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ORIGINAL ARTICLE

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal carcinomas with peritoneal carcinomatosis

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Summary

Purpose: *Cytoreductive surgery combined with intraperitoneal chemotherapy has been established as the standard treatment for selected patients with peritoneal malignancy. The purpose of the study was the presentation of the 10-year experience with cytoreductive surgery and intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal and appendiceal origin.*

Methods: *Clinical and histopathological variables were retrospectively reviewed in a prospectively maintained database. All patients underwent cytoreductive surgery with the purpose of complete or near-complete cytoreduction. The variables were correlated to survival, and recurrences. Morbidity and hospital mortality were recorded.*

Results: *From 2006-2016 100 patients underwent cytoreductive surgery for colorectal and appendiceal carcinomas with peritoneal carcinomatosis. The hospital mortality and morbidity were 2% and 43% respectively. Completeness of cytoreduction (CC) 0 surgery was possible in 51% of the patients. The median and 10-year survival were 13 months and 23% respectively. The completeness of cytoreduction, performance status and the lymph node status were identified as prognostic indicators of survival. The recurrence rate was 55%. The completeness of cytoreduction, the lymph node status, and the use of postoperative adjuvant systemic chemotherapy were identified as prognostic variables of recurrence.*

Conclusion: *Nearly half of the patients with peritoneal carcinomatosis of colorectal and appendiceal origin may undergo complete cytoreduction and nearly half of them may enjoy long-term survival.*

Key words: *appendiceal cancer, colorectal cancer, cytoreduction, HIPEC, survival*

Introduction

Cytoreductive surgery in combination with intraperitoneal chemotherapy has been proved as a potentially curative treatment in properly selected patients with colorectal cancer and peritoneal carcinomatosis [1-3]. Approximately 5-10% of colorectal carcinomas present with peritoneal carcinomatosis at the time of initial diagnosis [4-6]. Of colorectal cancer patients 20-50% present with peritoneal carcinomatosis during the natural course of their disease as tumor progression or recurrence [4]. Peritoneal carcinomatosis is the result of full bowel-wall invasion of the primary tumor after serosal penetration. The exfoliated cancer cells are distributed within the abdominal cavity and progress in avascular nodules. Systemic chemotherapy is used palliatively in peritoneal carcinomatosis of colorectal cancer origin [7-9]. So, peritoneal carcinomatosis is mostly associ-

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ated with poor prognosis [4,10-12]. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy has shown that both the overall survival and the disease-free survival rate are significantly improved in properly selected patients with peritoneal carcinomatosis [10,13]. Currently, this treatment strategy is considered the standard of care for patients with peritoneal carcinomatosis of colorectal origin in many countries [14].

The purpose of this study was the presentation of a 10-year experience in cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of appendiceal and colorectal origin.

Methods

The records of all patients with peritoneal carcinomatosis of colorectal and appendiceal origin were retrospectively reviewed in a prospectively maintained database. The protocol was approved by the Ethics Committee of the hospital and informed consent was signed by all patients.

Inclusion criteria

Patients with: a) acceptable Karnofsky performance status (Karnofsky scale >50%), b) normal liver and renal function, c) normal hematological and serum profile, d) no evidence of other malignancy or at risk for recurrence, except for basal cell carcinoma or *in situ* cervix cancer properly treated, e) age between 16 and 80 years, and f) satisfactory cardiopulmonary function were considered eligible for maximal cytoreductive surgery and hyperthgermic intraperitoneal chemotherapy (HIPEC).

Exclusion criteria

Patients with: a) metastatic and unresectable disease at distant sites, b) abnormal liver function, c) blood urea level > 50mg/dl or creatinine level >1.5mg/dl, d) white blood cell count <4000 and platelets <100000, e) recent myocardial infarction or cerebrovascular accident, f) severe chronic or recent acute pulmonary disease, and g) performance status < 50% were considered ineligible for cytoreductive surgery and HIPEC.

Performance status was assessed using the Karnofsky performance scale. The extent of previous surgery and the extent of peritoneal carcinomatosis were assessed using the prior surgical score (PSS) and the peritoneal cancer index (PCI) respectively, while the completeness of cytoreduction was assessed with the CC score [15].

Operational methods and intraperitoneal chemotherapy

All patients underwent surgical exploration with midline incision from the xiphoid process to the symphysis pubis. After lysis of adhesions the PCI was calculated. Cytoreductive surgery was possible using standard peritonectomy procedures. Resection of other viscera was also recorded in order to achieve the best surgical result.

Intraperitoneal chemotherapy was administered as HIPEC with the open abdominal technique (Coliseum), and as early postoperative intraperitoneal chemotherapy (EPIC). HIPEC was performed for 90 min at 42.5-43°C with Mitomycin-C at a dose of 20 mg/m^2 after tumor resection and before the reconstruction of the alimentary tract. A heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and four thermal probes was used for HIPEC (Sun Chip, Gamida Tech, Villejuif, France). A prime solution of 3 lit of normal saline was instilled prior to the administration of the cytotoxic drug. As soon as the mean abdominal temperature exceeded 40°C the cytotoxic drug was administered in the abdominal cavity. During perfusion, adequate fluids were infused in addition to dopamine 3 μg/kg, in order to maintain diuresis at 500 ml/h. Dopamine was also used for 24 hrs after the operation at the same dose to maintain diuresis at the same levels. The reconstruction of the alimentary tract was possible after the completion of HIPEC. After 2008 all patients received additionally 5-FU (400mg/m^2)+leucovorin (20mg/m^2) i.v. during surgical manipulations. EPIC was possible through a Tenckhoff catheter during the first 5 postoperative days using 5-FU (400-600mg/m^2)+$NaHCO_3$ (50mg) diluted in 1.5 lit of dextrose 1.5%.

Hospital morbidity and mortality was recorded and classified according to Clavier-Dindo classification [16]. During the immediate postoperative period, all patients stayed in the intensive care unit (ICU) for 24 hrs. The patients remained for 5 days in the ICU if EPIC was used. All surgical specimens were histopathologically examined in detail. For appendiceal carcinomas, the peritoneal mucinous adenocarcinomas (PMCA) or those of intestinal type were included. Specimens with diffuse peritoneal adenomucosinosis (DPAM) were excluded from the analysis.

All patients were followed-up in 3 month-intervals during the first year, and in 6 month-intervals later with physical examination, hematological-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), and radiologic examinations, preferably abdominal and thoracic CT scan. Recurrences and the sites of recurrence were recorded.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences version 17.0 (SPSS). The proportions of patients with a given characteristic were compared by chi-square test or by Pearson's test. Differences in the means of continuous measurements were tested by the Student's *t*-test. The survival curves were constructed using the Kaplan-Meier method, and the comparison of curves was carried out using the log-rank test. Cox regression analysis made possible multiple analyses of survival and logistic regression analysis made possible multiple analyses of recurrence and morbidity. A two-tailed p value <0.05 was considered statistically significant.

Results

From 2006 until 2016, 100 colorectal and appendiceal cancer patients with peritoneal carcinomatosis underwent cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. The general characteristics of the patients are listed in Table 1. All patients were identified with peritoneal carcinomatosis but without distant metastases. The mean patient age was 57.9+13.4 years (range 23-81). HIPEC was administered to 73 patients (73%), 9 of them received also EPIC, and 27 received 5-FU+leucovorin i.v. during surgery before the administration of HIPEC. Twenty-six patients who underwent incomplete cytoreduction (CC-3) did not receive intraperitoneal chemotherapy. One more patient who underwent CC-0 surgery did not receive intraperitoneal chemotherapy because of intraoperative complications (massive intraoperative bleeding). Systemic adjuvant chemotherapy was given to 72 patients approximately one month after surgery.

Table 1. Patient and disease general characteristics

Characteristics	*n*	%
M/F	44/56	
Karnofsky performance status (%)		
90-100	65	65
70-80	29	29
50-60	6	6
Lymph node status		
Positive	72	72
Negative	28	28
Tumor volume		
Large	98	98
Small	2	2
PCI		
0-13	46	46
14-20	10	10
21-39	44	44
PSS		
PSS 0	14	14
PSS 1	16	16
PSS 2	60	60
PSS 3	10	10
CC		
CC 0	51	51
CC 1	23	23
CC 2	2	2
CC 3	24	24
Anatomic distribution		
Appendix	15	15
Colon	75	75
Rectum	10	10
Infiltrated lymph nodes	72	72
Signet-ring histology	58	58

M: male, F: female, PCI: peritoneal cancer index, PSS: prior surgical score, CC: completeness of cytoreduction

Hospital morbidity-mortality

The incidence of hospital morbidity was 43% (43 patients). Grade 1,2,3,4 complications were 11, 6, 5 and 21%, respectively. The incidence of hospital mortality (30-day) was 2% (2 patients).

Survival

The median survival was 13 months. Five and 10-year survival rate was 23% (Figure 1). By univariate analysis, performance status, extent of previous surgery, extent of peritoneal carcinomatosis, completeness of cytoreduction, status of the resected lymph nodes, and the signet-ring cell histology were identified as the factors that were related to survival (Table 2). CC-0 surgery was possible in 51 (51%) patients. Median and

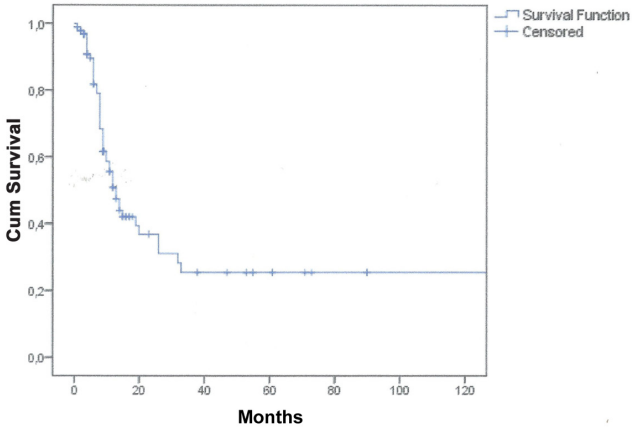

Figure 1. Overall 5- and 10-year survival rate.

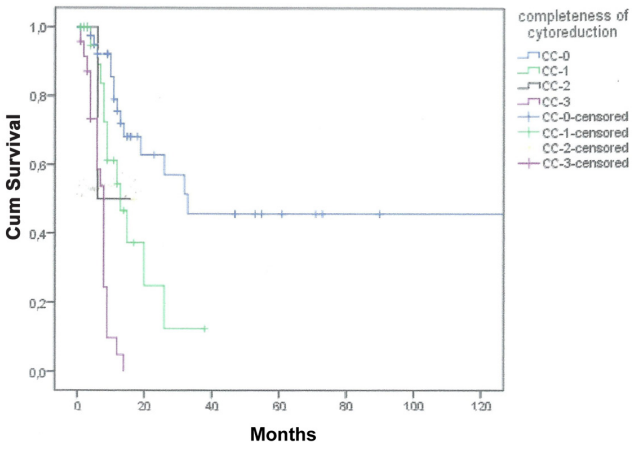

Figure 2. Survival in relation to completeness of cytoreduction score (p<0.01).

5-year survival for CC-0 surgery was 33 months and 43%, respectively. CC-1 surgery was possible in 23 (23%) of the cases. The median and 5-year survival was 13 months and 16%, respectively. The median survival for incomplete surgery (CC-2 and CC-3) was 6 months. The 1-year survival rate for CC-2 and CC-3 surgery was 50 and 13%, respectively (Figure 2). By multivariate analysis, completeness of cytoreduction, performance status and the lymph node status were identified as prognostic indicators of survival (Table 2).

Follow-up

The median follow-up time was 24 months. During follow-up 55 patients (55%) recurred. Local-regional recurrences were recorded in 16 (16%) patients and distant metastases in 39 (39%) patients. Univariate analysis showed that completeness of cytoreduction, lymph node status, use of adjuvant systemic chemotherapy and the signet-ring cell histology were related to the development of recurrence (Table 3). Completeness of cytoreduction, lymph node status and the use of adjuvant systemic chemotherapy were identified as prognostic indicators of recurrence by multivariate analysis (Table 3).

Discussion

Cytoreductive surgery in combination with intraperitoneal chemotherapy has been proved to be the only treatment that may offer significant survival benefit in patients with peritoneal carcinomatosis of colorectal and appendiceal cancer origin [1,17]. This treatment may achieve median and 5-year survival 46 months [10] and 51% respectively [13]. Despite the large number of published papers that emphasize the outstanding results of cytoreductive surgery in combination with intraperitoneal chemotherapy only 5% of patients with peritoneal carcinomatosis are currently treated in this way in contrast to more than 90% of them who undergo palliative treatment with systemic chemotherapy combined with a biological agent [17].

Numerous studies point out that only properly selected patients may be offered a survival benefit from cytoreductive surgery. In general, patients with acceptable performance status, less than 70 years of age, who may undergo major surgery in addition to those with normal renal and hematological status are eligible for cytoreductive surgery and intraperitoneal chemotherapy [18,19]. The presence of extraabdominal metastasis or massive retroperitoneal infiltration of the lymphatic network are rigid exclusion criteria for cytoreductive surgery [18]. Despite advances in imaging techniques proper patient selection is not entirely possible. The reliability and accuracy of the radiologic examinations is limited to about 60-65% since small nodules (<2.5mm) cannot be preoperatively identified. These lesions are identified only intraoperatively. On the other hand, there is a respectable number of patients with peritoneal carcinomatosis that present with bowel obstruction and require urgent

Table 2. Analysis of survival

Factors	*Univariate*		*Multivariate*	
	p value	*HR*	*p value*	*95% CI*
Performance status	<0.001	6.465	0.011	1.161-3.168
Lymph node status	<0.001	5.766	0.016	0.091-0.784
CC score	<0.001	20.523	<0.001	1.417-2.413
Prior surgical score	0.001			
Peritoneal cancer index	<0.001			
Adjuvant chemotherapy	<0.001			
Signet-ring histology	<0.001			

CC: completeness of cytoreduction, HR: hazard ratio, CI: confidence interval

Table 3. Analysis of recurrences

Factors	*Univariate*		*Multivariate*	
	p value	*HR*	*p value*	*95% CI*
Completeness of cytoreduction	0.001	4.426	0.035	0.319-0.960
Adjuvant chemotherapy	<0.001	9.181	0.002	1.931-21.507
Lymph node status	<0.001	4.621	0.032	1.119-11.385
Signet-ring histology	0.05			

For abbreviations see footnote of Table 2

operation. Under these circumstances it is easily explained why 24% of the patients underwent CC-3 surgery.

The completeness of cytoreduction has been documented as the most significant prognostic indicator of survival [1-4,10,13]. In a meta-analysis, it has been shown that after complete cytoreduction the median survival ranged from 11 to 62 months while after incomplete cytoreduction it ranged from 2.4 to 32 months [20]. In the present study, the learning curve of the authors was partly taken into account. The first 23 consecutive patients compised a small group of patients of the learning curve of the corresponding author (dr. Tentes) and as a consequence the results are not the best. Nevertheless, median survival for CC-0 was 33 months and 5-year survival 43%. Median and 5-year survival for CC-1 was 13 months and 16%, respectively. The median survival for incomplete surgery (CC-2 and CC-3) was 6 months and no patient with CC-3 surgery survived longer than 1 year.

Complete cytoreduction is not always possible. In a multicentric French study complete cytoreduction has been achieved in 84% of the included patients [3]. Extensive peritoneal dissemination at the peritoneal surfaces of the small bowel and its mesentery is the most important caveat for the performance of complete cytoreduction. A retrospective study showed that limited extent of peritoneal carcinomatosis was strongly related to survival [2] although the precise cut off point of peritoneal dissemination was not clearly defined. An older publication reported that the disease stage was strongly related to survival. Although the extent of peritoneal dissemination was assessed with the Gilly staging system which is similar but not identical to PCI, the authors clearly indicated that patients with extensive peritoneal dissemination had significantly worse prognosis than those with limited extent [4]. Other publications reproduced the same results [1,21] indicating that patients with PCI more than 20 had no chance to survive more than 5 years. The French multicentric study showed that cytoreductive surgery in patients with PCI>20 was meaningless because it did not improve survival at all [3]. As a consequence, the extent of peritoneal carcinomatosis has been established as one of the most significant prognostic indicators of survival. The accurate assessment of the extent and distribution of peritoneal dissemination using imaging techniques is not always possible preoperatively. Especially for those patients that have undergone previously extensive surgery and diagnostic laparotomy it is not possible and the extent of peritoneal carcinomatosis is assessed during laparotomy. Frequently, patients with peritoneal carcinomatosis are referred for surgery when systemic chemotherapy has been aggressively and ineffectively used, either after initial incomplete surgery or at initial diagnosis. All the above are reasons explaining why only 51% of the patients of the present study underwent complete cytoreduction.

Another equally significant indicator of survival has been shown to be the anatomic distribution of the tumor with the appendiceal malignancy which is less aggressive disease than colorectal malignancy. A number of publications has demonstrated that appendiceal tumors have significantly better prognosis than colorectal tumors [13,22-24]. In addition, incomplete cytoreduction in patients with appendiceal tumors has shown that there are long-term survivors. It has also been shown that intraperitoneal chemotherapy after cytoreduction may be used effectively in patients with CC-2 surgery improving survival [25]. In one study patients with appendiceal carcinomas have been shown to have the same survival as patients with colorectal carcinomas which is in concordance with our results [1].

The presence of infiltrated lymph nodes has a significant negative impact on survival [2,3,22,23]. This finding has been debated for appendiceal cancer [26]. Infiltration of the lymphatic network is a systemic disease with worse prognosis than local disease. The results of our study have reconfirmed that the infiltration of lymph nodes is a prognostic indicator of survival regardless of the anatomic distribution of the tumor.

Another variable that has been given limited attention in the international literature is the patients' performance status. It has been shown that performance status is related to long-term survival [24] and this has been reaffirmed in our study. The use of adjuvant systemic chemotherapy has also been identified as a prognostic indicator of survival [2,3]. Systemic chemotherapy has been shown to be a prognostic indicator of recurrence but has no impact on long-term survival in our study. There is high evidence that 3-4 cycles of neoadjuvant chemotherapy administered in candidates for surgery may have a positive effect. If the patient responds to neoadjuvant chemotherapy, then surgical resection becomes easier and the operation more radical. Bidirectional chemotherapy has been implemented and appears to be safe with minor side effects and effective in patients with peritoneal carcinomatosis [27]. The purpose of this treatment is the eradication of both microscopic residual tumor at the peritoneal surfaces as

well as of microscopic emboli that have entered the systemic circulation.

Our current policy in the treatment of peritoneal carcinomatosis of colorectal origin is the administration of Mitomycin-C intraperitoneally combined with i.v. infusion of 5-FU+Leucovorin or Isovorin that has been in use since 2008. No hematological toxicity has been recorded with the doses used. Grade 4 complications of the present study (21%) are higher than those recently reported in the literature which have decreased in the last few years from 25% to 17% [28,29]. It is obvious that the learning curve of the method plays a crucial role in morbidity [3]. Our results of the 2000-2010 study included 28 patients with 9.1% hospital mortality and 36.3% major morbidity [30]. Although a number of patients in this publication was included in the present study it is obvious that both hospital mortality and major morbidity have improved to 2% and 21% respectively.

Despite significant improvements in hospital morbidity and mortality, only half of the patients with peritoneal carcinomatosis of colorectal and appendiceal origin may undergo complete cytoreduction and nearly half of them may be long-term survivors.

Conflict of interests

The authors declare no conflict of interests.

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