

# Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis from rectal cancer

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## ABSTRACT

**Aim:** The long-term results of rectal cancer with peritoneal carcinomatosis have been controversial. The purpose of the study is the presentation of the results of cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with rectal cancer and peritoneal carcinomatosis. **Material and Methods:** From 2005-2014, ten patients with peritoneal carcinomatosis of rectal origin underwent cytoreductive surgery with perioperative intraperitoneal chemotherapy. Clinical indicators were correlated to survival, recurrences, morbidity, and hospital mortality. **Results:** Complete cytoreduction was possible in 80% of the patients. The median and the 5-year survival were 13 months and 32% respectively. No variable was found to be related to survival. Morbidity and hospital mortality were 30% and 0% respectively. The median follow-up time was 8.5 months and the recurrence rate 60%. **Conclusions:** Patients with rectal cancer and limited peritoneal dissemination are likely to be offered long-term survival if they undergo complete cytoreduction and perioperative intraperitoneal chemotherapy.

**KEY WORDS:** rectal cancer, peritoneal carcinomatosis, perioperative intraperitoneal chemotherapy, cytoreductive surgery, survival, morbidity, mortality

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## INTRODUCTION

Cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy has been established as the most effective treatment strategy for colorectal cancer with peritoneal carcinomatosis.<sup>1</sup> The results of treatment in patients with rectal cancer and peritoneal carcinomatosis

are conflicting. Some believe that these patients are offered the same survival benefit as those with colon cancer and peritoneal carcinomatosis.<sup>2</sup> Others report that there is no survival benefit even

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when complete cytoreduction is possible, because peritoneal carcinomatosis from rectal cancer is a particularly aggressive disease.<sup>3</sup>

The purpose of the study is to present the results of cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy from one medical center.

## PATIENTS AND METHODS

The present study is a retrospective one of a prospectively maintained database for patients who underwent surgery and perioperative intraperitoneal chemotherapy. From this database the records of the patients with colorectal cancer and peritoneal carcinomatosis that were treated from 2005 to 2014 were retrieved.

Data included age, gender, performance status, extent of prior surgery, extent of peritoneal carcinomatosis, completeness of cytoreduction, comorbidity, chemoperfusion agent, type of intraperitoneal chemotherapy (hyperthermic intraperitoneal-HIPEC, or early postoperative-EPIC), histopathological data, morbidity, mortality, recurrences, and survival. The performance status was assessed according to the Karnofsky performance scale. The extent of peritoneal carcinomatosis and of previous surgery was assessed according to peritoneal cancer index (PCI) and to prior surgical score (PSS) respectively. The completeness of cytoreduction was assessed according to the completeness of the cytoreduction score (CC-score).<sup>4</sup>

The past history of the patients was recorded in detail. All patients were assessed with physical examination, hematological-biochemical examinations, tumor markers, thoracic and abdominal CT-scanning, endoscopy, and, occasionally, whole body bone scanning.

All patients underwent surgery with the intent of complete cytoreduction. The types of peritonectomy procedures, the hospital mortality, the complications, the recurrences and the sites of recurrence were recorded. HIPEC and EPIC

were performed using the same technique described elsewhere.<sup>5</sup> The proportion of patients with a given characteristic was compared with chi-square analysis or Pearson's test. Differences in the means of continuous measurement were tested with the Student's t-test. The survival curves were obtained with the Kaplan-Meier method. A two tailed p value of <0.05 was considered statistically significant.

## RESULTS

The medical records of 74 patients with colorectal cancer and peritoneal carcinomatosis that underwent cytoreduction and perioperative intraperitoneal chemotherapy from 2005-2014 were retrieved. Ten of them (13.5%) were identified with rectal cancer. The general characteristics of the patients are listed in Table 1. The mean age of the patients was 56.7+12.8 (34-73) years. One patient had synchronous tumors of the sigmoid

**Table 1.** Patients' general characteristics

Variable	No of pts	%
Gender (M/F)	4/6	40/60
Performance status		
90-100%	7	70
70-80%	2	20
50-60%	1	10
PSS		
PSS-0	1	10
PSS-1	0	0
PSS-2	8	80
PSS-3	1	10
PCI		
PCI <10	7	70
PCI >10	3	30
CC-score		
CC-0	8	80
CC-1	1	10
CC-2	0	0
CC-3	1	10

and middle rectum and had not previously undergone surgery or any other treatment (PSS-0). The remaining patients had undergone surgery and had received systemic chemotherapy. Two of them had also received radiotherapy. All patients were in acceptable performance status. The extent of peritoneal carcinomatosis was limited (PCI<10) in the majority of the patients. Complete cytoreduction was possible in 8 patients (80%). The local disease was not resectable in one patient who underwent CC-3 surgery and did not receive intraperitoneal chemotherapy. Positive lymph nodes during initial surgery were found in 5 patients and at reoperation in 2 patients. Seven patients with CC-0 cytoreduction received HIPEC while one patient received EPIC. HIPEC and EPIC were administered in one patient who had undergone CC-1 surgery. Three patients that received HIPEC also received IV 5-FU and Leucovorine during surgery.

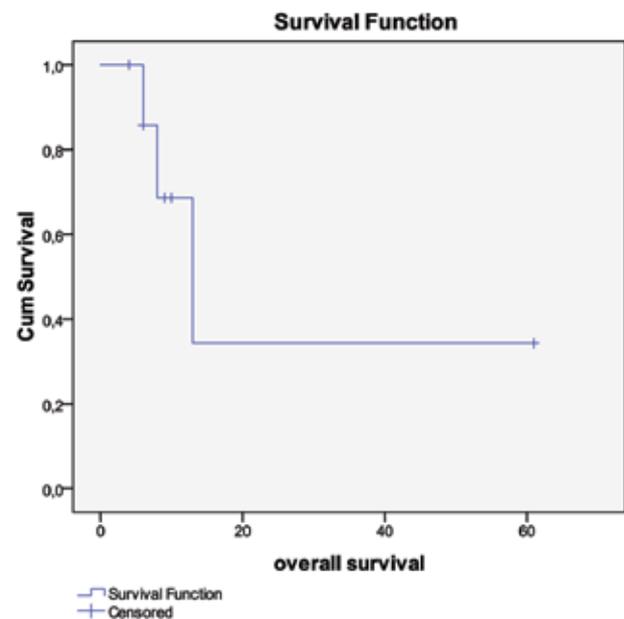
The performed peritonectomy procedures are listed in Table 2. There was no hospital mortality. The morbidity rate was 30%. The recorded complications were: wound infection in one patient, enterocutaneous fistula in one patient, and

**Table 2.** List of peritonectomy procedures

Procedures	No
Epigastric peritonectomy	7
Greater omentectomy	7
Right subdiaphragmatic	3
Splenectomy	1
Lesser omentectomy	1
Cholecystectomy	4
Right lateral peritonectomy	2
Left lateral peritonectomy	1
Pelvic peritonectomy	8
Sub-total colectomy	1
Right colectomy	1
Segmental intestinal resection	3
Abdominoperineal resection	1

an intra-abdominal abscess in another. Neither mortality nor morbidity was found to be related to any one variable by univariate analysis. The mean hospital stay was 15 days (9-25).

The median follow-up time was 8.5 months. The median survival was 13 months and the 5-year survival rate 32% (Figure 1). With univariate analysis no variable was identified to be related to survival. During follow-up 6 patients (60%) were recorded with distant metastases. Currently there are 2 patients alive without disease, 3 patients died because of recurrence, and 5 patients are alive with disease. No variable was identified to be related to disease recurrence.



**Figure 1.** Overall survival in months in patients with rectal cancer and peritoneal carcinomatosis.

## DISCUSSION

Cytoreductive surgery in combination with HIPEC has been established as the standard treatment for colorectal cancer with peritoneal carcinomatosis.<sup>1,6,7</sup> Two prospective randomized trials have shown that this treatment offers significant survival benefit compared to surgery and systemic chemotherapy.<sup>6,7</sup> The incidence of rectal cancer

with peritoneal carcinomatosis is low and varies from 4.4 to 23.3% of colorectal cancer with peritoneal carcinomatosis.<sup>1-3,6-8</sup> Peritoneal carcinomatosis from rectal cancer develops during surgery when the surgeon attempts to remove a tumor lying within narrow limits of resection such as the pelvis. Cancer emboli transected during surgical manipulations from interstitial tissue trauma, or severed lymphatic channels, or venous blood loss are entrapped in peritoneal surfaces. During wound healing, these emboli are deposited by fibrin. Inflammatory cells accumulate while growth factors operate and give rise to loco-regional recurrent tumors.<sup>9</sup> Spontaneous preoperative peritoneal carcinomatosis does not develop because the rectum is an extra-peritoneal organ. It seems that in one patient of the study with synchronous tumors of the sigmoid and rectum that had not previously undergone surgery, peritoneal carcinomatosis developed spontaneously because of the sigmoid tumor.

Peritoneal carcinomatosis from colon and rectal cancer is studied under the term colorectal cancer. Colon and rectal tumors are two distinct entities with different biological behavior. Limited survival of patients with rectal cancer and peritoneal carcinomatosis has been reported in one publication.<sup>3</sup> This finding has not been reproduced by other studies.<sup>2,7,8,10,11</sup> Despite the difference between colon and rectal tumors, it has been shown that the long term survival is the same and depends upon the completeness of cytoreduction, which is the most significant prognostic variable.<sup>1-3,6-8,10,11</sup> In our study the median survival of 13 months is consistent with the survival reported in other studies. The 5-year survival is 32% and one of the highest. The extent of peritoneal carcinomatosis is an equally significant variable of survival. The less the extent of the peritoneal dissemination the longer the survival.<sup>1-3,5-8,11</sup> The PCI is used for the selection of patients that may be candidates for complete, or near complete, cytoreduction. The majority of our patients had low PCI and complete cytoreduction was possible. Patients with high

PCI are not usually candidates for surgery.<sup>2,5-7,11</sup> One of the most frequent sites of recurrence is the bed of the resected tumor. The recurrent tumor is unresectable if it infiltrates anatomical structures such as the iliac vessels or the sacrum, despite the extent of peritoneal carcinomatosis.<sup>10</sup> One patient in our study presented with an unresectable tumor adherent to the sacrum, despite the low PCI. The infiltration of the lymph nodes and the performance status has been identified as a negative prognostic indicator of survival in one publication but has not been reproduced by others.<sup>2,10</sup> The second cytoreduction, the use of systemic chemotherapy, and the ages under 65 years are other variables that have also been identified as prognostic indicators of survival in one retrospective study.<sup>1</sup> The number of patients with rectal cancer and peritoneal carcinomatosis is small in all these publications and definitive conclusions about long-term survival cannot be conducted. The morbidity rate varies from 23 to 63%. The mortality rate is between 0-4%.<sup>1-3,5-8,10</sup> Neither morbidity nor mortality is different from surgery for colon cancer with peritoneal carcinomatosis. In the present study, no variable was found to be of prognostic significance for survival, probably due to the small number of patients it included.

In conclusion, rectal cancer with peritoneal carcinomatosis appears to be similar to colon cancer with peritoneal carcinomatosis in regard to eligibility criteria, survival, morbidity and hospital mortality. Long-term survival is likely to be dependent on the ability of performing a complete cytoreduction in patients with limited extent of peritoneal carcinomatosis.

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