Treatment of peritoneal carcinomatosis from colonic cancer by cytoreduction, peritonectomy and HIPEC: preliminary results in highly selected patients

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Treatment of peritoneal carcinomatosis from colonic cancer by cytoreduction, peritoneectomy and HIPEC: preliminary results in highly selected patients

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Aim. Peritoneal carcinomatosis (PC) is one of the routes of spread of abdominal neoplasms and is generally considered a lethal disease, with a poor prognosis by conventional chemotherapeutic treatments. While systemic chemotherapy has little impact on the treatment of peritoneal disease, some centers have reported encouraging results on overall survival (OS) and disease-free survival (DFS) with surgical cytoreduction associated with hyperthermic intraperitoneal chemotherapy (HIPEC). The purpose of this article is to evaluate the survival benefit and the morbidity in patients affected by colorectal PC treated at our institution by cytoreductive surgery associated with HIPEC.

Methods. In our institution, from October 1995 to June 2012, about 550 operations for PC were performed; in 300 cases cytoreduction plus HIPEC was carried out. Out of 90 operations for colorectal cancer: 50 cytoreduction plus HIPEC, 12 cytoreduction and EPIC (early postoperative intraperitoneal chemotherapy) and 28 debulking or exploratory laparoscopies/laparotomies were performed. For the present study, 50 patients who had undergone cytoreduction and HIPEC for PC of colorectal cancer origin (CRC) were considered.

Results. The morbidity and mortality rates were 34% (17/50) and 2% (1/50), respectively. The patients were divided in two groups according to PCI (peritoneal cancer index, range 0-39) and CC score (completeness of cytoreduction): in Group A (23 patients, PCI≤16, CC-2) the median survival time was 15 months compared to 48.1 months for Group B (27 patients, PCI>16, CC-0/1). The poor survival of Group A seemed to be related to higher PCI and CC score.

Conclusion. Patient selection based on a maximum PCI of 16 associated with a complete cytoreduction (CC-0) produced encouraging results.

KEY WORDS: Peritoneum - Colorectal neoplasms - Drug therapy.

Peritoneal carcinomatosis (PC) of colorectal origin has been considered for a long time as a systemic disease and treated by systemic chemotherapy often associated with palliative surgical operations. This approach has usually not significantly influenced the natural history of the disease which is characterized by poor prognosis with median survival ranging between 6 and 8 months. Modern systemic chemotherapy regimens based on oxaliplatin or irinotecan, possibly associated with biological agents, improved survival rates achieving in some series median survival of 18-20 months. Some better results are reported by using new drugs, alone or in association...
with angiogenesis inhibitors, but the best reported median survival is 24 months.\textsuperscript{2,3}

In the 1980s, some authors developed a multimodal technique to manage peritoneal carcinomatosis of different origin, based on surgical cytoreduction of the primitive cancer, peritoneectomy procedure (stripping of implants on the peritoneal surface) and hyperthermic intraperitoneal chemotherapy (HIPEC).\textsuperscript{4,5} The theoretical advantage of the intraperitoneal distribution of cytostatic drugs is a high local concentration of the used agents and a reduced systemic toxicity due to the presence of the “peritoneal-plasma barrier”: this anatomical structure, in fact, prevents leakage into the systemic circulation of high molecular weight drugs. Moreover, hyperthermia increases drug penetration into the tissues, the cytotoxicity of selected drugs and it leads to direct cytotoxic effects such as protein denaturation, induction of apoptosis and inhibition of angiogenesis.\textsuperscript{6-9}

Best candidates to this procedure are patients presenting a disease limited to peritoneal cavity without distant metastases.\textsuperscript{10} Many studies based on this new approach in patients affected by PC from colorectal cancer reported an impact on overall survival (OS) and disease free survival (DFS).\textsuperscript{11-16}

In this study, preliminary results on 50 patients affected by PC from CRC, treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are reported; particular attention has been given to postoperative complications and the impact of peritoneal carcinomatosis index (PCI) and completeness of cytoreduction (CC score) on long-term survival.

**Materials and methods**

From a database of 550 operations for PC of varied origin performed between October 1995 and June 2012 (300 cases treated with surgical cytoreduction plus HIPEC), 90 patients affected by PC of CRC origin were extracted: of those, 50 had undergone cytoreduction plus HIPEC, 12 cytoreduction plus EPIC (early postoperative intraperitoneal chemotherapy) and 28 debulking or explorative operations. For the present study 50 patients submitted to cytoreductive surgery associated with HIPEC were considered.

**Patient selection**

The preoperative evaluation always included thoracic and abdominal CT scan to stage the peritoneal disease and exclude distant metastases. Upper digestive endoscopy and colonoscopy generally completed the tumor staging. A careful preoperative evaluation of patient’s general condition was always performed and included complete blood tests, electrocardiogram, cardiac ultrasound and spirometry.

Inclusion criteria were: neoplasm histologically or cytologically confirmed; age between 18 and 68 years old; performance status (PS) <2 according to the Eastern Cooperative Oncology Group (ECOG); no evidence of disease outside the peritoneal cavity (liver metastasis easily removable are not an absolute exclusion criterion); absence of bowel obstruction; absence of concomitant non-compensated cardio-respiratory, hepatic, renal and metabolic diseases; no prior radiotherapy for abdominal carcinomatosis upon large abdominal areas. The presence of non-reatcetable hepatic metastases or extra-abdominal disease and massive ileum involvement were considered absolute contraindications to the treatment. Informed consent was obtained from all the patients.

**Surgical technique**

Surgery was performed through a large midline incision. All adhesions were liberated. The first part of the procedure was to record the extent of PC according to Sugarbaker classification,\textsuperscript{17} a combined numerical score of lesion size and tumor localization. The numerical score combines lesion size scored between 0 and 3 points according to the lesion diameter and tumor localization in 13 abdomino-pelvic regions including small bowel (region 0-12). In each region
the lesion size has to be determined and summated leading to a score ranging from 0 to 39.

CRS consists of numerous surgical resections depending on the extent of peritoneal tumor manifestation. The peritoneectomy procedure was performed according to the Sugarbaker criteria:18

— central peritoneectomy: removal en bloc of surgical scar, round and falciform ligaments;
— anterolateral peritoneectomy: omentectomy, removal of the anterior leaflet of transverse meso-colon, eventually splenectomy and removal of lateral peritoneum;
— right diaphragmatic peritoneectomy;
— left diaphragmatic peritoneectomy;
— peritoneectomy of the omental bursa: cholecystectomy, liberation of hepato-duodenal ligament, removal of the lesser omentum;
— pelvic peritoneectomy: eventual resection of recto-sigmoid colon, uterus, ovaries and bladder peritoneum.

Implants on the visceral serosa were removed by electrosurgical local dissection.

The aim of CRS is to obtain complete macroscopic cyto reduction (CC-0/1) as a precondition for the application of HIPEC. The residual disease is classified intraoperatively using the completeness of cyto reduction (CC) score. CC-0 indicates no visible residual tumor and CC-1 residual tumor nodules <2.5 mm. CC-2 and CC-3 indicate residual tumor nodules between 2.5 mm and 2.5 cm and >2.5 cm, respectively.19

HIPEC technique

HIPEC was performed according to the original “semi-closed” abdomen technique20 with five drain tubes placed in the abdominal cavity, 2 for inflow and 3 for outflow. Backhaus forceps are used to close the cranial and caudal portion of the abdominal wound. The skin is then suspended on a self-retaining retractor (Thompson retractor), placed at about 15 cm from the abdomen by plastic self-blocking strings. This kind of placement creates the virtual cavity needed to perform HIPEC. The central portion of the wound is also suspended by the retractor and covered with a laparoscopic device with a hole in the middle. The drain tubes are connected to a perfusion system formed by two pumps and a heat exchanger to heat the perfusate. The pumps (inflow and outflow) are connected through a reservoir in order to grant a continuous circulation of the liquid at a speed of approximately 1 l/min. The pumps are controlled by a computerized system that sets the flow rate and temperature of the heat exchanger. Four temperatures, (inflow, outflow, intraperitoneal and esophageal) are checked by probes. The volume of the circulating perfusate (solution for peritoneal dialysis) is calculated according to the patient’s body surface. During perfusion, the surgeon mixes the perfusate by hand through the hole in the sterilized drape. When the ideal intraperitoneal temperature is reached, drugs are added to the circuit and HIPEC is performed for 60 minutes. The drugs used were: cisplatinum (CDDP) 100 mg/sm plus C mytomycin (MMC) 16 mg/sm21 at a temperature of 41.5 °C or MMC as single agent 35 mg/sm for 60 minutes at a temperature of 40.5 °C, according to the Netherlands protocol,13 if patient presented intolerance to platinum compounds.

Using this technique the surgeon can mix the perfusate solution and check the peritoneal cavity. The procedure allows both the homogeneous distribution of temperature and drugs and low risk of drug leakage from the abdominal cavity.

Statistical Analysis

The data of all patients who completed the treatment (cytoreduction associated with HIPEC) were included in a retrospective study. Complications were analyzed according to Dindo-Clavien classification.22 The survival time was calculated from the date of first cytoreduction and HIPEC. The disease-free survival (DFS) was calculated from the date of the operation until the first diagnosis of recurrence. An event was defined as a relapse at any site or disease related death. Survival curves were performed
using Kaplan-Meier method and compared with log-rank test. Categorical variables were compared using two-tailed chi-square test or Fisher test; continuous variables were compared by t-test. Potential clinical and pathologic prognostic factors for recurrence or disease-related death that were investigated included age, gender, previous systemic chemotherapy, primary tumor histology and site origin, lymph node involvement, PCI and CC-status. The choice for independent factors in the multivariate model was based on the univariate results. Multivariate analysis of factors related to overall survival (OS) and disease-free survival were performed with the Cox proportional hazards model. Patients of Group A and Group B were compared on the basis of clinical variables and outcome. All analyses were stratified for the number of procedures of cytoreduction and HIPEC. Patients with missing data were excluded. Significance was defined as a P value less than 0.05.

Results

The median age was 51.8 years (range: 19-68), 29 were male (58%) and 21 female (42%). The primitive cancer arose from left colon or rectum in 28 cases (56%) and from right colon in 22 cases (44%). For all the patients histology was colonic adenocarcinoma: 23 patients (46%) presented the histological feature of mucinous cancer. Forty patients (80%) received systemic chemotherapy before the HIPEC operation. The median PCI was 14.5.

Peritonectomies were variously combined with resections of viscera with tumor involvement: colon (N=36), greater omentum (N=34), small bowel (N=22), rectum (N=22), uterus/ovaries (N=10), spleen (N=9), appendix (N=9), gallbladder (N=7). Peritonectomy procedures performed were: 44 central, 20 right upper quadrant, 12 left upper quadrant, 42 pelvic, 16 left abdominal wall, 14 right abdominal wall. One bowel anastomosis was performed in 26 patients (52%), 2 in 11 (22%) and in 13 patients no bowel anastomosis was performed (26%).

In 25 cases (50%) the anastomosis was protected with lateral temporary ileostomy, in 3 cases (6%) a definitive colostomy was performed.

All patients were subjected to HIPEC according to the semi-closed technique with a protocol based on administration of Cisplatin (CDDP) 100 mg/sm plus C Mytomycin (MMC) 16 mg/sm for 60 minutes, at a peritoneal temperature of 41.5 °C. The mean duration of surgery (including HIPEC) was 9.5 hours (range 5-16.5). At the end of the operation, the patients were admitted to intensive care unit and then returned to the surgical department when cardiovascular and pulmonary functions became stable.

For this analysis the cohort of 50 patients was divided into two groups. In Group A (23 patients) the median PCI was 21 (68% of the patients had a PCI higher than 16) and 8 patients were classified as CC2 cytoreducted. The median duration of the operation was 13 hours (range 7-16 hours). In Group B (27 patients), because of preliminary experience acquired with Group A, patients were selected with a PCI <16. Median PCI was 11, the CC score was 0 (no residual disease) for all the patients and the median duration of the operation was 8 hours (range 5-12.5 hours).

In Group A, long-term results were not very satisfactory, with a median overall survival of 15.0 months compared to 48.1 months in Group B (P=0.01). The median DFS was 11.0 months in Group A and 15 months in Group B (P=0.01). In the univariate analysis of overall survival we considered sex, age, lymph node involvement, origin site and differentiation of the primary tumor, extent of carcinomatosis assessed by PCI, neoadjuvant chemotherapy and completeness of the cytoreduction as independent variables. The extent of primary tumor (pT, P=0.02), the differentiation grade (P=0.01), the extent of peritoneal carcinomatosis (PCI, P=0.05) and the completeness of cytoreductive surgery (P<0.001) had a statistically significant prognostic impact. In the multivariate analysis, the completeness of cytoreduction was the only significant variable on the outcome. The same
variables were considered for univariate analysis of DFS: the differentiation grade (P=0.02), the extent of peritoneal carcinomatosis (P=0.02) and the completeness of cytoreductive surgery (P=0.003) were found having a strong prognostic impact; even in this case the completeness of cytoreduction was the only significant variable in the multivariate analysis.

In order to determine which parameters had a significant influence on the change in outcome between the two groups, the different variables of Group A and Group B were then compared using chi-square test. Best candidates resulted those presenting lower PCI, in which it was possible to achieve an optimal cytoreduction.

Overall morbidity and mortality rates were 34.0% (17/50) and 2.0% (1/50), respectively. Main surgical complications were intestinal/biliary fistulas (N=3), prolonged ileus (N=4), bleeding (N=2), intestinal obstruction (N=2) and one multiorgan failure. Main medical complications were: haematological toxicity (N=2), pleural effusion (N=4) and sepsis (N=1). In 5 cases (10%) re-intervention was necessary (2 for bowel perforations, 2 for haemorrhage and 1 for biliary fistula).

The association between morbidity and clinical independent variables was evaluated: duration of surgery, number of anastomosis, extent of carcinomatosis (PCI>16) and incomplete cytoreduction were associated with a higher incidence of postoperative complications.

**Discussion**

Traditionally, the treatment of peritoneal carcinomatosis was represented by debulking or palliative surgery followed or not by systemic chemotherapy resulting in a median survival lower than 6 months. The limited efficacy of systemic chemotherapy has been demonstrated in numerous studies, despite the evolution of therapeutic schemes and the introduction of biological agents. In the early 1990s Sugarbaker et al. introduced cytoreductive surgery (CRS) and HIPEC as a new innovative therapeutic option for selected patients presenting peritoneal carcinomatosis. Feasibility, efficacy and safety of CRS and HIPEC have been proved in numerous clinical trials.

Only a prospective randomized trial conducted by Verwaal documented a significant increase in median survival of patients treated by cytoreductive surgery, HIPEC and postoperative systemic chemotherapy than those treated by the same systemic chemotherapy with or without palliative surgery. Median and 2-year survival rate were 12.6 months and 22%, respectively, in the control arm compared to 22.3 months and 44% in the experimental arm. We should, however, report a bias within this study: control arm patients received systemic chemotherapy almost exclusively based on 5-fluorouracil.

Three case-control studies demonstrated results in favour of groups treated by CRS and HIPEC: in the analysis by Franko and Chua median survival of 38.0 and 34.7 months, respectively, are reached in the study arms compared to 16.8 and 9.0 months in the standard group (P<0.001). Elias reported in a retrospective case-control study a median and 2-year survival rate of 23.9 months and 65% respectively in the control arm compared to 62.7 months and 81% in the study arm. A study by Glehen including a large population of 506 patients, showed interesting survival results: median survival time was 19.2 months, 3 and 5-year survival rates were 39% and 19%, respectively.

These data supported the idea that surgical removal of PC associated with HIPEC may change the natural history of PC. Despite this, numerous factors limit the applicability of such procedure in clinical practice: the high cost, the need of a specialized team, the learning-curves and last but not least, the strong impact on patient quality of life. In fact cytoreduction, peritoneectomy procedures and HIPEC were characterized, in all series, by high morbidity rates. In the present study, overall morbidity and mortality rates were 34% (17/50) and 2.0% (1/50), respectively. These results are similar to
those reported in literature by the most experienced centers: in fact, perioperative morbidity and mortality rates presented in different studies are ranging from 23% to 40% and from 0% to 12%, respectively.\textsuperscript{11-16, 23, 24}

In the present study, in Group A the median PCI was 21 (68% of the patients had a PCI higher than 16) and CC-score was 2 for 8 patients; the median duration of the operation was 13 hours due to a widespread carcinomatosis requiring aggressive visceral resections consequently linked with a high postoperative complication rate. However, in this group, patients with a complete cytoreduction and PCI ≤16 showed an overall survival of 20.5 months, higher than the median survival of the entire cohort.

In literature the duration of surgery, the number of anastomosis, the extent of carcinomatosis (PCI) and the CC score are reported as the most statistically significant prognostic factors for postoperative morbidity.\textsuperscript{25, 26} In agreement with these data, the analysis of 200 surgical cytoreductions published by Stephens\textsuperscript{27} has detected the duration of the intervention, the number of peritoneectomies and anastomosis as independent risk factors of postoperative morbidity. Kusamura\textsuperscript{28} reported a strong correlation between the extent of cytoreduction and the development of postoperative complications in a series of 209 patients affected by peritoneal carcinomatosis.

In literature, the main morbidities associated with HIPEC combined with cytoreductive surgery are often surgical complications. The most common complications are infections and anastomosis release. Glehen et al.\textsuperscript{13} reported an anastomosis dehiscence rate of 6.5% and an infection rate of 7.2%. Their complications incidence, similar to the studies mentioned above, is closely linked to the duration of surgery and extent of peritoneal carcinomatosis.

The most dangerous surgical complication of this treatment is represented by intestinal fistula with an incidence ranging from 4% to 28% in world records; in order to avoid this kind of complication we used to protect anastomosis by an ileostomy. Medical complications reported in literature are hematological toxic effects and renal toxicity: we solved this problem by hyperhydration and forced urination by furosemide continuous infusion during HIPEC associated with Amifostine\textsuperscript{®} administration.

High morbidity rates suggest that the process of patients’ selection is a crucial moment and prognostic factors are needed in order to identify patients who most may benefit from this treatment. PCI and CC-score, as enunciated in literature, are strictly related to complications rate and OS.\textsuperscript{25, 26} PCI is directly related to the required aggressiveness of surgery and then to the morbidity rate and the patient’s outcome. Fewer complications and a higher survival rate are achieved in patients with no residual disease at the end of cytoreduction.

Results of our experience and data reported in literature, suggest to make a strict patients’ selection, treating patients with a maximum PCI index of 16 in which a complete cytoreduction is obtainable.

Based on this consideration, patients of Group B were selected according to criteria mentioned above. Median PCI was 11 and complete cytoreduction (CC-0) was achieved in all the patients. In this selected group median survival climbed up to 48.1 months.

Conclusions

Complete cytoreduction associated with HIPEC showed encouraging results both in terms of OS and DFS in the treatment of peritoneal carcinomatosis from colonic cancer. Lower complication rate and better long-term outcomes have been achieved in patients presenting modest extension of peritoneal carcinomatosis and positive prognostic factors concerning the primary tumor. The completeness of cytoreduction and extent of peritoneal disease were the most important prognostic indicators.

A standardization of the procedure in terms of timing and drugs used and phase III studies are still necessary in order to determine the true role of HIPEC independently from cytoreductive surgery. On the
basis of these considerations and with new trials' results, an adequate patients' selection will allow surgeons and oncologists to treat patients with early presentation of disease, obtaining better results in terms of prognosis and postoperative morbidity.

**Riassunto**

*Trattamento della carcinosi peritoneale di origine colorettale mediante citoreduzione, peritonectomia e HIPEC: risultati preliminari in pazienti altamente selezionati.*

**Obiettivo.** La carcinosi peritoneale (CP) è una delle vie di diffusione delle neoplasie abdominali ed è generalmente considerata una malattia letale, con una prognosi sfavorevole se trattata esclusivamente mediante chemioterapia standard. Mentre la chemioterapia sistemica ha scarsissimo impatto sul trattamento della malattia peritoneale, alcuni centri hanno riportato risultati incoraggianti in termini di sopravvivenza globale (OS) e di sopravvivenza libera da malattia (DFS) mediante citoreduzione chirurgica associata a chemioterapia ipertermica intraperitoneale (HIPEC). Lo scopo di questo articolo è valutare il beneficio in termini di sopravvivenza e la morbidità nei pazienti affetti da CP di origine colorettale trattati presso il nostro Istituto a chirurgia citoreductive associata ad HIPEC.

**Metodi.** Nel nostro Istituto, dall'ottobre 1995 a giugno 2012, sono state eseguite circa 550 operazioni per CP, in più di 300 casi si è trattato di citoreduzioni associate ad HIPEC. Su 90 operazioni eseguite per coloretto colorettale vi sono state: 50 citoreduzioni e HIPEC, 12 citoreduzioni e EPIC (chemioterapia postoperatoria intraperitoneale) e 28 debulking o laparoscopia/laparotomia esplorativa. Per il presente studio, sono stati presi in considerazione 50 pazienti sottoposti a citoreduzione e HIPEC per CP di origine colorettale.

**Risultati.** I tassi di mortalità e mortalità globale sono stati del 34% (17/50) e del 26% (13/50), rispettivamente. I pazienti sono stati suddivisi in due gruppi in base al PCI (indice di cancro peritoneale, range 0-59) e al CC-score (complezzarezza della citoreduzione): nel gruppo A (23 pazienti, PCI ≥ 16, CC-2) la mediana di sopravvivenza globale è stata di 15 mesi rispetto a 48,1 mesi raggiunti dal gruppo B (27 pazienti, PCI ≤ 16, CC-0/1). La scarsa sopravvivenza del gruppo A sembra essere correlata al più alto PCI e alla minor completezza della citoreduzione.

**Conclusioni.** La selezione dei pazienti sulla base di un PCI massimo di 16 associato alla possibilità di ottenere una citoreduzione completa (CC-0) hanno raggiunto risultati incoraggianti.

**Parole chiave:** Peritoneo - Colon, neoplasie - Chemioterapia.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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