

## Cytoreductive Surgery (CS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Treatment of Peritoneal Surface Malignancies: Report of a Phase II Clinical Study

S. ASERO<sup>1</sup>, M. CARUSO<sup>2</sup>, N. VALLONE<sup>3</sup>, A.G. LUCIANI<sup>3</sup>, V. LOMBARDO<sup>1</sup>,  
G. TERRANOVA<sup>4</sup>, G. ETTORE<sup>2</sup> and G. GIANNONE<sup>1</sup>

<sup>1</sup>Division of Surgical Oncology, <sup>2</sup>Division of Gynecology, and  
<sup>3</sup>Departments of Clinical Radiology and Department of Oncology,  
Azienda Ospedaliera di Rilievo Nazionale ed di Alta Specializzazione Garibaldi,  
S Luigi-S. Currò, Ascoli Tomaselli, Catania, Italy

**Abstract.** Peritoneal surface malignancy is the expression of a spectrum of disease involving the peritoneum primary or secondary to gastrointestinal and gynecological neoplasms. Even if intraperitoneal therapy has now been demonstrated in multiple randomized trials to improve the outcome of chemotherapy for patients with optimally debulked or small volume ovarian carcinoma, it is believed that peritoneal carcinomatosis is considered an advanced stage of disease; for this reason, it is treated with systemic chemotherapy and surgery plays only a palliative role (1). In the last twenty years, some centres have developed surgical treatment of peritoneal carcinomatosis that involves aggressive cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy. This treatment has improved and prolonged survival, despite the associated high morbidities and mortalities (3-14).

The purpose of this study was to analyze the assessment for cytoreductive surgery (CS), hyperthermic intraperitoneal chemotherapy (HIPEC) and to evaluate postoperative systemic toxicity and procedure-related mortality (PRM) in the treatment of peritoneal surface malignancies (PSMs).

### Patients and Methods

From February 2005 to July 2008, we reviewed our 44 consecutive cases. These include 4 peritoneal mesotheliomas (one desmoplastic), 5 pseudomixomas, 13 ovarian carcinomas, 6 colon carcinomas, 7 mucinous colon carcinomas, 5 mucinous ovarian carcinomas and 5

Correspondence to: Salvatore Asero, MD, Ph.D., Via Teseo 14, 95126 Catania, Italy. Tel: +39 0957595017, Fax: +39 0957595015, e-mail: s.asero@iol.it

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gastric carcinomas. Inclusion and exclusion criteria were established according to guidelines of the last International Workshop of Peritoneal Diseases held in Milan in 2006.

Inclusion characteristics: age less than 70 years; absence of distant metastasis; adequate renal, liver and bone marrow function; performance status (ECOG) 0, 1 or 2; and signed patient consent; Exclusion criteria: inability to resect the primary tumor; adequate follow-up not possible; presence of other malignancy; active infection or other interfering pathology; distant metastasis; complete bowel obstruction; inadequate renal, liver and bone marrow function.

In order to evaluate the inclusion characteristics, patients were evaluated preoperatively as follows: complete history and physical examination, complete blood count, metabolic panel, liver function tests, prothrombin time (PT), partial thromboplastin time (PTT), international normalised ratio (INR), tumor markers, beta 2 microglobulin, electrocardiogram (EKG) and Echocardiogram (ECHO), pneumology evaluation and spirometry. All patients were evaluated with chest and abdomen computed tomography (CT) scan with intra venous (IV) contrast and magnetic resonance imaging (MRI) of the abdomen. The multidisciplinary approach involves the surgeon and the radiologist; An MRI with per os (PO) contrast and late phase fat suppression markedly improved the detection of carcinosis with an accuracy of 76%; it was compared to the CT thin-cut images with contrast. Peritoneal disease was stratified preoperatively, according to CT scan and MRI findings and according to Peritoneal Cancer Index of Sugabaker (PCI); Surgery was performed under general anesthesia with arterial and venous invasive devices to monitor the patient's hemodynamic status. A midline, xifo-pubic incision was performed along the previous scar if present. After the intraoperative clinical evaluation, the umbilicus was excised, and peritoneal washing and biopsies of suspicious lesions were taken for frozen section.

A "OmniTrack" retractor was used in order to facilitate adequate exposure of the entire abdominal cavity. Cytoreductive Surgery (CS) was carried out according to the extent of disease and to the PCI. At the end of the CS, a score was assigned according to the intraoperative PCI: lesion size (LS) 0 no evidence of disease, LS 1 nodules up to 0.5 cm diameter, LS 2 nodules up to 5 cm and LS 3 nodules larger than 5 cm diameter or confluents. The median PCI was 21 (range 8-37).

Before the intraoperative perfusion, after the diaphragmatic peritoneum is taken, 2 chest tubes are inserted bilaterally and are discontinued postoperatively when the patient's respiratory status is fine and the drainage is less than 100 cm<sup>3</sup> in 24 h; 2 atrio-ventricular catheters were placed in the abdomen and connected to the perfusion device with Y - shaped tubing on one flank (input) and two on the other flank (output) connecting to the circuit of the perfusional machine. All the anastomosis were completed before perfusion; only when a pelvic extenteratio was carried out, was a definitive colostomy performed before perfusion and, in those cases, the urethrostomies were carried out at the end of perfusion. The closed - abdomen technique was always used, suturing only the skin with a running stitch. During perfusion temperature was monitored with thermal devices (Medtronic, Medolla, Italy) in the upper abdomen, pelvis and esophagus joined to a perfusional machine "Performer" (RAND, Medolla, Italy). A three-way foley catheter was placed in the bladder to irrigate during the hyperthermic phase.

Perfusion was performed with the following: For mesothelioma and ovarian carcinoma patients: doxorubicin 15.25 mg/m<sup>2</sup>/l, cisplatin 43 mg/m<sup>2</sup>/l, with a median temperature of 42.5°C and perfusion time of 90 minutes; for pseudomixoma peritonei and colon cancer patients: cisplatin 25mg/m<sup>2</sup>/l, Mitomicina C 3.3mg/m<sup>2</sup>/l with a median temperature of 42.5°C and perfusion time of 60 minutes. With the closed - abdomen technique, 4-5 l of perfusion solution were used, with a flow from 600-800 to 1200 ml/min. in order to keep the intra - abdominal temperature and abdominal perfusion constant; temperature that are too low diminish chemotherapy drug penetration while temperatures which are too high are harmful to the tissues. The Performer - LRT (RAND, Medolla Italy) allows constant monitoring of all temperatures, perfusion levels and flows.

At the end of perfusion, the abdomen were re-opened and the previous surgical sites (anastomosis, resected organ beds) and hemostasis were carefully examined. Four J-P drains are placed through the small opening previously used for the perfusion catheters and the abdominal wall is closed. In the early postoperative period, patients were cared for in the Intensive Care Unit and were extubated on postoperative day 1. Postoperative ileus can persist, as a matter of fact total parenteral nutrition (TPN) is started on postoperative day 3, without lipids.

## Results

Of a total of 44 patients, 14 were excluded after the preoperative work-up had showed the extension of the disease.

In 4 patients who underwent cytoreductive surgery, the results of preoperative MRI findings were consistent with the intraoperative PCI.

Seven patients (3 gastric carcinomas, 3 ovarian carcinomas, 1 mesothelioma) were intraoperatively assessed as not being curable and underwent palliative treatment; 23 patients underwent cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

The median operating room time was 642 minutes (range 510-786 minute); the median length of stay was 24 days (range 20-36 days); Postoperative morbidity and toxicity events were evaluated according to WHO criteria (20).

The two chemotherapy regimens used gave rise to fewer complications, even than in other groups that used the same regimens. According to the Sugarbaker Classification (CC-0 no residual disease, CC-1 0-2.5 mm residual disease, CC-2 from 2.5 to 2.5 cm, CC-3 >2.5 cm residual disease), CCR was good (CC 0/1) in 14 patients and quite good (CC1/2) in 8 patients. Two patients had hematological toxicity GIII, while one patient had renal toxicity GII, NCI CTCAE (20).

We detected the following complications: 1 patient had a low-output pancreatic fistula treated with medical therapy, 1 patient had a pulmonary embolism treated medically, 1 patient had nosocomial pneumonia, 1 patient suffered prolonged postoperative ileus, 3 patients died in the early postoperative period (1 patient with disseminated intravascular coagulation (DIC), 1 patient with pulmonary embolism (PE), 1 patient with systemic inflammatory response syndrome (SIRS), 4 patients died with recurrent systemic disease and 15 patients are alive and disease-free.

The 15 disease-free patients were initially treated for the following carcinomatosis: 2 patients had colorectal carcinoma, 5 ovarian carcinoma, 5 mucinous colorectal carcinoma, 2 mucinous ovarian carcinoma carcinomatosis, and 1 patient gastric carcinoma carcinomatosis.

Of these 15 disease-free patients, all resumed their regular personal activities. Persistent complications include symptoms of gastroesophageal reflux disease in 1 patient, who underwent total gastrectomy, impotence in 1 patient and thrombocytopenia in 1 patient, who underwent splenectomy. All patients have been following with physical examination, extensive laboratory tests and ECOG every 2 weeks during the first 2 months, then every 4 months with the addition of a chest and abdomen CT scan with iv contrast.

## Discussion

Peritoneal carcinomatosis has been considered a fatal disease and is often still treated with palliative intent. Cytoreductive surgery and peritonectomy followed by hyperthermic intraperitoneal chemotherapy, in selected centers, is now the treatment of choice to be considered. Even today, there are different parameters in the evaluation of cytoreductive surgery and perfusion techniques (open or closed abdomen). Accurate patient selection is important (19-21).

In our series, the preoperative radiological evaluation was important in patient selection. All inclusion and exclusion criterias have be carefully analyzed, the performance excellence of the surgical team and the refinement in the technique delivered good results. The morbidity and mortality reported by other groups are still high.

Patient survival is enhanced by increased by an adequate cytoreductive surgery and is related to the histological type, even though some series report a good survival without adequate cytoreduction.

Cytoreductive surgery with peritonectomy and hyperthermic intraperitoneal chemotherapy is the treatment of choice that gives a possibility of cure and prolongs the survival in patients affected by pseudomixoma, mesothelioma and other mucinous carcinomas; in advanced ovarian carcinomas, stage III/IV according to the biology of the disease and well-known studies, the treatment of choice is cytoreductive surgery with peritonectomy and intraperitoneal chemohyperthermia (4-5).

Certainly, despite with accurate patient selection, the cooperation between the surgical oncologist, the medical oncologist, the anesthesiologist and other important members of this multidisciplinary team will provide a great contribution to this surgical procedure.

## References

- Van Leeuwen BL, Graf W, Pahlman L and Mahteme H: Swedish experience with peritonectomy and HIPEC in peritoneal carcinomatosis. *Ann Surg Oncol* 15: 745-753, 2008.
- Muñoz-Casares FC, Rufián S, Rubio MJ, Lizárraga E, Díaz-Iglesias C, Aranda E, Cirja R, Muntané J, Barrios P, Torres-Melero J, González-Moreno S, González-Bayón L, Camps B, Bretcha P, Farré J, Ortega-Pérez G and Gómez-Portilla A: Treatment of peritoneal carcinomatosis from ovarian cancer. Present, future directions and proposals. *Clin Transl Oncol* 9: 652-662, 2007.
- Kusamura S, Baratti D, Antonucci A, Younan R, Laterza B, Oliva GD, Gavazzi C and Deraco M: Incidence of postoperative pancreatic fistula and hyperamylasemia after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 14: 3443-3452, 2007
- Raspagliesi F, Deraco M and Rossi CR: Stage III/IV epithelial ovarian cancer with macroscopic residual disease after 1st line Chemotherapy: a multicentric prospective randomised study comparing loco regional approach + systemic chemotherapy vs. systemic chemotherapy alone. <http://www.sitilo.org>
- Deraco M, Raspagliesi F and Kusamura S: Management of peritoneal surface component of ovarian cancer *Surg Oncol Clin N Am* 12: 561-583, 2003
- Capone A, Valle M, Proietti F, Federici O, Garofalo A and Petrosillo N: Postoperative infections in cytoreductive surgery with hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis. *J Surg Oncol* 96: 507-513, 2007
- Sugarbaker PH: Peritonectomy procedures. *Cancer Treat Res* 134: 247-264, 2007.
- Yan TD, Links M, Fransi S, Jacques T, Black D, Saunders V and Morris DL: Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy - a journey to becoming a Nationally Funded Peritonectomy Center. *Ann Surg Oncol* 14: 2270-2280, 2007.
- Cavaliere F, Valle M, De Simone M, Deraco M, Rossi CR, Di Filippo E, Verzi S, Giannarelli D, Perri P, Pilati PL, Vaira M, Di Filippo S and Garofalo A: 120 peritoneal carcinomas from colorectal cancer treated with peritonectomy and intra-abdominal chemohyperthermia: a S.I.T.I.L.O. multicentric study. *In Vivo* 20: 747-750, 2006.
- Yan TD, Edwards G, Alderman R, Marquardt CE and Sugarbaker PH: Morbidity and mortality assessment of cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma - a prospective study of 70 consecutive cases. *Ann Surg Oncol* 14: 515-525, 2007.
- Kusamura S, Deraco M, Baratti D, Inglese MG, Costanzo P, Favaro M, Manzi R and Gavazzi C: Cytoreductive surgery followed by intra peritoneal hyperthermic perfusion in the treatment of peritoneal surface malignancies: morbidity and mortality with closed abdomen technique. *J Exp Clin Cancer Res* 22(4 suppl): 207-212, 2003.
- Cotton F, Pellet O, Gilly FN, Granier A, Sournac L and Glehen O: MRI evaluation of bulky tumor masses in the mesentery and bladder involvement in peritoneal carcinomatosis. *Eur J Surg Oncol* 32: 1212-1226, 2006.
- Kusamura S, Younan R, Baratti D, Costanzo P, Favaro M, Gavazzi C and Deraco M: Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. *Cancer* 110(6): 1144-1153, 2006
- Younan R, Kusamura S, Baratti D, Oliva GD, Costanzo P, Favaro M, Gavazzi C and Deraco M: Bowel complications in 203 cases of peritoneal surface malignancies treated with peritonectomy and closed-technique intraperitoneal hyperthermic perfusion. *Ann Surg Oncol* 12: 910-918, 2005.
- Sugarbaker PH: Strategies for the prevention and treatment of peritoneal carcinomatosis from gastrointestinal cancer. *Cancer Invest* 23: 155-172, 2005
- Harmon RL and Sugarbaker PH: Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. *Int Semin Surg Oncol* 16: 2-3, 2005
- Sugarbaker PH: Managing the peritoneal surface component of gastrointestinal cancer. Part 1. Patterns of dissemination and treatment options. *Oncology* 18(1): 51- 59, 2004.
- Sugarbaker PH: Managing the peritoneal surface component of gastrointestinal cancer. Part 2. Perioperative intraperitoneal chemotherapy. *Oncology* 18: 207-219, 2004.
- Sugarbaker PH: Peritonectomy procedures. *Surg Oncol Clin N Am* Jul; 12: 703-727, 2003.
- Cancer therapy evaluation program, common terminology criteria for adverse events, version 3.0 DCTD, NCI, NIH, DNHS. March 31st, 2003 (<http://ctep.cancer.gov>).
- Glehen O, Osinsky D, Cotte E, Kwiatkowski F, Freyer G, Isaac S, Trillet-Lenoir V, Sayag-Beaujard AC, François Y, Vignal J, Gilly FN: Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. *Ann Surg Oncol* 10: 863-869, 2003
- Kusamura S, Baratti D, Younan R, Laterza B, Oliva GD, Costanzo P, Favaro M, Gavazzi C, Grosso F and Deraco M: Impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on systemic toxicity. *Ann Surg Oncol* 14: 2550-2558, 2007.

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