Cytoreductive approach to peritoneal carcinomatosis originated from colorectal cancer: turkish experience

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Peritoneal carcinomatosis (PC) in contrast to lymph nodes and liver metastases was assumed as a terminal condition with no curative treatment options having a 5 to 9 months median survival rate until recently. Today, in properly selected patients, curative surgical treatment of PC is possible like resection of lymph nodes and liver metastases. Between 1996 and 2005, 29 patients who underwent cytoreductive surgery combined with intraperitoneal chemotherapy for PC originated from colorectal cancer (CRC) were analysed prospectively at the Department of Surgery in Dokuz Eylül University Hospital. Mean age was 54 year (range, 23-75 years). There was no perioperative mortality in 29 patients. The morbidity rate was 41% (12/29) and 6 (20%) patients required reoperation(s) for major complications. Mean and median survival time was 34 and 21 months, respectively. The overall 1-year, 3-year, and 5-year survival rates were 72%, 13%, and 7%, respectively. Mean survival time was 56 months in patients with peritoneal cancer index (PCI) <10, and 22 months in patients with PCI >10 \( (P=0.075) \). The mean survival time was 62 months in patients with complete cytoreduction (CC)-0 score, 21 months in patients with CC-1 score, and 7 months in patients with CC-2 and 3 scores. Patients who had CC-0 score had better survival than patients having CC-1 and CC-2 scores \( (P = 0.003 \text{ and } P = 0.000, \text{ respectively}) \). Patients who had CC-0 and 1 scores had better survival than patients with CC-2 score \( (P = 0.000) \). The overall 1-year, 3-year, and 5-year survival rates for patients with CC-0 score were 87%, 37%, and 25%, respectively. There was a positive correlation between the PCI and CC score \( (P = 0.001, \text{ correlation coefficient } = 0.585 \text{ with correlation is significant at level } 0.01) \). Cytoreductive approach combined with intraperitoneal chemotherapy and systemic chemotherapy prolongs survival in selected patients with PC of CRC with acceptable morbidity and mortality. Prognosis is better in patients with limited disease and in whom complete cytoreduction is achieved. In patients with PC of CRC, the key issue is to select the patients in whom complete cytoreduction is feasible. Better patient assessment with new diagnostic tools such as (PET)-CT or PET-magnetic resonance imaging will be used to detect more precisely the patients with low tumor burden in the new feature.

Key words: preperitoneal carcinomatosis, cytoreductive surgery, colorectal carcinoma

INTRODUCTION

Colorectal cancer (CRC) disseminates via three routes; lymphatic, hematogenous (mainly liver), and peritoneal spread. In patients with CRC, metastases at the time of primary resection are seen 50% in the regional lymph nodes, 20% in the liver, and 10% in the peritoneal surfaces. Peritoneal carcinomatosis (PC) in contrast to lymph nodes and liver metastases was assumed as a terminal condition with no curative treatment options having a 5 to 9 months median survival rate until recently. However, Sugarbaker introduced radical cytoreductive oncological surgical approach with intraperitoneal chemotherapy which increased the 5-year survival rates up to 50% for selected patients with colorectal cancer. Now, in properly selected patients, curative surgical treatment of PC is possible like resection of lymph nodes and liver metastases. With combined approach, that includes peritonectomy procedures and intraperitoneal chemotherapy, PC is no longer considered evidence of incurable disease.

PATIENTS AND METHODS

Between 1996 and 2005, patients who underwent cytoreductive surgery for PC originated from CRC were analysed prospectively at the Department of Surgery in Dokuz Eylül University Hospital. After assessing the patients' preoperative characteristics and evaluating the preoperative risk for surgery, computed tomography of chest,
abdomen and pelvis with intravenous, oral, and rectal contrast were performed. Therefore the extent of the disease and systemic metastases were documented. A preoperative exclusion criterion for curative intent cytoreductive surgery was presence of long distant metastasis (like liver, lung).

In the operating theatre, to assess the tumor extent intraoperatively, peritoneal cancer index (PCI) which divides the peritoneal surfaces into 13 parts as described by Sugarbaker (central, right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank, upper jejunum, lower jejunum, upper ileum, and lower ileum) was used. This index is a clinical integration of both peritoneal implant size and distribution of peritoneal surface malignancy. For each of 13 regions, a lesion score (LS) ranging from 0 to 3 according to the tumor size was determined to assess the PCI. In patients with PCI \(<10\), the disease was graded as mild and in patients with PCI \(>10\) the disease was graded as severe.

Treatment of PC consisted of in 3 modalities; cytoreductive surgery (peritonectomy procedures and visceral resections), early postoperative intraperitoneal chemotherapy (EPIC), and postoperative systemic chemotherapy (SCT).

**Cytoreductive Surgery**

The aim of the cytoreductive surgery (CRS) is to remove, if possible, all visible tumors within the peritoneal cavity. A combined approach of parietal and visceral peritonectomy consisted of one to six peritonectomy procedures in conjunction with visceral organ resections (Table 1).

Peritonectomy and organ resections were performed only on sites with tumor deposits. The normal peritoneum and organs were left in place. If resection was not feasible, then the aim was reframed to leave no tumor thicker than 2.5 mm; because, this is the maximum penetration depth of intraperitoneal chemotherapeutic agent.

The extent of cytoreduction was assessed by the completeness of cytoreduction (CC) score at the end of the surgery (Table 2). CC-1 is a nodule size thought to be penetrable by intraperitoneal chemotherapy. CC-0 and CC-1 are considered as complete cytoreduction while CC-2 and CC-3 cytoreductions incomplete as described previously.

**Intraperitoneal Chemotherapy**

In general, intraperitoneal chemotherapy (IPC) was composed of perioperative intraperitoneal heated chemotherapy and/or early postoperative intraperitoneal chemotherapy (EPIC). However, in the present series, we performed intraoperative non-heated chemotherapy and EPIC. After the completion of resective procedures, the chemotherapeutic agent, 5-FU, 1000 mg, in 2 litres of 1.5% dextrose peritoneal dialysis solution was applied into the peritoneal cavity for 20 minutes and conducting surgeon continuously manipulated the fluid and gauzed debrises. Reconstructive surgery was performed after intraoperative chemotherapy. Four closed suction drains (right subhepatic space, left and right subdiaphragmatic space, and pelvis) and a Tenckhoff catheter (beneath the loops of small bowel) were placed through the abdominal wall. An immediate postoperative abdominal lavage at the day of surgery with 1 litre 1.5% dextrose peritoneal dialysis solution (warmed to body temperature prior to instillation) with no dwell time and drained by gravity through the Tenckhoff catheter and abdominal drains. Irrigations were repeated every one hour for four hours, and every four hours until the fluid returns clear; then every 8 hours till the administration of EPIC. In postoperative days one to five EPIC was given by the Tenckhoff catheter, dwelled for 23 h and drained for 1 h prior to next instillation (750 mg/m² per day 5-FU and 50 mEq sodium bicarbonate in 1 litre of 1.5% dextrose peritoneal dialysis solution).

**Systemic Chemotherapy**

5-FU based regimens were administered postoperatively (after discharging the patients) for six months.

**Statistical Method**

Quantitative variables are expressed as median and range. Relationship between qualitative variables was compared by the chi-square test or by two-tailed Fisher’s
exact test where appropriate and between quantitative variables by Pearson’s correlation or Spearman’s ranks correlation. The comparison of mean and median values of quantitative variables was compared by Student’s t-test and Mann-Whitney U test, respectively. Overall survival from the date of operation was calculated by the Kaplan-Meier estimate. The univariate association between clinicopathologic variables and overall survival were estimated by the log-rank test. Standard probability cut-off, $P < 0.05$, was chosen as the significance level.

**Follow-Up**

All patients followed-up with a standard protocol; seen once every 3 months in the first two years, once every 6 months in the third year, and annually thereafter. Follow-up visits of patients included history, clinical examination, serum carcinoembryonic antigen in every three months, abdominopelvic CT in every 6 months, chest X-ray and endoscopy annually.

### RESULTS

During the period of 1996 and 2005 we performed cytoreductive approach in 29 patients with PC originated from CRC. Mean age was 54 year (range, 23-75 years). The female: male ratio was 0.6. In 25 patients (86%) primary tumor was located in colon, and in 4 patients (14%) in rectum. The PC was synchronous in 17 (59%) patients while as metachronous in 12 (41%) patients.

**Surgical Treatment**

Organs resected during peritonectomy procedures were summarised in Table 3.

**Complications and Peroperative Mortality**

There was no peroperative mortality in 29 patients. The morbidity rate was 41% (12/29) and 6 (20%) patients required reoperation(s) for major complications.

**Follow-Up**

Mean follow up time was 24 months (range, 2-101 months). Seventeen (58.6%) patients died postoperatively. Sixteen patients died due to tumor-related causes, and one patient had expired because of pneumonia.

**Survival**

Mean and median survival time was 34 and 21 months, respectively. The overall 1-year, 3-year, and 5-year survival rates were 72%, 13%, and 7%, respectively.

Mean survival time was 56 months in patients with PCI $\leq$10, and 22 months in patients with PCI $>10$ ($P = 0.075$) (Figure 1).

The mean survival time was 62 months in patients with CC-0 score, 21 months in patients with CC-1 score, and 7 months in patients with CC-2 and 3 scores (Table 5). Patients who had CC-0 score had better survival than patients having CC-1 and CC-2 scores ($P = 0.003$ and $P = 0.000$, respectively). Patients who had CC-0 and 1 scores had better survival than patients with CC-2 score ($P = 0.000$) (Figure 2). The overall 1-year, 3-year, and 5-year survival rates for patients with CC-0 score were 87%, 37%, and 25%, respectively.

We found a positive correlation between the PCI and CC score ($P = 0.001$, correlation coefficient = 0.585 with correlation is significant at level 0.01).

**DISCUSSION**

Peritoneal carcinomatosis from colorectal origin should not be considered as an incurable disease. Today, cytoreductive surgery combined with intraperitoneal chemotherapy is a promising therapy for PC of colorectal origin. To date, 20 clinical studies (three of them were controlled) have been published reporting the CRS and IPEC-IPCH results of patients with PC of colorectal origin. These studies verified the efficacy of CRS and IPEC-IPCH. The results in terms of survival after CRS and IPCH appeared much better than those obtained in historical controls.
In a multi-institutional study from 28 centres including 506 patients, with a median follow-up time of 53 months, the 5-year overall median survival was 19% with CRS combined with IPC for CRC. The survival of patients who had complete cytoreductive surgery (CC-0) was 32 months compared with 8 months in whom complete cytoreduction was not possible (P<0.001). Limited disease (PCI <13), low CC score, age <65, female gender, second-look surgery, and postoperative systemic chemotherapy were found to be independent prognostic factors prolonging survival.

Survival rates for patients with CC-0 and/or CC-1 scores in different series including our results are summarised in Table 6. Our study showed shortened 5-year survival presumably due to lacking of intraoperative heated chemotherapy facility. In addition, the patients in our series were not highly selected cases. The only exclusion criterion for surgery was distant metastasis.

This study pointed out that there was a positive correlation between the PCI and CC score. This clear evidence showed that patient selection is one of the crucial factors for the successful outcome. Sugarbaker proposed preoperative radiological exclusion criteria according to CT findings as bowel segments obstructed by tumor, mesentry drawn together by tumor, and tumor greater than 5 cm located in small bowel mesentery. Hopefully, better patient assessment with new diagnostic tools such as (PET)-CT or PET-magnetic resonance imaging will be used to detect more precisely the patients with low tumor burden in the new feature.

CONCLUSION

Cytoreductive approach combined with intraperitoneal chemotherapy and systemic chemotherapy prolongs survival in selected patients with PC of CRC with acceptable morbidity and mortality. Prognosis is better in patients with limited disease and in whom complete cytoreduction is achieved. In patients with PC of CRC, the key issue is to select the patients in whom complete cytoreduction is feasible.

SUMMARY

Peritoneal carcinomatosis, (PC) for a small amount of peritoneal dissemination, is regarded as a terminal stage not amenable to cure but with the introduction of cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC), a cure is possible in selected cases. CRS combined with IPC improves median survival compared to patients with only IPC (P<0.001). The survival of patients who had complete cytoreductive surgery (CC-0) was 32 months compared with 8 months in whom complete cytoreduction was not possible (P<0.001). Limited disease (PCI <13), low CC score, age <65, female gender, second-look surgery, and postoperative systemic chemotherapy were found to be independent prognostic factors prolonging survival.

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