Curative treatment of peritoneal carcinomatosis of colorectal origin

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Abstract

Up to 8% of all patients with colorectal cancer have peritoneal carcinomatosis (PC) as the only site of disease at some point in time. Traditional treatment by limited palliative surgery and systemic chemotherapy has poor results with few patients surviving longer than 3 years. Complete cytoreductive surgery combined with Hyperthermic Intra Peritoneal Chemotherapy (HIPEC), using Mitomycin C, followed by adjuvant chemotherapy has been extensively tested. Both in Phase II and in randomised phase III trials this combination therapy has shown superior results, with a median survival of 2 years and a 5-year disease-free survival of 20–25%.

Introduction

About 10% of all colorectal cancer patients already have peritoneal carcinomatosis (PC) at first diagnosis. Another 25% has PC as part of their recurrence pattern. Even after extensive imaging, at least a quarter has no other metastases. Therefore, up to 10% of colorectal cancer cases will have PC as only tumour site at some time of their disease, making it the second most frequent site after liver metastases. Until recently, most PC patients were treated with limited so-called palliative surgery and systemic chemotherapy. Results of this approach are poor, with a median survival from 6 to 12 months reported. Sugarbaker has pioneered the treatment based on aggressive cytoreduction combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in PC of appendiceal origin [1]. In recent years, at least 20 small series have been published on the use of this approach in PC of colorectal origin. Many of these publications were brought together in a multicentre review on 504 cases, performed by Glehen [2]. In addition, our group has published a randomised phase III study [3].

Patient selection

There is some consensus that cytoreductive surgery and HIPEC should be reserved for patients with proven PC without liver or other distant metastases. All published studies show that patients with limited disease do better then those with extensive peritoneal involvement. There are several indices in use to record the extent of peritoneal involvement. Most widely used is the Peritoneal Cancer Index propagated by Sugarbaker [4]. This index records tumour in 12 abdominal regions, and takes the amount of tumour in account. In the Netherlands Cancer Institute, we use a more simple system with 7 regions, but with equal prognostic significance. The main difficulty is the poor sensitivity of imaging techniques for PC, making reliable judgement only possible during laparotomy. Most centres use only extensive involvement of small bowel and its mesentery as absolute contra-indication for this approach.

Technique of cytoreductive surgery

Completeness of cytoreduction is the strongest prognostic factor in most series. The aim of cytoreductive surgery is therefore to leave no macroscopic disease behind. This can be easily achieved in some regions such as the pelvis, omentum, and the subdiaphragmatic regions. The sub-hepatic and pancreatic region is technically difficult. Extensive small bowel involvement makes complete cytoreduction impossible. Besides peritonectomy procedures as described by Sugarbaker, it is often needed to do extensive visceral resections to achieve complete cytoreduction [5]. In our experience, we were able to achieve complete cytoreduction in 40% of cases. In 40%, a residue of a few millimetres was left behind, while in 20% major residues had to be left behind. None of the last patients survived long, and they were responsible for all treatment related deaths. For these reasons we now stop the procedure as soon as it becomes clear that complete or near complete cytoreduction is impossible.

Technique of HIPEC

Hyperthermia is established by perfusion of the abdominal cavity with heated fluid at a rate of 1 litre per minute or more (Fig. 1). Most experience has been gained using mild hyperthermia (40–42 °C) [6]. Most groups perfuse during 60 to 90 minutes, using either an open or a closed technique. There are no good data proving superiority of either system. Most groups use Mitomycin C, at a dose varying from 15 to 35 mg/m^2. The main systemic toxicity is leucocytopenia, which characteristically reaches its nadir at 10 days post HIPEC. Even at the higher end of the dose (35 mg/m^2), grade III leucocytopenia occurs in less then 10% of cases. There are several perfusion machines commercially available.

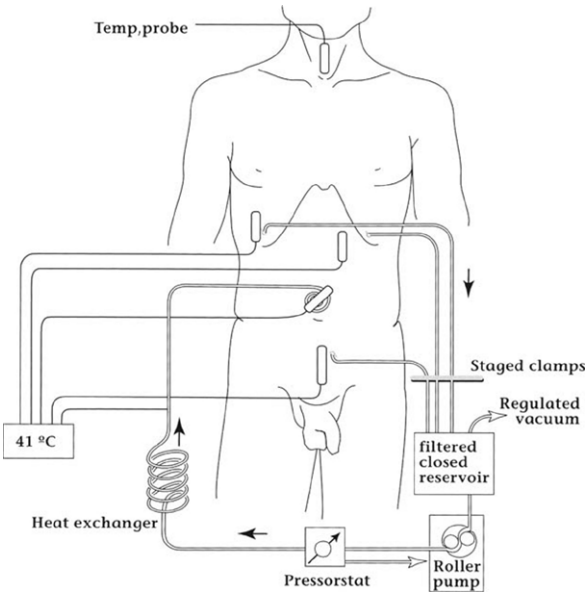

Fig. 1. Scheme of the HIPEC perfusion circuit used in the Netherlands Heart Institute.

Adjuvant systemic chemotherapy

Although no randomised data are available supporting systemic chemotherapy, most groups will give patients up to 6 months of 5FU based chemotherapy after HIPEC. The reasoning is that these patients remain high-risk for recurrence, and have an optimal chance of a lasting response if treated for minimal residue disease. It will be interesting to see whether modern combination chemotherapy will further improve results. In many published studies, patients were progressive on systemic chemotherapy before their HIPEC treatment [2].

Results

In the only randomised study published, there is a very significant survival benefit for treatment with cytoreductive surgery and HIPEC (Fig. 2) [3]. This includes all randomised patients. It is also important that the survival curve after HIPEC shows a plateau with an estimated 5-year disease-free survival of 20%. If patients with extensive disease and those in whom major residue had to be left behind are excluded, results are even better. The collected series by Glehen shows similar results.

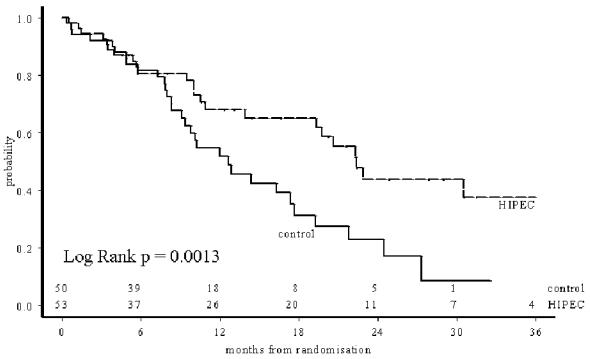

Fig. 2. Comparison in survival between cytoreductive surgery with HIPEC plus systemic chemotherapy and limited surgery with systemic chemotherapy (phase III study).

Conclusions

PC of colorectal origin should be grouped with isolated liver and lung metastases as potentially curable. Cytoreductive surgery with HIPEC doubles live expectancy of these patients compared to systemic chemotherapy alone. Complete cytoreduction is a prerequisite for long-term success. Patients with extensive disease, and in those where (near) complete cytoreduction is impossible, should be excluded from HIPEC treatment.

References

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