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Original article

Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei

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Background: Pseudomyxoma peritonei remains a fatal disease. However, extensive surgical cytoreduction combined with intraoperative heated intraperitoneal chemotherapy (HIPEC) has recently emerged as a new treatment modality, which might improve survival.
Methods: Patients underwent treatment if the tumour appeared to be technically resectable on preoperative abdominal computed tomography and there were no distant metastases. After aggressive surgical cytoreduction, HIPEC with the administration of mitomycin C was performed for 90 min. Depending on histological grading, patients received adjuvant 5-fluorouracil and leucovorin therapy.
Results: Forty-six patients were treated. Optimal surgical cytoreduction was obtained in 40 patients. Postoperative surgical complications occurred in 18 patients. Four patients died as a direct result of the treatment. Bone marrow suppression due to mitomycin C toxicity occurred in 22 patients. There was no other major toxicity related to the HIPEC procedure. After a median follow-up of 12 months, 40 patients are alive, eight of whom have proven recurrence. The actuarial survival rate (Kaplan–Meier) at 3 years was 81 per cent.
Conclusion: These results confirm that extensive surgery combined with HIPEC is feasible in patients with pseudomyxoma peritonei and that improved long-term survival might be achieved.

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Introduction

Pseudomyxoma peritonei is a rare condition characterized by intra-abdominal extracellular gelatinous fluid collections and non-invasive mucinous implants on the peritoneum containing mucus-producing epithelium[1,2]. The recent development of immunohistochemical techniques has led to a better understanding of the aetiology and pathogenesis of this disease[3–5]. It is now generally accepted that pseudomyxoma peritonei is a result of neoplastic mucus-secreting cells within the peritoneal cavity that have low-grade, relatively benign, cytological features and are sparsely distributed within the extracellular mucinous collections[1]. In most cases these cells derive from a ruptured appendiceal cyst, benign adenoma or a low-grade appendiceal adenocarcinoma. It is thought that perforation of this primary process leads to the distribution of atypical cells into the abdominal cavity, the so-called redistribution phenomenon, as described by Sugarbaker[6]. Pseudomyxoma peritonei is usually diagnosed by combining the clinical findings ('jelly belly'[7]) and the histological features. The difficulty in differential diagnosis is the differentiation between pseudomyxoma peritonei and carcinosis peritonei due to well differentiated mucinous carcinoma.

Despite its relatively benign character and better understanding of its aetiology and prognostic features, the long-term survival of patients with pseudomyxoma peritonei remains poor with reported 5- and 10-year survival rates of 50 and 10–30 per cent respectively[1]. In recent decades repetitive and sometimes extended operations have usually been the sole therapeutic modality. All macroscopic tumour was removed if possible, including the appendix and in women the ovaries. Complete cure, however, could never be achieved and the disease-free interval between different surgical interventions became progressively shortened. Finally, further surgery became impossible because of

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extensive tumour entrapment of bowel surfaces; consequently patients eventually died from cachexia.

In the 1980s a new combined treatment option was introduced: aggressive maximal surgical cytoreduction in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC)[8,9]. With this combined treatment modality a 5-year survival rate of 86 per cent was described by Sugarbaker *et al.*[10,11]. Because HIPEC in combination with surgical cytoreduction is a high-risk and demanding procedure, associated with a high complication rate, this treatment option has not gained wide application and so comparable data on its morbidity, toxicity and effectiveness in larger groups of patients with pseudomyxoma peritonei have not yet been published.

Since 1996, HIPEC in combination with extensive surgical cytoreduction has been used as a treatment schedule in patients with pseudomyxoma peritonei in this institute. This paper describes the treatment-related morbidity, disease-free interval and survival in the first series of 46 patients.

Patients and methods

Patient selection

Patients with pseudomyxoma peritonei were treated by aggressive surgical cytoreduction and HIPEC with mitomycin C (MMC) if they fulfilled the following criteria: diagnosis proven by histological or cytological examination; no sign of distant metastasis on computed tomography (CT) of the abdomen and chest; the tumour had to be technically resectable; and the patient considered medically fit to undergo major surgery. The local ethics committee approved the treatment protocol, and informed consent was obtained from all patients.

Surgical aspects

The abdomen was approached through a median incision from the xyphoid process to the pubic symphysis. Comprehensive adhesiolysis was performed. The tumour distribution was recorded according to the presence of tumour deposits in seven abdominal areas: left and right subdiaphragmatic, subhepatic, omentum/transverse colon, small intestine/mesentery, ileocaecal and pelvic. The primary tumour and/or recurrences were excised, and all visceral or parietal peritoneal surface tumour deposits were removed as completely as possible. The objective of optimal cytoreductive surgery was to leave no macroscopic tumour behind or, when this could not be achieved, only tumour deposits less than 2·5 mm in diameter. If it was impossible to peel the malignancy from the surface of an organ, the involved organ or a segment of it was excised. After bowel resection anastomoses were postponed until after the intraperitoneal MMC perfusion to prevent suture-line seeding. When parietal peritoneal surfaces were significantly involved, peritonectomy procedures, as described by Sugarbaker[12], were performed.

Perfusion

After cytoreductive surgery was completed, a Tenckhoff inflow catheter (Curl Cath^{TM}; Quinton, Bothell, Washington, USA) was introduced centrally into the abdominal cavity. Three silicone outflow drainage tubes (Dura-Sil; Biometrix, Jerusalem, Israel) were placed subphrenically on both sides and in the pelvis. Temperature sensors (Mon-a-therm^{TM}; Mallinckrodt Medical, St Louis, Missouri, USA) were attached to the catheters. The catheters were connected through a reservoir with a filter (Safe II Filtered Cardiotomy Reservoir; Polystan, Copenhagen, Denmark) to the heat exchanger (Baxter, Uden, The Netherlands) and roller pump (Polystan, Copenhagen, Denmark) and back to the patient. The skin surrounding the laparotomy wound was sutured to a retractor ring placed above the anterior surface of the abdomen. In this way expansion of the peritoneal cavity was achieved, resulting in better exposure of the entire seroperitoneal surface to the perfusate. Plastic sheeting was sutured over the laparotomy wound to prevent spillage of the perfusate and loss of heat. Centrally in the plastic cover a small hole was made to allow entrance of the surgeon's hand. The perfusion system was filled with isotonic dialysis fluid (Dianeal® PD1; Baxter). The perfusate circulated at a rate of approximately 1 l/min.

The MMC was added in three divided doses with a 30-min interval. Initially, MMC 15–40 mg/m^2 was given. In the majority of patients MMC 35 mg/m^2 was administered. At standard time intervals, samples of perfusion fluid and plasma were taken for pharmacokinetic studies. The intraperitoneal temperature was maintained between 40 and 41°C, and the perfusion lasted for 90 min. To achieve uniform temperature and drug distribution, the surgeon gently stirred the perfusate and bowel loops by hand.

After completion of the perfusion the excess fluid was drained from the abdominal cavity. Because of the expected prolonged ileus, a gastrostomy was performed for gastric decompression and a feeding tube was positioned in the proximal jejunum for early postoperative enteral nutrition. Surgical complications and toxicity attributed to MMC were recorded, according to the World Health Organization (WHO) grading for chemotherapy toxicity.

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Adjuvant chemotherapy and follow-up

Based on histological findings patients were classified as having benign or malignant pseudomyxoma peritonei. Patients with malignant disease received adjuvant 5-fluorouracil (5-FU) and leucovorin if they had not previously been treated with this regimen. Some 6–12 weeks after discharge, weekly intravenous administration of 5-FU 400 mg/m^2 in bolus injection, following leucovorin 80 mg/m^2 in a 1-h infusion, was started. Adjuvant chemotherapy was continued for 6 months or until progression of the tumour was observed or intolerable toxicity occurred. Six weeks and 3 months after discharge, and then at 3-monthly intervals, patients were seen in the outpatient clinic. Physical and laboratory examination, including estimation of carcinoembryonic antigen (CEA) and CA-19.9 levels, was performed. CT of the abdomen and chest radiography were performed every 6 months, starting 3 months after operation. Time to recurrence and survival were recorded.

Results

Patients

From April 1996 until March 2000, 46 patients (19 men and 27 women with a mean age of 56 (range 34–76) years) were treated. Twenty-one patients presented with recurrent disease. Forty-one patients already had been operated on before referral, with a mean of 2 (range 1–5) laparotomies. Seven patients had also received systemic chemotherapy previously, and one had been pretreated with intraperitoneal cisplatin. Two patients had previously undergone radiotherapy.

Surgery and heated intraperitoneal chemotherapy

In 33 patients the tumour deposits were spread over five or more abdominal regions, in ten the tumour was limited to two to four abdominal regions, and in three cases tumour was limited to only one region. Optimal surgical cytoreduction, leaving only tumour deposits smaller than 2·5 mm behind, was achieved in 40 patients. Major visceral resections were needed to achieve this, including partial gastrectomy, bowel resection, splenectomy, cholecystectomy, and ovariectomy and hysterectomy in women (*Table 1*). A mean of 2 (range 0–6) bowel anastomoses was needed per patient, while a colostomy was performed in 17 patients and an ileostomy in one. In 19 cases a (distal) gastrectomy with Billroth I reconstruction was performed, and in one patient partial gastrectomy was followed by a Billroth II reconstruction. The mean duration of operation was 10 (range 5·5–18) h, and the mean total estimated blood loss was 13 (range 1·6–55) litres.

In one patient a MMC dosage of 15 mg/m^2 was used, in two patients 30 mg/m^2, in 38 patients 35 mg/m^2 and in the remaining five patients 40 mg/m^2. In one patient the perfusion was stopped after 60 min because of severe diffuse bleeding. In all other patients the perfusion was performed as planned for 90 min. During and directly after the HIPEC procedure the MMC concentration in plasma and perfusion fluid was measured and the area under the curve (AUC) calculated. The mean ratio of perfusate : plasma AUC was 11·5. There was a wide interindividual variability in intraperitoneal MMC concentrations (3·6–25·8 g/ml), independent of the dosage used.

Postoperative course: morbidity and toxicity

The mean hospital stay was 31 (range 16–146) days. Major complications related to operation occurred in 18 patients, resulting in a morbidity rate of 39 per cent: stomach or bowel perforation (ten patients), enteral fistula (six), pancreatitis (one), pulmonary embolism (three), peripheral pressure neuropathy (five), pneumonia (three) and intra-abdominal or wound abscess (four). Eleven patients had to undergo reoperation for postoperative complications. Four patients died in the immediate postoperative period, resulting in an in-hospital mortality rate of 9 per cent. Causes of death were septic shock (three patients; in one case this occurred in combination with grade 4 leucocytopenia) and sudden death probably due to a pulmonary embolism (one patient). One patient developed multiple and persistent enteral fistulas for which he was treated by multiple bowel resections. This resulted in a short bowel syndrome, and the patient required prolonged parenteral feeding at home. All other patients resumed normal enteral feeding. MMC toxicity consisted mainly of bone marrow suppression. Twelve patients developed a grade 1 or 2 leucocytopenia (WHO Common Toxicity Criteria), and in ten patients grade 3 or 4 was observed. Thrombo-cytopenia

Table 1 Characteristics of resections needed to achieve optimal surgical cytoreduction

	Women (n = 27)	Men (n = 19)
Partial gastrectomy	8	12
Ileocaecal resection	16	12
Rectal resection	10	9
Hysterectomy	9	—
Splenectomy	12	12
Cholecystectomy	5	8

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occurred in four patients. Well documented MMC toxicities such as nephrotoxicity and cardiotoxicity were not observed. Prolonged gastric paresis was seen in almost all patients, which delayed oral intake for a mean of 16 (range 5–33) days. This was probably due to the direct toxic effect of MMC and/or hyperthermia. No long-term toxicity related to MMC, such as haemolytic–uraemic-like syndrome, was observed.

Adjuvant chemotherapy and follow-up

Twenty-two patients received systemic chemotherapy with 5-FU–leucovorin after operation. In five of these patients this treatment was stopped because of intolerable toxicity ($n = 4$) or progressive disease ($n = 1$). After a median follow-up of 12 (range 1–43) months, 40 patients are still alive; eight have proven local recurrence. No distant metastases were observed. The mean interval between HIPEC and recurrence was 13 months. One patient died from recurrent disease 26 months after HIPEC; another died from an unrelated cause. The actuarial survival rate (Kaplan–Meier) at 2 and 3 years was 91 and 81 per cent respectively.

Discussion

During the past decade increasing attention was paid to HIPEC as a treatment option in patients with peritoneal carcinosis from different origins, such as colorectal carcinoma, gastric carcinoma, mesothelioma and sarcoma[13–16]. Theoretically, pseudomyxoma peritonei is always limited to the peritoneal cavity and should show no organ infiltration because of its benign character. Therefore, the surgical removal of tumour deposits should be possible and, because of its locoregional character, pseudomyxoma peritonei provides an ideal situation for additional locoregional (i.e. intraperitoneal) chemotherapy. The first clinical report on this treatment modality in pseudomyxoma peritonei was published in 1980 by Spratt *et al.*[8]. A significant survival benefit in patients treated by additional intraperitoneal chemotherapy compared with adjuvant systemic chemotherapy has been observed[11,17,18]. Since then, different treatment schedules have been used with regard to timing and duration of the perfusion, open or closed perfusion models, and the choice and dosage of chemotherapeutic agents. To optimize exposure of the surface of the abdominal contents to the perfusion fluid, peritoneal expansion is applied in some centres. This may be achieved by different methods[19]. In this report, a technique of peritoneal cavity expansion by elevation of the skin of the laparotomy wound using a retractor ring placed above the abdomen is described. The abdominal cavity is kept open, allowing the surgeon's hand to 'stir' the abdominal content during perfusion, resulting in better exposure of the peritoneal surfaces and more uniform distribution of drug and heat through the entire abdominal cavity. MMC was chosen as the chemotherapeutic agent because of its known activity in colorectal cancer, its direct cytotoxic effect, the thermal enhancement of its activity and penetration depth, and its favourable pharmacokinetics in HIPEC procedures[20,21].

Because the penetration depth of cytostatic drugs in tissue is limited, it is generally accepted that HIPEC should be combined with extensive cytoreductive surgery with the aim of leaving only limited macroscopic tumour deposits. Sugarbaker[12] introduced the technique of large peritonectomy procedures with the diathermy knife. The use of this technique combined with an aggressive surgical approach towards affected intra-abdominal organs made it possible to obtain optimal cytoreduction in most patients. However, this ultraradical cytoreductive approach in combination with HIPEC is associated with a significant surgical complication rate. In the series described here, four patients died after operation as a direct result of the treatment, resulting in a mortality rate of 9 per cent. This is comparable to the mortality rate after HIPEC reported by others (of up to 14 per cent) regardless of the technique and indication used[15,19,22–24]. However, the reported morbidity rate of 39 per cent appears to be relatively high compared with that observed by others after HIPEC procedures (up to 36 per cent[22,24]). One of the most important reasons for this is probably that, in this study, most patients had had extensive pretreatment. Postoperative surgical morbidity proved to be related mainly to the number of previous laparotomies and other intraperitoneal therapies, rather than to the intraperitoneal MMC concentration[25]. This finding has been confirmed by others[26]. Thus it seems likely that postoperative mortality and morbidity rates may be reduced substantially when patients are treated by cytoreductive surgery and HIPEC at primary diagnosis. Despite the high morbidity rate encountered, almost all patients had fully recovered by 6 months after operation. Haematological toxicity (bone marrow suppression) was observed in 48 per cent of patients. The latter is a result of the intraoperative chemotherapy and is related to the intraperitoneal MMC concentration. Although in most patients the leucopenia caused no extra morbidity, the combination of bone marrow suppression and surgical complications may be fatal. This was unfortunately demonstrated in one patient. No late toxicity related to MMC perfusion was observed. The significant morbidity associated with this aggressive regional treatment modality is probably one of the reasons for hesitating about the use of HIPEC and cytoreductive surgery in a comparatively benign disease such as pseudomyxoma peritonei. However, because of the poor long-term

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prognosis of pseudomyxoma treated with standard surgical therapy alone, with a 10-year survival rate of 10–30 per cent and considerable disease-related morbidity, the exploration of such an aggressive treatment modality in the search for better long-term results is justified[27].

An actuarial 3-year survival rate of 81 per cent after a median postoperative follow-up of approximately 12 months was observed, regardless of the histological character of the disease. Although the length of follow-up in this study was limited, the results are in accordance with those shown by Sugarbaker and colleagues, who found an overall 5-year survival rate of 60 per cent after HIPEC and radical surgery. When patients were divided into subgroups, these authors reported a 5-year survival rate of 86 per cent in patients with tumours with non-invasive histological features[10,11]. These results suggest that it might be important to look for more accurate (histological) prognostic factors[28].

To determine the precise benefit of HIPEC after radical surgery, randomized studies are needed. However, in a rare disease such as pseudomyxoma peritonei, this seems impossible to realize. The treatment of this condition should be centralized in order to reduce treatment-related morbidity and to improve the length of disease-free survival.

In conclusion, extensive cytoreductive surgery in combination with HIPEC and MMC is an aggressive locoregional therapy in patients with pseudomyxoma peritonei. Although this treatment modality is associated with considerable early postoperative mortality and morbidity rates, long-term results suggest that a better survival may be achieved than with conventional palliative surgery alone.

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