



Perioperative morbidity and quality of life in long-term survivors following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

U. Schmidt^{a,1}, M.H. Dahlke^{b,1}, J. Klempnauer^a, H.J. Schlitt^b, P. Piso^{b,*}

^aDepartment for Visceral and Transplant Surgery, Medical School of Hannover, D-30623 Hannover, Germany

^bDepartment for Surgery, University of Regensburg, D-93053 Regensburg, Germany

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Abstract *Background.* Improved prognosis can be achieved in selected patients with peritoneal carcinomatosis (PC) by major surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).

Method. Sixty seven patients with PC were operated with the aim of complete macroscopical cytoreduction followed by HIPEC (using cisplatin, mitomycin or mitoxantrone). Quality of life was assessed with the EORTC QLQ-C30 questionnaire.

Results. The patients had a variety of primary tumours, including appendix carcinomas (22/67). Mean operating time was 7 hours and complete cytoreduction was achieved in 58% of the patients. Overall morbidity was 34%. Post-operative mortality was 4.5%. The mean score for global health status of long-term survivors (20 questionnaires/25 patients) was 62.6 (73.3 for the control population, $p=0.07$). Functional status, particularly the role (56.4) and the social functioning (53.9) were impaired.

Conclusion. Cytoreductive surgery combined with HIPEC is associated with an increased morbidity and mortality. Complications are predominantly related to major surgery. Following this aggressive treatment, survivors may achieve a satisfactory quality of life.

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Introduction

Peritoneal carcinomatosis (PC) is associated with a poor prognosis.¹ Good long-term results can be achieved in selected patients with gastrointestinal malignancies by a combination of cytoreductive surgery, including parietal and visceral peritonectomy procedures, and intraoperative hyperthermic

* Corresponding author. Tel.: +49 941 9446801; fax: +49 941 9446802.

E-mail address: pompiliu.piso@klinik.uni-regensburg.de (P. Piso).

¹ S.U. and D.M.H. have contributed equally to the study.

intraperitoneal chemotherapy (HIPEC).^{2,3} However, the removal of large tumor masses requires major surgery in a number of cases, leading to long operating time and significant blood loss.

Series of patients treated with this aggressive treatment concept have been reported recently.⁵ These reports show an increased morbidity and mortality. The risk of post-operative anastomotic and small bowel leakage is increased, as is bone marrow toxicity.

Few studies present a detailed analysis of the morbidity and mortality associated with cytoreductive surgery and HIPEC.^{6,7}

The aim of this study was to analyze the post-operative morbidity and mortality of patients treated for peritoneal surface malignancies at our institution and to assess the quality of life of these patients after treatment.

Patients and methods

Sixty seven patients with peritoneal surface malignancies were treated between March 1995 and February 2003 (Table 1).

The aim of surgery was to remove all macroscopically visible tumor nodules from the visceral and parietal peritoneum. Cytoreductive surgery consisted of a variety of peritonectomy procedures, as previously described by Sugarbaker.⁸ These included: omentectomy and splenectomy, left subdiaphragmatic peritonectomy, right

subdiaphragmatic peritonectomy, pelvic peritonectomy and sigmoidectomy, and cholecystectomy with lesser omentectomy. Following surgery, intraoperative intraperitoneal hyperthermic chemotherapy (HIPEC) was performed using a heat exchanger, two roller pumps and a heater/cooler unit (Stoeckert, Munich). This was performed as an open procedure with the Coliseum technique using either mitomycin (11 patients, 12.5 mg/m²), cisplatin (51 patients, 75 mg/m² and 150 mg/m²) or mitoxantrone (5.15 mg/m²) depending on the primary disease.

Patient data were compiled into a database (SPSS, 11.5., 2003) including epidemiologic, surgical, pathologic and survival figures. For the analysis of post-operative morbidity and mortality, all minor and major complications were included. All hospital deaths were considered. Data of different groups were compared with the Fisher's exact test, mean values with either the unpaired *t*-test or with the Welsh *t*-test for unequal variances.

For measuring quality of life a European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30, EORTC Study Group on Quality of Life, Brussels, Belgium) was used.^{9,10} The QLQ-C30 core questionnaire was used because it includes items that address symptoms associated with disseminated peritoneal carcinomatosis. The questionnaire was self-assessed by the patients. The QLQ-C30 questionnaire is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales, a global health status/quality of life scale, and six single items. Each item was assessed as a score ranging from 1 to 4. The total score was calculated as a percentage, with 100% being the highest score possible.

Results

Perioperative course

Most of the patients had undergone one or two laparotomies in their history (32 and 23 patients, respectively). In addition, 26 patients (39%) had received systemic chemotherapy or radiation therapy due to the primary tumor.

A mean of three parietal or visceral peritonectomy procedures (see Section 2) were performed per patient. Most of the patients received at least one digestive suture overall. The mean operating time

Table 1 Characteristics of 67 patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Age	
Mean	52
Range	20-72
Gender	
Male	27
Female	40
Primary site	
Appendix	22
Ovary	15
Colon	7
Peritoneum	4
Stomach	3
Pancreas	3
Unknown (CUP)	3
Liver	3
Small bowel	3
Retroperitoneal sarcoma	2
Uterus	1

was 7 hours (2-20) and patients received a mean of three blood units intraoperatively.

In the group of patients studied in this report, a macroscopically complete cytoreduction could be achieved in 39 patients. For intraoperative chemotherapy, cisplatin was used in 51 patients, mitomycin in 11 patients and mitoxantrone in 5 patients. Median intraabdominal inflow temperature during chemotherapy was 41.5 °C (range 40.2-42.8). A second intraperitoneal chemotherapy (normothermic) was given to 15 patients, a third to 10 patients. The median stay on the intensive care unit was 5 days (1-116 days), the median hospital stay 25 days (6-116 days).

The overall morbidity was 34% (44 patients). The complications are listed in Table 2. Re-operation had to be performed in 15 patients. The extent of surgery was the main factor to differentiate patients with or without complications (Table 3). The morbidity and mortality rate was lower in patients with an operating time of up to 8 hours compared to those with longer operating times (19 vs 60% and 2 vs 8%, respectively).

The overall post-operative mortality was 4.5% (3 patients). One patients died due to peritonitis following small bowel perforation. Another patient died due to pneumonia and the third one due to bone marrow toxicity and septicemia.

Quality of life

At the time of the survey, 25 of the 67 patients were still alive. The questionnaires for life quality assessment were sent to all 25 patients. A total of 20 patients (13 females, 7 males) returned completed forms. The mean time after treatment with surgery and HIPEC at our institution was 4 years

Table 2 Complications occurring after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy ($n=67$ patients)

Complication	<i>n</i>
Anastomotic leakage	6
Pneumonia	6
Abscess	5
Post-operative bleeding	5
Systemic sepsis	4
Small bowel fistula	3
Rectal/duodenal stump leak	3
Pancreatitis	3
Pancreatic fistula	2
Small bowel obstruction	1
Neurological complication	1
Grade 3/4 bone marrow toxicity	2
Grade 3/4 renal toxicity	1

Table 3 Comparison of patients after cytoreductive surgery and intraperitoneal chemotherapy, with or without complications, respectively (significant difference only for * and **)

	No complications ($n=44$)	Complications ($n=23$)
Age	52.5	48
Previous laparotomy	40	21
Previous chemotherapy	18	8
Peritonectomy procedures (mean)	3	4
Anastomoses*	29	22
Blood loss (median)	3 units	6 units
Operating time	6 hours	10 hours
Complete cytoreduction**	26	19
ICU stay (median)	3 days	22 days
Hospital stay (median)	19 days	50 days

* $p=0.01$; ** $p=0.05$.

(range, 1-8 years). Mean age was 51 years (range 20-64 years). Most of them had an appendix carcinoma ($n=11$). Mean operating time had been 7.6 hours (range 2-11 hours). In all 20 patients a mean of 1.5 anastomoses had been performed. Post-operative complications occurred in 11 patients.

The mean score for global health status was 62.6. The 2 patients who received a stoma during operation had a mean score of 16.7 whereas patients without stoma ($n=18$) had a mean score of 67.7.

The results of the functional status and gastrointestinal symptoms (QLQ-C30) are listed in Table 4. These include global health status, functional status and the symptoms of all 20 patients. As reference values were considered those of a general Norwegian population, as published by EORTC.^{9,10} Leading symptoms were fatigue (48.6), insomnia (38.1) and pain (35.6).

Discussion

Peritoneal carcinomatosis originating from gastrointestinal malignancies is a severe condition and the median survival time of these patients is usually limited to 3-9 months.¹ However, in selected patients, particularly with an appendix carcinoma, cytoreductive surgery with parietal and visceral

Table 4 Functional status and gastrointestinal symptoms in patients after peritonectomy and HIPEC compared to control population (general norwegian population) (QLQ-C30)

	All	95% CI		Control	p-value
		Left	Right		
<i>n</i>	20				
Global health	62.6+24,5	51.1	74.1	73.3	0.07
Physical functioning	72.8+34,8	56.5	89.1	89.9	0.04
Role functioning	56.4+34,3	40.3	72.5	83.3	0.002
Emotional functioning	69.3+32,4	54.1	84.5	82.8	0.07
Cognitive functioning	74.8+29,5	61.0	88.6	86.5	0.09
Social functioning	53.9+37,5	36.3	71.5	85.8	0.001
Symptoms					
Fatigue	48.6+32,1	33.6	63.6	28.8	0.01
Nausea/vomiting	10+7,8	6.35	13.7	4.0	0.002
Pain	35.6+34,8	19.3	51.9	20.4	0.06
Dyspnea	24.8+24	13.6	36.0	14.3	0.06
Insomnia	38.1+37,8	20.4	55.8	20.4	0.05
Loss of appetite	9.9+11	4.8	15.0	7.4	0.3
Constipation	21.6+22	11.3	31.9	10.7	0.03
Diarrhea	26.5+23,5	15.5	37.5	9.4	0.004
Financial difficulties	11.6+27	0	24.2	9.0	0.6

peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) may improve the prognosis.¹¹ This aggressive therapy is associated with an increased morbidity and mortality, mainly due to the extended surgery that is required for complete cytoreduction in patients with diffuse peritoneal carcinomatosis. Operations generally last for many hours, the blood loss can be considerable and the general condition of the patients is often poor due to the underlying disease.

In recent years, an increased number of centers worldwide started to perform peritonectomy with HIPEC. An overview of the published data regarding morbidity and mortality is given in Table 5. These

data show an increased morbidity of up to 54% and a mortality of up to 9% for this procedure.

We analyzed the data of 67 patients with peritoneal carcinomatosis treated in our institution. The site of the primary tumor was variable including 11 different entities. However, the largest homogenous group was that of patients with appendix carcinoma.¹⁷

The aim of the operation was complete cytoreduction, and this could be performed successfully in two thirds of our patients. As HIPEC increases the penetration depth of cytostatic agents by 2-3 mm, it should be considered only for patients with complete cytoreduction (restant nodules <2 mm).

Table 5 Literature data to morbidity and mortality published over the last 5 years

Author	Year	Number of patients	Morbidity (%)	Mortality (%)
Stephens ¹²	1999	183	27	1.5
Elias ³	2001	64	54.6	9.3
Culliford ¹³	2001	64	46	0
Pilati ¹⁴	2003	46	35	0
Glehen ⁴	2003	56	28.5	1.7
Verwaal ¹⁵	2003	48	65% grade 3 toxicity 45% grade 4 toxicity	8
Shen ¹⁶	2003	109	36	8
Own data	2003	64	34	4.5

However, we have treated during the learning curve in the first years of the present study all patients by HIPEC, including those after incomplete resection. The main reason to do so was to treat debilitating ascites. The extent of surgery correlated to the mean operating time, the mean number of peritonectomy procedures and numbers of anastomoses performed, and was the main factor to differentiate between patients with or without post-operative complications. Patients with an operating time of up to 8 hours had a lower morbidity and mortality than those with longer operating time (19 vs 60%, and 2.4 vs 8%, respectively). The data regarding the extent of surgery are in line with other published reports.^{12,18} Patients who have an extended disease that needs an operation longer than 8 hours have not only a significant higher morbidity, but also a poor prognosis. 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 complications rate.

The overall morbidity was 34%, similar to other major centres which treat peritoneal carcinomatosis. The most frequent surgical complications were anastomotic leakage, stump leakage and small bowel fistula. These are probably caused by the surgical trauma to the intestinal wall with seromuscular tears during removal of the tumour masses.¹⁸ HIPEC alone does not seem to increase this risk,¹³ although some spontaneous small bowel fistulas were reported after closed intraperitoneal hyperthermic chemotherapy.¹² This may be due to continuous high inflow temperature at a single site. Open chemotherapy e.g. with the Coliseum technique, allows for better heat distribution and should reduce this risk. However, early post-operative chemotherapy within the first five post-operative days, as described by some protocols,^{2,11} with gastrointestinal sutures floating in the chemotherapy solution is considered by others to increase the risk of leakage³ and was abandoned.

Re-operations were performed in 15 patients, which is in line with other published data.^{3,19} Because we performed less stripping of the omental bursa, we had less peripancreatitis, which was a major complication in the largest series published so far.^{11,12}

Morbidity related to chemotherapy is determined by the type of substance used and particularly by the dosage and regimen of administration. We started by using cisplatin in rather high doses (150 mg/m²) and had more renal and bone marrow toxicity, although serious complications such as grade three or four toxicity occurred in 3 patients only. This improved after reducing the doses to

75 mg/m². Over the last 2 years, mainly regimens with mitomycin (12.5 mg/m²) were used with low toxicity. Similar figures were published.^{4,12,14}

Mortality in our study group was 4.5%. As in other series^{3,8} the patients who died had undergone extensive surgery for massive diffuse peritoneal carcinomatosis. However, similar to other major interventions, morbidity and mortality are increased during the learning curve and decrease with cumulative experience.^{3,18} Post-operative deaths occurred during the first years in our study-group. Particularly after having defined appropriate selection criteria (good general condition, no organ metastases, limited peritoneal disease making complete cytoreduction probable), perioperative morbidity could be decreased.

At the time of this study, 25 patients were still alive and an analysis of their life quality could be undertaken. Of these patients, 20 returned the completed questionnaires.²⁰ Quality of life is impaired during the first 6-12 months after peritonectomy.¹⁵ Our patients had a mean time interval of 4 years after operation and HIPEC, as we assessed only long-term survivors.

The EORTC has published data of the QLQ-C30 questionnaire assessing health in the general Norwegian population.^{6,9} These scores allow a comparison with the participants in this study. A comparison with age-matched non-cancer-patient controls would probably have been more accurate. However, we considered the comparison with the general population's norm appropriate for the purpose of our analysis. The score for global health status of the general population was 75.3 as compared to 62.6 in our study group. The difference was not significant ($p=0.07$), however, due to the small patient collective, interpretation should be made very carefully. Particularly because some of the symptoms like nausea or diarrhea were significantly more frequent in operated patients.

Compared to a study assessing the quality of life in patients who underwent a Whipples procedure using the same core questionnaire the score for global health status 1 year post-surgery was less than 40.²¹ In the study performed by McQuellon et al. 87% of long-term survivors after major surgery and HIPEC rated their general health good to excellent.^{6,7} While loss of appetite, weight loss, nausea and vomiting, and financial difficulties were relatively rare in our study collective, major complaints seemed to be fatigue, insomnia and pain, which could be related to depression.⁶

Overall, our data indicate that cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is associated with an acceptable mortality rate. The morbidity rate is rather high and is

related mainly to major surgery.²² In order to decrease morbidity and mortality rates, it is important to perform this major cancer surgery in high-volume oncology centres.²³ Following this aggressive treatment, however, the majority of these very ill patients can return to satisfactory quality of life. Appropriate patient selection may reduce morbidity and mortality associated with this aggressive therapy.

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