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## Cytoreductive surgery and intraperitoneal chemotherapy for pseudomyxoma peritonei

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**Abstract** *Background and aims:* Surgical improvement can be achieved in selected patients with pseudomyxoma peritonei (PMP) by major cytoreductive surgery and intraperitoneal chemotherapy (IPEC). The purpose of this retrospective study was to analyze morbidity, mortality, and survival following therapy. *Patients and methods:* Between July 1995 and September 2003, 28 patients (mean age 56 years, range 28–79) with PMP were operated on with the aim of complete macroscopical cytoreduction. Surgery was followed by IPEC. *Results:* A macroscopically complete cytoreduction was achieved in 11 patients (40%). The mean operating time was 6 h with a mean of three peritonectomy procedures per patient. Cisplatin (15 out of 28), mitomycin C (6 out of 28) and 5-FU (7 out of 28) were used for the intraoperative chemotherapy. Overall mor-

bidity was 36%. Most frequent surgical complications were digestive fistulae (3 out of 28), abscesses (5 out of 28) and bleeding (2 out of 28). Two patients died postoperatively. Patients with low tumor volume (mean survival time  $78 \pm 11$  vs.  $37 \pm 9$  months,  $p=0.05$ ) and complete cytoreduction ( $73 \pm 10$  vs.  $24 \pm 8$  months,  $p<0.05$ ) had an improved prognosis. *Conclusions:* Cytoreductive surgery combined with IPEC is associated with acceptable morbidity and mortality. Complete cytoreduction may improve survival, particularly in selected patients with PMP who have a low tumor volume, complete cytoreduction, and no organ metastases.

**Keywords** Pseudomyxoma peritonei · Peritonectomy · Intraperitoneal chemotherapy

### Introduction

Pseudomyxoma peritonei (PMP) was first described by Werth in 1884 (cited in [1]) and characterizes a progressive disease with a massive production of mucus in the abdominal cavity. A precise definition of PMP is still difficult and other issues, e.g., site of origin or prognosis, are discussed controversially [2]. However, it seems that most PMPs originate in the appendix and the mucinous ascites and is followed by an increase in abdominal girth with a fatal outcome if no treatment is performed [3].

The traditional treatment approach was based on repeated surgical debulking resections, sometimes com-

bined with chemotherapy, in order to reduce the tumor mass and to remove mucinous ascites [1].

In the 1980s, Sugarbaker established a systematic approach to all affected peritoneal areas by performing parietal and visceral peritonectomy with the aim of complete cytoreduction and cure [4, 5]. These peritonectomy procedures were classified according to the distribution of peritoneal nodules and are well described [6]. The distribution of the nodules follows the flow of the peritoneal fluid to dependent sites such as the pelvis and right retrohepatic space, and to sites of peritoneal fluid resorption. Mobile surfaces, such as the small bowel and its mesentery, may be completely spared [7]. Concomitant,

perioperative intraperitoneal chemotherapy (IPEC) is performed immediately after resection as hyperthermic chemotherapy (HIPEC), using either an open or closed abdomen technique, with mainly cisplatin, mitomycin C, and, recently, oxaliplatin [8, 9].

This aggressive treatment has a rather high morbidity and the most commonly reported complications are anastomotic leakage, peripancreatitis, and small bowel perforation. However, complete cytoreduction and HIPEC result in survival rates of up to 80% after 5 years and 60% after 10 years.

The concept proposed by Sugarbaker has been adopted by several surgical departments, although there is a wide range of proposed alternatives, not only regarding the surgical procedure but also the technique of IPEC, e.g., optimal temperature, closed or open abdomen, cytostatic agent, number of therapies, etc. [8, 10].

Since 1995, cytoreductive surgery and HIPEC have been performed in our institution for several peritoneal surface malignancies. Out of 80 treated patients, 28 patients had a clinical syndrome of PMP. The aim of the present study was to analyze the treatment-related morbidity and survival in these patients focusing on selection criteria for those patients who might be the best candidates for this aggressive treatment concept.

Only one group worldwide has published large series of patients with PMP (National Cancer Institute, Washington, DC) [11]. All other centers reported only on relatively small patient collectives. However, these contribute to a better understanding of the selection criteria, associated morbidity and mortality, or impact on prognosis. To our knowledge, this is the largest German series of PMP treated by cytoreductive surgery and HIPEC presented.

## Patients and methods

A total of 28 patients were treated in the Department of Visceral and Transplant Surgery of the Hannover Medical School between July 1995 and September 2003 due to PMP. The aim of surgery was to remove all visible tumor nodules from the visceral and parietal peritoneum so that only affected peritoneal regions were surgically removed. Cytoreductive surgery consisted of different peritonectomy procedures, as previously described by Sugarbaker [6]. These included omentectomy and splenectomy, left subdiaphragmatic peritonectomy, right subdiaphragmatic peritonectomy, pelvic peritonectomy and sigmoidectomy, and cholecystectomy with lesser omentectomy. Complete cytoreduction was defined as residual tumor nodules of less than 2 mm. The tumor volume was quantified according to the peritoneal cancer index [11].

Following surgery, intraoperative intraperitoneal hyperthermic chemotherapy (HIPEC) was performed using a heat exchanger, two roller pumps, and a heater/cooler unit (Stoekert, Munich, Germany). This was performed as an open procedure with the Coliseum technique using either cisplatin (150 mg/m<sup>2</sup>, over the last 4 years 75 mg/m<sup>2</sup>) or mitomycin C (12.5 mg/m<sup>2</sup>) for 90 min. The median intra-abdominal temperature during the procedure was 41.5°C. Normothermic IPEC consisted of 5-FU (650 mg/m<sup>2</sup>) and was applied if the small bowel was involved to a great extent,

which did not allow any type of resection. After instillation of the chemotherapy solution, the drain was clamped for 24 h.

Patient data were compiled on a database (SPSS, Version 11.5, 2003; Chicago, IL, USA) including epidemiologic, surgical, pathologic, and survival figures. For analysis of postoperative morbidity and mortality, all minor and major complications were included. All hospital deaths were considered. Data of different groups were compared using the Fisher's exact test, mean values using the unpaired or the Welch *t*-test. Survival rates were calculated using the log-rank test (*p*<0.05 was considered statistically significant).

## Results

Demographics for the study population included 17 females and 11 males with a mean age of 56 years (range 28–79). In 24 patients, the originating tumor site was the appendix. However, despite intense histopathological examinations in 4 patients, it remained unclear whether the originating site was the appendix or the ovary. None of the patients had solid organ metastases, but 3 patients had locoregional lymph node involvement.

Out of all 28 patients, 25 patients had previously undergone laparotomy (89%). Most of these patients had one or two abdominal operations in their history (46 and 32% respectively). In addition, 10 patients (35%) had received systemic chemotherapy or immunotherapy prior to admission. The mean time between initial diagnosis and operation in our institution was 15.4 months (range 1–86).

According to the intraoperative tumor extent, the tumor volume was classified as low (peritoneal cancer index <15) in 6 patients and high (peritoneal cancer index >15) in 22 patients.

During peritonectomy, a mean of three procedures per patient were performed. These included omentectomy and splenectomy (11 out of 28), left (12 out of 28) or right (15 out of 28) subdiaphragmatic peritonectomy, pelvic peritonectomy with sigmoidectomy or anterior rectal resection (14 out of 28), and cholecystectomy with lesser omentectomy (11 out of 28). Most of the patients had at least one digestive suture (21 out of 28, 75%). The mean operating time was 6 h (range 2–12) and patients received a mean of four blood units intraoperatively.

Macroscopically complete cytoreduction was achieved in 11 patients (40%). The types of parietal and visceral peritonectomy procedures are illustrated in Table 1.

For intraoperative chemotherapy, cisplatin was used in 15 patients, mitomycin C in 6 patients and 5-FU in 7 patients. If HIPEC was performed (*n*=21, 75%) the mean intra-abdominal inflow temperature was 41.5°C. A second IPEC (normothermic) was given to 9 patients and a third to 3 patients postoperatively.

The mean ICU stay was 15 days (range 1–116), the mean hospital stay 29 days (range 6–116).

**Table 1** Procedures performed with complete cytoreduction in patients with pseudomyxoma peritonei (procedures performed are marked by bullet points)

Number	Omentectomy splenectomy	Left upper quadrant peritonectomy	Right upper quadrant peritonectomy	Lesser omentectomy cholecystectomy	Pelvic peritonectomy/resection of the rectosigmoid	Distal gastric resection	Large or small bowel resection	Adenectomy/ hysterectomy
1	•	•	•	•	•	•	•	
2	•	•	•	•		•	•	
3	•	•	•	•			•	
4			•				•	
5			•	•	•		•	
6	•	•	•	•	•			•
7	•	•	•	•	•		•	
8	•	•	•	•				
9			•	•	•			
10	•	•	•	•	•		•	•
11	•	•	•	•	•		•	

**Table 2** Complications occurring after cytoreductive surgery with hyperthermic and normothermic intraperitoneal chemotherapy respectively

Complication	Number of patients
Surgical complications	
Anastomotic leakage	2
Abscess	5
Postoperative bleeding	2
Small bowel perforation	1
Non-surgical complications	
Pneumonia	5
Systemic sepsis	3
Arrhythmias	1
Neurological complication	1
Grade 3/4 bone marrow toxicity	2
Grade 3/4 renal toxicity	1

The overall morbidity was 36%. The complications are listed in Table 2. To treat postoperative complications, reoperation was necessary in 6 patients (21%) due to anastomotic leakage (2 out of 28), bleeding (2 out of 28), small bowel perforation (1 out of 28) or intra-abdominal abscess (1 out of 28).

Patients with an operating time of up to 8 h had a lower morbidity and mortality compared with those with longer operations (11 vs. 80% and 0 vs. 20% respectively). Ta-

ble 3 demonstrates the differences in patients who did or did not have postoperative complications.

The postoperative mortality was 7% (2 patients). One patient died due to septic shock following anastomotic leakage with peritonitis and 1 patient died because of severe pneumonia and respiratory failure.

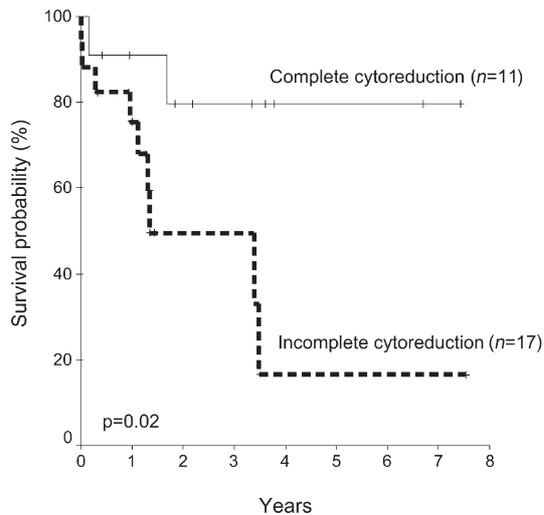
The surgical resection status significantly impacted on survival (Fig. 1). The overall median survival for patients with PMP was 51 months. If a complete cytoreduction could be performed, the mean survival time was 73±10 months versus 26±5 months in patients in whom only a R2 resection state could be achieved. A lower tumor volume also influenced the survival time positively (78±11 vs. 37±9 months,  $p=0.05$ ; Fig. 2)

In cases of laparotomy with no tumor resection the mean survival time was 12±3 months. These patients were more than 60 years of age and had many associated diseases, large tumor volumes, and small bowel infiltration. Even debulking resection was not possible; only IPEC for debilitating ascites could be performed.

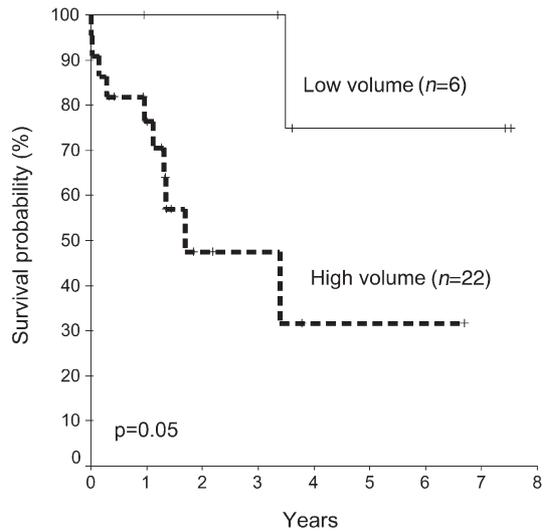
There was no statistically significant survival difference between patients with complete cytoreduction treated using HIPEC with mitomycin C and cisplatin respectively ( $p=0.23$ ). However, this can be explained by the small patient groups that have been analyzed.

**Table 3** Comparison of patients after cytoreductive surgery and intraperitoneal chemotherapy, with or without complications

	No complications ( $n=18$ )	Complications ( $n=10$ )	$p$ Value
Age	56.5	55.6	0.50
Previous laparotomy	16/18	9/10	0.46
Previous immunotherapy or chemotherapy	7/18	3/10	0.29
Peritonectomy procedures (mean)	2±1.5	4±1.6	0.003
Anastomoses	11/18	10/10	0.02
Blood loss (mean)	2.6±3 units	7±6.5 units	0.06
Operating time	4.8±2.3 h	8.1±2.5 h	0.002
Complete cytoreduction	6/18	5/10	0.37
Hospital stay (mean)	20.7±8 days	44.2±35 days	0.06



**Fig. 1** Survival curves following complete and incomplete cytoreduction in patients with pseudomyxoma peritonei.



**Fig. 2** Influence of tumor volume on the prognosis of patients with pseudomyxoma peritonei following cytoreduction surgery and regional chemotherapy.

## Discussion

Until recently, the traditional approach to treating PMP was directed toward palliation in order to delay the lethal outcome of this disease. Sugarbaker pioneered the therapy of peritoneal surface malignancies, introducing cytoreductive surgery in combination with HIPEC [4]. Single-institution data for 400 patients with appendiceal malignancy operated on by him have been reported and the results are encouraging, with an overall 5-year survival rate of 74% [12]. Over the last decade, many centers worldwide have adopted this strategy, with good results, not only for peritoneal carcinomatosis arising from co-

lorectal cancer but also for patients with gastric cancer, ovarian cancer, mesothelioma or sarcoma [9, 13–16]. However, most other series are small and only a few included more than 50 patients.

In 1995, we published our experience with debulking resections for PMP and were disappointed by the high mortality and short survival after debulking resections alone [17]. We then decided to change our treatment concept and started to perform parietal and visceral peritonectomy procedures with the aim of complete cytoreduction followed by HIPEC [18].

Complete cytoreduction succeeded in 40% of the patients in the present series. The mean number of peritonectomy procedures, the number of anastomoses performed, and the mean operating time illustrate the extent of surgery. These data regarding the extent of surgery are in line with other reports published [19, 20]. Over the last few years, we have performed HIPEC only in patients with complete cytoreduction (i.e., residual tumors smaller than 2 mm in diameter). Heat enables chemotherapy to have a supplementary penetration depth of up to 3–4 mm and makes possible the destruction of small residual nodules [8].

The overall morbidity was 36%; digestive fistulae were the most frequent surgical complication. These were probably caused by the surgical trauma of the intestinal wall with seromuscular tears, particularly if intraabdominal adhesions are present [20]. This was the case for 90% of our patients, as they had had prior abdominal surgery. Intraoperative chemohyperthermia does not seem to increase the risk of bowel perforation [21], although small bowel fistulae were reported after closed intraperitoneal heated chemotherapy [19]. Mortality was 7%. As in other series [9, 22], the patients who died had undergone extensive surgery for massive diffuse peritoneal disease. A particularly difficult situation was the occurrence of digestive fistulae associated with bone marrow toxicity. However, similar to other major interventions, morbidity and mortality are increased during the learning curve and decrease with cumulative experience [9, 20]. The patients we lost died within the first 2 years of the present study and we have had no other postoperative deaths since then.

The best survival data can be achieved in patients with PMP, complete cytoreduction, and low peritoneal cancer index. Five-year survival data in these patients are as high as 86% [11]. This is confirmed by our results, showing a 5-year survival rate of 80% after complete cytoreduction and 75% in patients with low tumor volume.

Patients who have extensive disease that needs an operation longer than 8 h not only have a significantly higher morbidity but also a poor prognosis. These patients have an increased risk of recurrence, mainly in the subdiaphragmatic areas and small pelvis [23]. Therefore, patients should be carefully selected for this treatment (low volume disease, no organ metastases, good general

condition) as this has a major influence on the complication rate [24].

The decision process for peritonectomy and HIPEC is difficult for two reasons. First, PMP is a slowly progressing disease with a better prognosis than other colorectal neoplasms and second, the controversial histological definition, which may include both benign mucinous tumors and well-differentiated carcinomas of the appendix [2, 25].

The Sugarbaker procedure is an invasive treatment requiring not only long hospitalization but also a long recuperation phase. However, in studies performed by McQuellon et al. [26, 27], 87% of long-term survivors

after major surgery and HIPEC rated their general health as being good to excellent. There are just a few financial evaluations of this procedure and further research would be valuable in order to find out the cost-effectiveness ratio of the treatment described [28].

Our data indicate that cytoreductive surgery and hyperthermic IPEC for PMP are associated with acceptable mortality and morbidity related mainly to major surgery (with an increased risk of anastomotic leakage and small bowel fistulae). Survival may be improved in selected patients with PMP who have a low tumor volume, allowing complete surgical cytoreduction and no organ metastases.

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