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Peritoneal Colorectal Carcinomatosis Treated with Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

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ABSTRACT

Background-Aims: Peritoneal colorectal carcinomatosis is a potentially curative disease. The purpose of the study is the retrospective analysis of survival of the patients with peritoneal colorectal carcinomatosis that underwent cytoreductive surgery and perioperative intraperitoneal chemotherapy and the identification of prognostic variables of the disease. **Patients-Methods:** Patients with primary or recurrent colorectal cancer and peritoneal carcinomatosis were included in the study. Clinical variables were correlated to survival, recurrence, hospital mortality, and morbidity. **Results:** From 2000-2010, 28 patients underwent 33 cytoreductive operations. The hospital mortality and morbidity rate was 9.1% and 45.5% respectively. The overall 5-year and median survival time was 29.2% and 19 months respectively. The extent of peritoneal carcinomatosis ($p = 0.0003$) and the completeness of cytoreduction ($p = 0.0002$) were related to survival. The completeness of cytoreduction ($p = 0.003$) was the single prognostic variable of survival. The recurrence rate was 42.4% and the use of systemic chemotherapy was identified as the single prognostic variable of recurrence ($p = 0.047$). **Conclusions:** Patients with limited extent of peritoneal colorectal carcinomatosis who undergo complete cytoreduction may be offered long-term survival.

Keywords: Colorectal Cancer; Peritoneal Carcinomatosis; Cytoreductive Surgery; Intraperitoneal Chemotherapy

1. Introduction

The liver and the peritoneal surfaces are the most frequent sites of metastatic disease of colorectal cancer in order of sequence [1]. Peritoneal carcinomatosis is not considered a real metastatic disease but only a dissemination of cancer [2,3].

As a consequence colorectal peritoneal carcinomatosis is a potentially curative disease. The macroscopically visible tumor may be resected when maximal cytoreductive surgery with standard peritonectomy procedures is used. Even if the entire macroscopically visible tumor is resected microscopic cancer emboli remain in the abdominal cavity and give rise to secondary tumors if left untreated. The eradication of microscopic tumor is possible with the use of perioperative intraperitoneal chemotherapy [4,5]. The method has been successfully used and has been recently considered the standard treatment for peritoneal carcinomatosis of colorectal cancer origin [6].

The purpose of the study is the retrospective analysis of those patients with peritoneal carcinomatosis of colorectal cancer origin that underwent treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy and the identification of prognostic variables of the disease.

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2. Patients-Methods

From 2000-2010, all patients with colorectal cancer and peritoneal carcinomatosis were included in the study in order to undergo cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. The study was approved by the hospital's ethical committee.

The inclusion criteria were primary or recurrent colorectal cancer with peritoneal carcinomatosis, without liver or other extra-abdominal metastatic disease as assessed from CT-abdominal-thoracic scanning, and whole body bone scanning. Patients with good performance status (>50% according to Karnofsky performance status) were included for surgery. Prior surgical score was assessed, as well as the extent and distribution of the peritoneal carcinomatosis, according to PCI. The completeness of cytoreduction was assessed using the completeness of cytoreduction score

(CC-score) [7]. Complete cytoreductions were considered only CC-0 operations in contrast to CC-1, CC-2, and CC-3 which were considered incomplete cytoreductions. Informed consent was obtained from each patient.

2.1. Treatments

A midline incision from the xyphoid process to the symphysis pubis was used for maximal exposure of the abdominal cavity. The extent of the peritoneal carcinomatosis was assessed intraoperatively after the lysis of adhesions. Maximal cytoreductive surgery was possible using standard peritonectomy procedures. After tumor resection, and before the reconstruction of the continuity of the gastrointestinal tract, hyperthermic intraperitoneal chemotherapy (HIPEC) with the Coliseum technique (open abdomen) was used for the eradication of the microscopic residual tumor. HIPEC was possible with a continuous closed circuit of four drains (two inlet and two outlet) one heat exchanger and two roller pumps connected to the inlet and the outlet drains (Sun-Chip, Gamida-Tech, France) at 42.5˚C - 43˚C for 90 min. Mitomycin–C diluted in 2 - 3 lit of Ringer lactate solution was used for HIPEC. Early postoperative intraperitoneal chemotherapy (EPIC) was possible through a Tenckhoff catheter during the first five postoperative days. 5-FU diluted in 1.5 lit of 1.5% Dextrose was used for EPIC [7].

All patients remained in the ICU for 24 hours after surgery. If EPIC was used the patients remained in the ICU for 5 days. Postoperative complications were recorded and were assessed according to following criteria. The uncomplicated patients were assessed by Grade 0. Grade 1 complications were those that required no intervention or minor intervention such as oral antibiotics, bowel rest or basic monitoring. Grade 2 complications were those that required moderate intervention such as IV antibiotics, prolonged tube feeding or chest tube draining. Grade 3 complications were those that required hospital readmission, surgical or radiological intervention. Grade 4 complications were those producing chronic disability, organ resection, or bowel diversion. Grade 5 complications were those that resulted in death. Grade 1 and 2 complications were grouped as minor and grade 3-5 as major complications.

2.2. Follow-Up

All patients were followed-up every four months during the first year after surgery with physical examination, haematological-biochemical examinations, abdominal and thoracic CT-scanning, and tumor markers (CEA, CA 19-9, CA-125). Recurrences and the sites of recurrence were recorded.

2.3. Statistical Analysis

Statistical analysis was possible using SPSS (Statistical Package for Social Sciences-version 11) statistical software. The Pearson's chi-square test was used to compare parametric data. Univariate survival analysis was possible using the Kaplan-Meier method and the comparison of survival curves was calculated using the log-rank test. Multivariate analysis was possible using the Cox proportional hazards model for the identification of the prognostic variables of survival. Logistic regression analysis was used to identify the prognostic factors of recurrence. A two-tailed p value < 0.05 was considered statistically significant.

3. Results

From 2000-2010, 28 patients with primary or recurrent colorectal cancer and peritoneal carcinomatosis underwent 33 cytoreductive operaqtions. The patients' age was 60.6 ± 13.3 (28 - 82). The primary tumor was located at the colon in 26/28 patients (92.9%) and only in 2 cases (7.1%) at the rectum. As demonstrated in **Table 1** the majority of the patients were in excellent performance status. Complete cytoreductive surgery was possible in 63.6% of the patients although 69.7% had recurrent colorectal cancer and 36.4% of them had previously undergone extensive surgery in more than 5 abdominopel-

Table 1. General characteristics.

	No of patients	%
M/F ratio	9/24	27.3/72.7
Performance status		
90% - 100%	29	87.9
70% - 80%	3	9.1
50% - 60%	1	3
Completeness of cytoreduction		
CC-0	21	63.6
CC-1	8	24.2
CC-2	4	12.1
Prior surgical score		
PSS-0	10	30.3
PSS-1	3	9.1
PSS-2	8	24.2
PSS-3	12	36.4
PCI		
<13	22	66.7
>13	11	33.3
Intraperitoneal chemotherapy		
EPIC	7	21.2
HIPEC	16	48.5
HIPEC+EPIC	10	30.3
Systemic chemotherapy	11	33.3

vic regions. The performed peritonectomy procedures are listed in **Table 2**.

3.1. Hospital Mortality-Morbidity

Hospital mortality was 9.1% (3 patients). During the immediate postoperative period 15 patients (45.5%) developed complications **(Table 3)**. No hematologic toxicity was recorded. Minor complications were recorded in 3 patients (9.1%) and major complications in 12 (36.3%) patients. Morbidity was not found to be related to any variable.

Only 11 patients (33.3%) accepted to receive systemic chemotherapy.

3.2. Survival

The overall 5-year and the median survival rate were 29.2% and 19 months respectively **(Figure 1)**. By uni - variate analysis it was found that survival was related to the completeness of cytoreduction (p = 0.0002) **(Figure 2)**, and to the extent of peritoneal carcinomatosis (p = 0.0003) **(Figure 3)**. Patients that underwent complete cytoreductive surgery had 5-year and median survival 40% and 35 months respectively. Patients that underwent

Table 2. Peritonectomy procedures.

procedure	No
Greater omentectomy	15
Splenectomy	10
Lesser omentectomy	3
Pelvic peritonectomy	22
Right subdiaphragmatic	9
Left subdiaphragmatic	7
Right parietal	14
Left parietal	10
Cholecystectomy+resection of the omental bursa	7
Segmental intestinal resection	5
Subtotal colectomy	9
Antrectomy	1

Table 3. Postoperative complications.

	No of patients	%
Intra-abdominal sepsis	7	21.2
Anastomotic failure	2	6.1
Wound infection	1	3
pancreatitis	1	3
Enterocutaneous fistula	1	3
Deep venous thrombosis	1	3
others	2	6.1

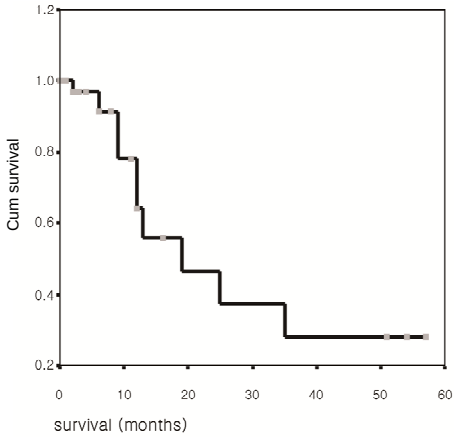

Figure 1. Overall survival of patients treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy.

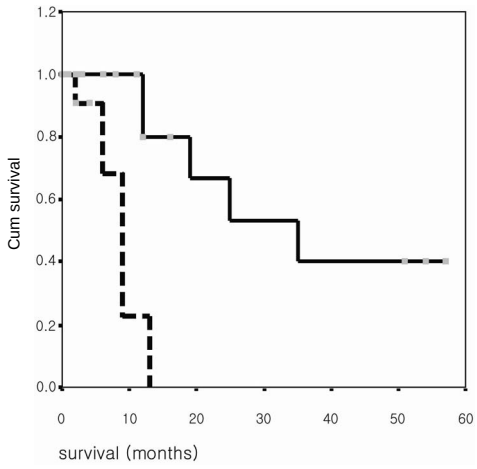

Figure 2. Survival according to completeness of cytoreduction. Survival of patients with complete (CC-0) (continuous line), and incomplete cytoreduction (dotted line) (p = 0.0002).

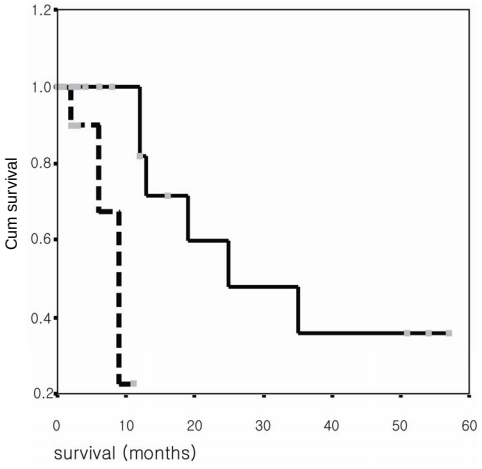

Figure 3. Survival according to the extent of the peritoneal carcinomatosis. Survival of patients with PCI < 13 (continuous line), and PCI > 13 (dotted line) (p = 0.0003).

incomplete cytoreductive surgery had 0% 5-year survival rate and 9 months median survival. However, by multivariate analysis only the completeness of cytoreduction was identified as being prognostic for survival (HR = 12.826, p = 0.003, 95% CI = 2.354 - 69.897).

The median disease free survival was 4.5 months.

3.3. Follow-Up

The median follow-up time was 12 months. During follow-up 14 patients (42.4%) were recorded with recurrence. Eight patients (24.2%) were recorded with loco-regional recurrences and 6 (18.2%) with liver metastatic disease. By univariate analysis it was demonstrated that prior surgical score (p = 0.044) and the use of systemic chemotherapy (p = 0.017) were found to be related to the development of recurrences. By multivariate analysis only systemic chemotherapy was found to be of prognostic significance for the development of recurrence (HR = 1.674, p = 0.047, 95% CI = 1.025 - 27.758).

4. Discussion

Colorectal cancer with peritoneal carcinomatosis was considered an incurable disease three decades ago and these patients usually died because of intestinal obstruction [8, 9]. The last two decades aggressive cytoreductive surgery in combination with intraperitoneal chemotherapy has demonstrated improved results in properly selected patients [10-12].

One prospective randomized trial showed that patients who underwent cytoreductive surgery and HIPEC had significantly higher survival than those who underwent cytoreductive surgery and received systemic chemotherapy [13]. The data have been reconfirmed with a new study evaluating the long-term results of the study [14]. Recently the procedure has been officially documented in the guidelines of the National Institute for Health and Clinical Excellence [6] and has been accepted in the guidelines for colorectal cancer in France [15].

One large retrospective multi-institutional study showed that this procedure is beneficial for patients with limited extent of peritoneal dissemination that undergo complete cytoreduction [16]. These two clinical variables are the most significant prognostic for survival and have been reproduced in the present study. The same study demonstrated that the age <65 years, and the use of systemic chemotherapy were also significant prognostic variables for survival [16]. Since then, systemic chemotherapy has been integrated in the treatment of peritoneal carcinomatosis from colorectal cancer in addition to cytoreduction and intraperitoneal chemotherapy [10] and has been reproduced as being an independent prognostic variable of survival [12]. The integration of systemic chemotherapy during surgery and HIPEC is associated with profound haematological toxicity [17,18]. In the present study no haematological toxicity was recorded because systemic chemotherapy was not used during HIPEC.

The peritoneal cancer index, unfavourable peritoneal sites, synchronous or previously resected liver metastases, and the completeness of cytoreduction were identified in another study as independent prognostic variables of survival [19].

Complete cytoreductive surgery is usually feasible in more than 80% of properly selected patients [12]. Patients with extensive peritoneal carcinomatosis may not be offered complete cytoreduction particularly if the small bowel is extensively seeded. In the present study 33.3% of the patients had extensive peritoneal carcinomatosis with a PCI > 13. However in a few of them complete cytoreduction was possible and CC-0 surgery was performed in 63.6% of the cases. Patients with a PCI more than 20 have an unfavourable prognosis and by many institutions are considered ineligible for surgery because it is likely that they can not be offered complete or near complete cytoreduction [5,10-12,15,20]. It is evident that proper patient selection plays the most important role for long-term survival.

Mitomycin-C is a non-cell cycle specific cytostatic drug that has been used effectively in colorectal cancer [13,14,20] with minimal adverse effects on wound healing. Because of its large molecular weight the drug is retained at the peritoneal surfaces for long, acts intensively, and is an ideal drug for HIPEC. 5-FU is a cytostatic drug that acts during the G_2 phase of the cell cycle. Therefore it is an ideal drug for EPIC but cannot be used during HIPEC. Intraperitoneal chemotherapy can not penetrate more than 2 mm - 3 mm of tumor confined at the peritoneal surfaces which means that it is effective after CC-0 or CC-1 cytoreductive operations.

Although hospital mortality is low, major morbidity rate is reported from several institutions varying from 20% - 66% [5,9-13,15-20]. The most frequent complications are enterocutaneous fistula, anastomotic leaks, intra-abdominal abscess, and hematologic toxicity.

Considering that the median follow-up time was short the recurrence rate in the present study was high (42.4%). This may be related to the small number of patients that agreed to receive systemic chemotherapy once treatment with systemic chemotherapy was identified as the single independent variable of recurrence.

5. Conclusion

Patients with primary or recurrent colorectal cancer with peritoneal carcinomatosis who have limited peritoneal dissemination and undergo complete cytoreductive surgery combined with perioperative intraperitoneal chemotherapy may be offered long-term survival.

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