorectal cancers subcategories on the same protocols. The results of the medical treatment show a median survival of 1 to 2 years. Large randomized trials show even better results with the newest agents.[11]

It is important to realize that the inclusion criteria for the randomized trials is "measurable disease." Peritoneal carcinomatosis is typically not seen on computed tomography (CT) scans, and therefore not seen as a measurable disease.[12] For that reason, medical oncologic studies mainly include patients with CT measurable liver metastasis and not with immeasurable peritoneal carcinomatosis patients. In most of the chemotherapy trials on treatment of stage IV, colorectal cancer patients with peritoneal carcinomatosis are "deselected."

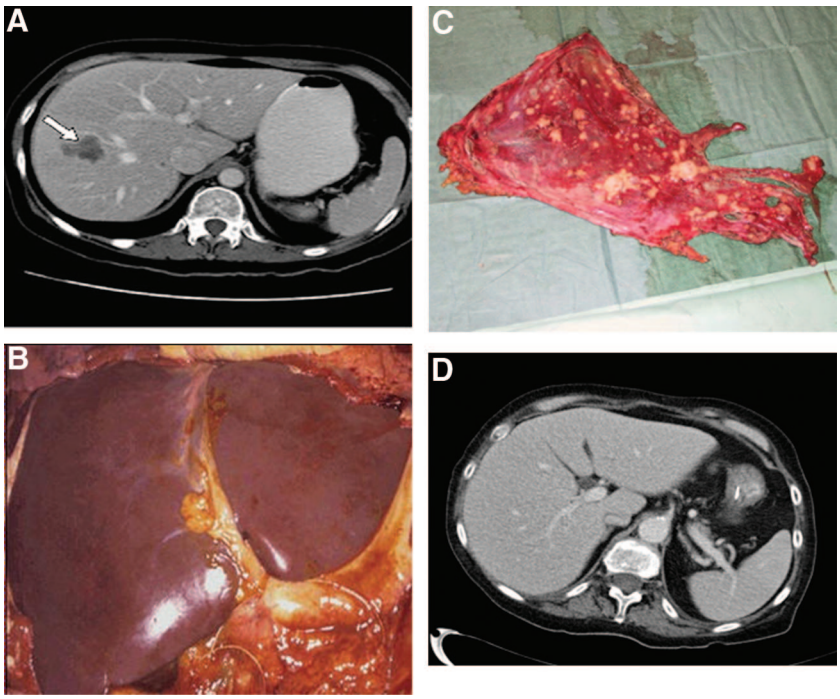

FIGURE 4. A–D, Different forms of colorectal cancer.

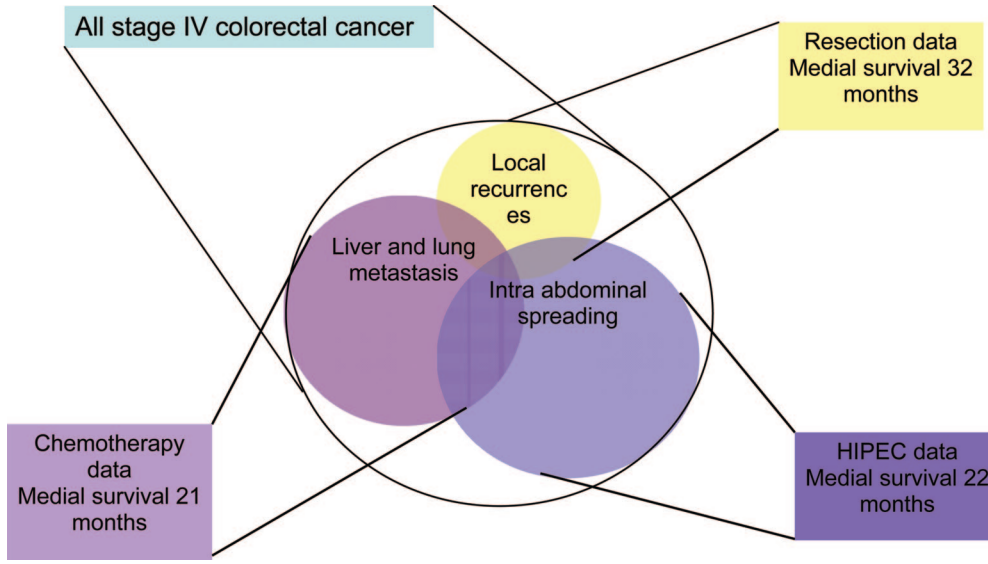

FIGURE 5. Summary of the results of treatment subgroups of stage IV colorectal cancer.

Figure 4 shows the different form of stage IV colorectal cancer. It displays a typical CT scan of a liver metastasis on the left upper picture (Fig. 4A), beneath it is an intraoperative picture of the same liver shown (Fig. 4B). On the right side an intraoperative picture of peritoneal carcinomatosis is shown (Fig. 4C), with beneath it the CT scan of the same area (Fig. 4D). The difference in intraoperative observations and CT findings are obvious.

Peritoneal carcinomatosis often presents itself with multiple colon obstructions. This reduces the patient's tolerance of chemotherapy. Folprecht et al[13] performed a study on effectiveness of chemotherapy in patients affected with peritoneal carcinomatosis; they reported that they had a diminished response. Newer studies indicate differences in gen progressions between liver metastasis and peritoneal metastasis. These data are still preliminary, but they reflect differences in tumor biology between liver metastasis and peritoneal carcinomatosis. For these reasons, the results of the treatment of stage IV colorectal cancer in studies containing mainly liver metastasis cannot be transferred to peritoneal carcinomatosis. In my opinion, there are no reliable data available on the long-term results of the medical treatment of peritoneal carcinomatosis.

QUALITY OF LIFE STUDIES

The HIPEC procedure is a complex treatment and can come with serious complications. It is often discussed whether the HIPEC procedure is worthwhile in perspective of quality of life. There are

only a few data available on this issue. McQuellon et al[14] studied this topic extensively. He found in 109 patients, interviewed between 3.1 to 8.0 years after treatment, that 10 patients (62.5%) had a very good to excellent health status. Furthermore, he found no limitations on moderate activity were reported in 94% of the patients.

One must realize that, alongside the favorable quality of life results, there is the misery of those patients who failed the treatment. Verwaal et al studied in his thesis, the quality of life of patients treated for peritoneal carcinomatosis of colorectal origin. He found that there was a decreased quality of life shortly after the procedure. In the long run, he found that the quality of life was mostly related to the presence of recurrences of disease and not to the treatment.

GUIDELINES

The international guidelines for the HIPEC procedure were considered in the consensus meeting in Milano in 2006. The guidelines included eligibility, workup, and treatment details. These guidelines are based on scientific evidence and formulated by an international panel of experts. The guidelines have been published; based on this evidence, cytoreduction followed by HIPEC is incorporated in many national guidelines for treatment.[15]

CONCLUSIONS

Based on this data, and lack of other data, cytoreduction followed by HIPEC should be considered for colorectal peritoneal carcinomatosis in those patients who fit to undergo major surgery. Long-term survival with acceptable quality of life can be achieved in select patients. Selection of the patients is still a critical issue. Unfortunately, there are limited data available for peritoneal carcinomatosis patients treated with systemic chemotherapy and recommendations for the use of systemic chemotherapy in these patients are not available. Figure 5 shows a summary of the results of treatment of 4 subgroups of stage IV colorectal cancer.

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