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The hyperthermic intraoperative intraperitoneal chemotherapy in the treatment of advanced abdominopelvic cancer. Personal experience on 103 procedures during a seventeen year period in a single Italian center

D. DI MICELI, C. CINA, C. FIORILLO, G.B. DOGLIETTO, S. ALFIERI

Department of Digestive Surgery, Gemelli Foundation, Catholic University of the Sacred Heart, School of Medicine, Rome, Italy

Abstract. – OBJECTIVE: Integration of different therapeutic strategies in cancer surgery in the last years has led from treating primary lesions to the surgical treatment of metastases. The purpose of this paper is to report a single Italian center experience of treatment of peritoneal carcinosis of the abdominopelvic malignancies.

PATIENTS AND METHODS: 103 HIPEC procedures were performed in 17 years on 94 selected patients affected by abdominopelvic cancer. The PCI score was calculated at laparotomy. The CC score was calculated before doing HIPEC. HIPEC was carried out according to the Coliseum technique.

RESULTS: The surgical cytoreduction allowed 89 patients to be subjected to HIPEC treatment with a CC score 0; 9 patients with a CC 1; 3 patients with a CC 2 and 2 patients with a CC 3. In 22 patients postoperative complications were recorded. No operative mortality occurred. The median follow-up of 53 months shows a rate of survival equivalent to 49 %, with a relapse in 46 patients, 29 of them reached exitus.

CONCLUSIONS: The surgical resection alone for patients affected by advanced cancer with peritoneal carcinomatosis cannot be considered a sufficient treatment any longer and HIPEC would help to prolong survival in these patients.

Key Words:
Carcinomatosis, Chemotherapy, Hyperthermia, Intraoperative, Intraperitoneal.

Introduction

In the last years, oncology surgery has greatly developed adopting a multidisciplinary approach in the treatment of advanced malignant cancer[1]. As a matter of fact surgeons passed from the treatment of a primary lesion alone to surgical treatment of metastases. Specifically, as regards digestive tumours, the advances have concretized following the positive results obtained with resection of local recurrences of the colon and rectum combined with complementary radio-chemotherapic treatments[2,3]. Sugarbaker[4,5] extended this concept studying in depth the problem of surgical radicalness of carcinosis to allow long-term survival also for patients with neoplastic localizations on the peritoneal surface.

The purpose of this work is to report the principles of prevention and treatment of peritoneal carcinosis of the abdominopelvic cancer together with our case series on 103 procedures in 17 years.

Patients and Methods

Between April 1999 and February 2016, 103 procedures of hyperthermic intraoperative intraperitoneal chemotherapy were carried out after cytoreduction surgery for advanced abdominopelvic cancer in the Digestive Surgery Division of the Catholic University of the Sacred Hearth in Rome, Italy. The approval of the local Ethic Committee was obtained before starting the study, conforming to the provisions of the World Medical Association's Declaration odd Helsinki in 1995 (as revised in Tokyo 2004). All surgery was performed by the same team of general surgeons. Patients with histologically documented cancer, with carcinosis at laparotomy, were included in the protocol. Further entry criteria were as follows: age 18-80 years, normal cardiac, respiratory, liver and renal functions and no haematological alterations. Before the operation, all patients were required to provide a writ-

Corresponding Author: Dario Di Miceli, MD, Ph.D; e-mail: dardimic@gmail.com

ten informed consent to the protocol. Exclusion criteria were as follows: concurrent malignancies at other sites; uncontrolled severe infection and/or medical problems unrelated to malignancy which would limit full compliance with the protocol or expose the patient to extreme risk of life.

All patients were submitted to a complete clinical evaluation, including laboratory tests, with complete blood cell count and serum chemistry. In order to exclude extra-abdominal disease and to assess the possibility of optimal cytoreduction all patients underwent to a MRI and/or CTscan or FDG-PET/CT scan. The peritoneal cancer index (PCI) score was calculated at laparotomy[1]. The cytoreduction score (CC) was calculated for all patients before doing hyperthermic intraperitoneal chemotherapeutic treatment (HIPEC)[1].

HIPEC was administered after performing cytoreductive surgery at 41°C (min 39°C-max 42°C) according to literature [6]. HIPEC was carried out according to the Coliseum technique [[1]. Two inflow and two outflow 29 French catheters were placed in the upper and lower abdominal quadrants, respectively. By our knowledge, in literature there is no data that shows that one technique is better than the others (open, semi open or closed)[7,8].

After 90 minutes of perfusion, the abdomen was cautiously re-explored to control the haemostasis.

The temperature was monitored by using digital probes placed in abdominal cavity at circuit level and an electric endoesophageal thermostat.

Intraoperative and early post-operative (within 30 days) parameters and complications have been recorded. The events requiring re-intervention or re-admission within 30-days from surgery were considered as major treatment-related complications. Perioperative mortality was defined as death both during surgery procedure and within 30 days from operation.

Results

From April 1999 to September 2016 a total of 94 abdominopelvic cancer patients resulted eligible to underwent cytoreduction and HIPEC at the Surgical Digestive Division. The patients, 36 men and 58 women, suffered from gastric carcinoma (34 cases), colon-rectum carcinoma (30 cases), appendiceal carcinoma (10 cases), pseudomyxoma peritonei (10 cases), ovarian carcinoma (4 cases), small intestine carcinoma (3 cases), mesothelioma (2 cases), peritoneal sarcomatosis (1 case), respectively [Figure 1]. Median age was 54 years (range 28-78 years). No patient was affected with neoplastic ascites. One hundred-three surgical procedures were performed: 4 exploratory laparatomy and 99 major operations. Eight patients of these underwent to a "second look" and one these patients to a "third look", all followed by HIPEC.

The postoperative histological reports found a prevalence of poor differentiated adenocarcinomas and mucinous adenocarcinomas.

The PCI had an average of 5.6 (min. 0 and max. 39) [Figure 2].

The hyperthermic intraperitoneal chemotherapic treatment was carried out using Mitomycin C (84 cases), Oxaliplatinum (1 case), Cisplatin (2 cases), Cisplatin and Farmorubicin (4 cases). Cisplatin and Mitomycin C were used in combination in three patient.

The duration of hyperthermic intraperitoneal chemotherapeutic treatment was 60-90 minutes, depending on anatomo-pathology and on administred drugs. The intraperitoneal temperature was 41°C (min 39°C-max 42°C)[6].

89 patients had a CC score 0; 9 patients a CC 1; 3 patients a CC 2 and 2 patients a CC 3 [Figure 3].

The cause of an incomplete cytoreduction was due to the failure to perform a radical surgery able

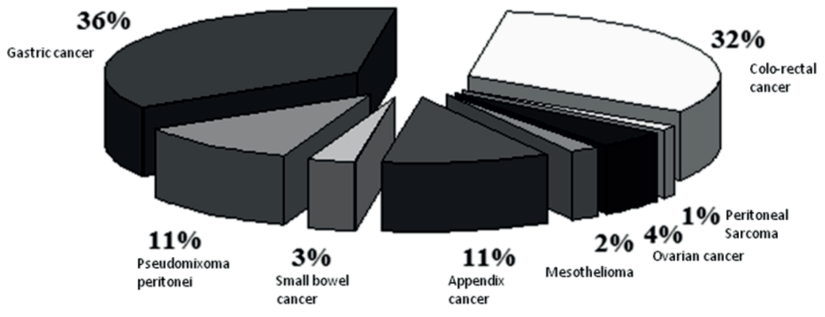

Figure 1. Pathology of the patients treated.

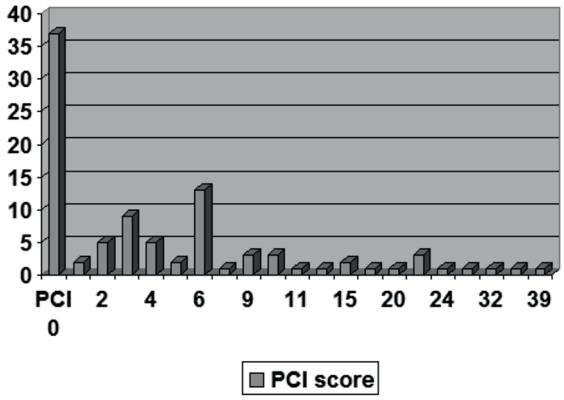

Figure 2. PCI score.

to preserve the structures (vascular or parenchymatous). The median hospitalization was 12 days (range 5-42).

In 22 patients (23 %) postoperative complications were recorded. Some patients experienced more than one postoperative complication. The most frequent complication was haemorrhage (1 case of melena treated with conservative therapy and 2 haemoperitoneum: one of these patients required a re-laparotomy). Other major complication observed were pancreatic fistula, chylous fistula, respiratory insufficiency, entero-cutaneous fistula. No peri-operative mortality were reported.

The median follow up of 53 months (range 1-204) shows a rate of survival equivalent to 49 %, with a relapse in 46 patients (48%), 29 of them reached exitus (63 %).

The evaluated 5-years survival of the entire population examined was 56.5%, with a 5-years disease free survival of 43.9% [Figures 4, 5]. Because of the heterogeneity of the population examined and of the poor number of patients affected by some of the pathologies considered, a statistical analysis of survival was feasible only for patients affected by the most represented pathologies (gastric cancer and colon-rectal cancer). The evaluated 5-years survival for patients with gastric cancer was 32.8% [Figure 6], for patients with colo-rectal cancer 62.5 % [Figure 7] (p=0.006).

The evaluated 5-years disease-free survival for patients with gastric cancer was 17.9% [Figure 8], for patients with colorectal cancer 52.0% [Figure 9] (p=0.004).

Discussion

Most of the malignant abdominal tumour spread by three routes: haematic route, lymphatic route and through the direct seeding of the neoplastic cells on the peritoneal surface.

The execution of an extended lymphadenectomy, may reduce the incidence of the lymph nodal recurrence and combined with adjuvant systematic chemotherapy may reduce the rate of haematogenous metastasis[9]. However, neither the surgery nor systematic chemotherapy, nor radiotherapy, have given effective results for the treatment of peritoneal carcinosis. Specifically, the results obtained from systematic chemotherapy in the treatment of the peritoneal carcinosis from adenocarcinoma of the gastroenteric tract are rather disappointing with no patient survives more than

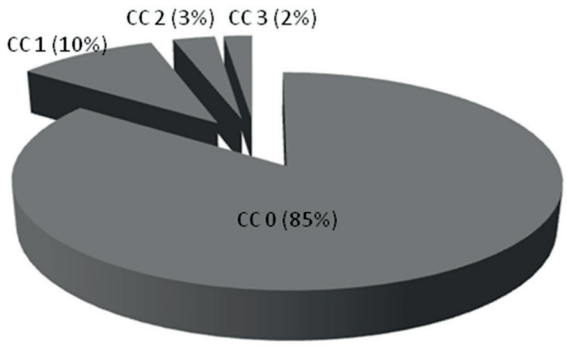

Figure 3. CC score.

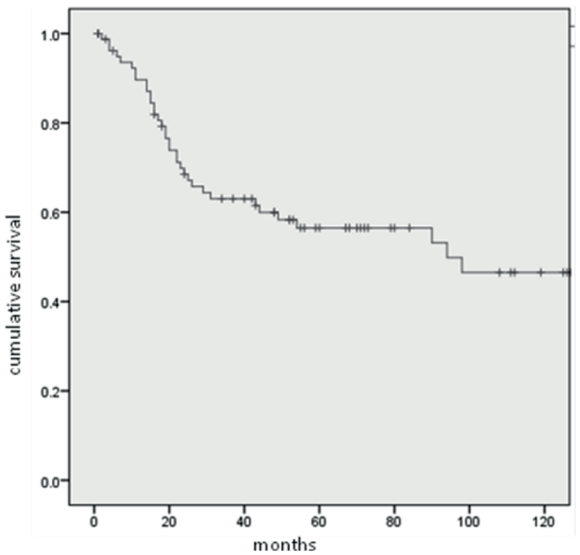

Figure 4. Overall survival in the examined population.

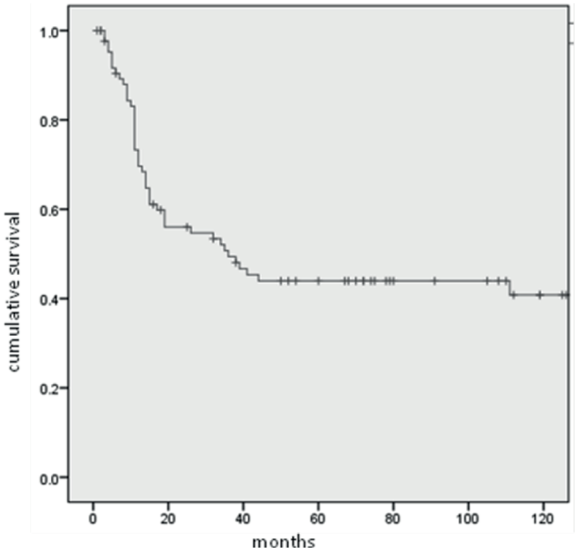

Figure 5. Disease-free survival in the examined population.

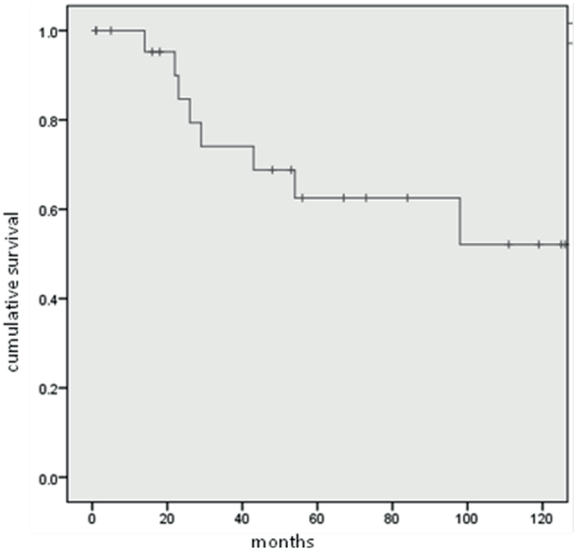

Figure 7. Overall survival in patients affected by colorectal cancer.

5 years[9]. Many of the failures of the surgical treatment are to be correlated both to the presence of a peritoneal carcinosis as well as the local recurrence at level of the margin of the section and the peritoneal recurrence.

The peritoneal carcinosis may be a consequence of different factors: the neoplastic cells in the peritoneum may already be present at the laparotomy, both at a macroscopic and a microscopic level (the cytology of the laparotomic lavage does not give any reliable results), the spread may occur during the manipulation of the tumour surfacing the serosa or during the lymphadenectomy because of the accidental breaking of the capsule of the metastatic lymph node.

Sugarbaker and Yonemura[9] have devoted much time to the problem of peritoneal carcinosis studying some procedures for the administration of chemotherapeutic drugs via intraperitoneal route as an integrant part of the surgical treatment for patients with advanced digestive neoplasia. This new technique introduces two new basic concepts: the "route" and the "timing" of medication.

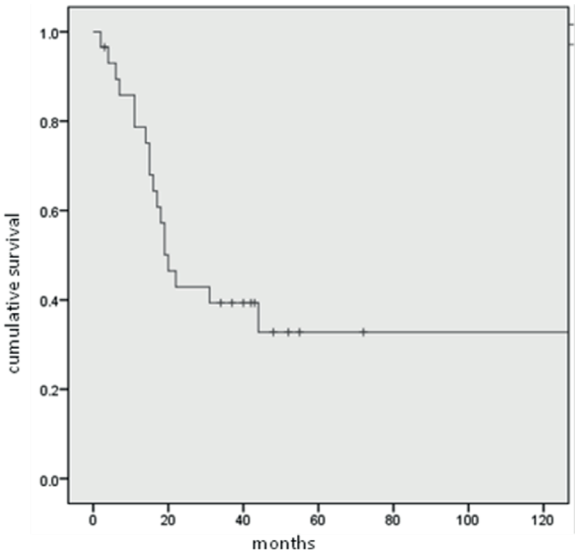

Figure 6. Overall survival in patients affected by gastric cancer.

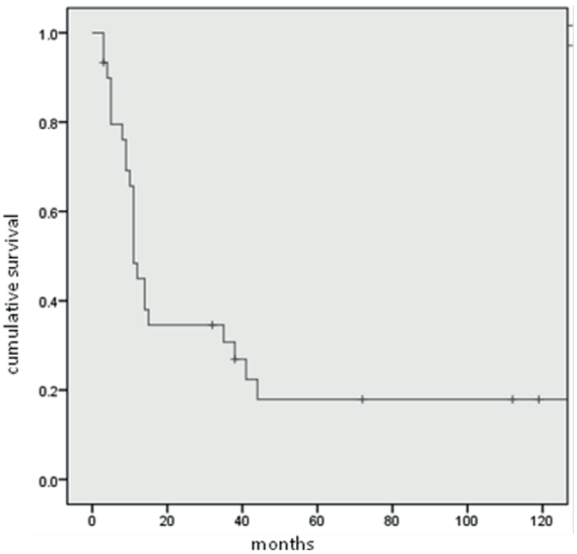

Figure 8. Disease free survival in patients affected by gastric cancer.

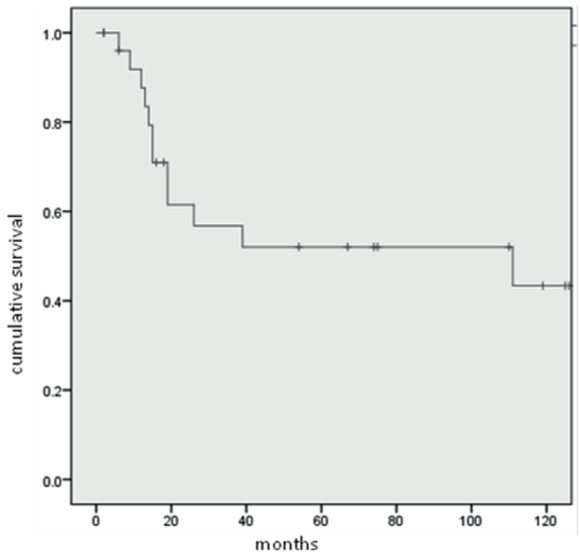

Figure 9. Disease free survival in patients affected by colorectal cancer.

The route naturally is the peritoneum which assures a high concentration of the drug in contact with the peritoneal surface while the timing is early perioperative.

Another factor which is probably decisive is the combination of hyperthermia with the intraoperative intraperitoneal chemotherapy. As a matter of fact, heat not only enhances the tissue absorption of the drug, but also increases cytotoxicity of the chemotherapeutic agent and has an anti tumoral effect in itself[11,12].

When the intraoperative chemotherapy is administered with the open technique it allows a manual distribution of the drug and the heat evenly on the whole abdominal and pelvic surface.

Generally the time needed for the open procedure in gastrointestinal tumours is 90 minutes[7,8].

Before introducing the intraperitoneal chemotherapy, combined with the peritonectomy, the peritoneal carcinosis was a slow and inexorable route until the exitus which frequently occurred as a consequence of intestinal obstruction over a period of some months from the diagnosis.

The results of intraperitoneal chemotherapy show a decrease of the local recurrence and the recurrence on the peritoneal surface in carrier patients of intraabdominal cancer[12].

The fundamental criterion for the selection of candidate-patients in chemotherapic intraperitoneal treatment is the extension of the peritoneal tumour (PCI). Namely chemotherapic intraperitoneal treatment is carried out only in the cases of invasive cancer of the abdominal cavity cytoreducible by means of surgery.

In the present work we report our own personal experience (April 1999-February 2016) at the Surgical Digestive Division of the Catholic University of the Sacred Hearth in Rome, Italy. We performed 103 procedures of hyperthermic (41-42.5°C) intraoperative intraperitoneal chemotherapy on 94 patients, because eight patients underwent to a "second look" and one patient underwent to a "third look".

The cytoreduction was radical with a score of CC 0 in 80 patients (85%) [Figure 3].

No cases of operative mortality were recorded nor any complications directly correlated to the use of the chemotherapeutic technique or hyperthermia. No toxicities of the intraoperative drugs used were recorded.

Yonemura et al[13], Fujimoto et al[14], Hirose et al[15] and Yoo et al[16] have shown that an aggressive surgical approach (complete cytoreduction) combined with intraperitoneal chemotherapy, administered intraoperatively or early after the operation (with an intraoperative or precociously intraperitoneal chemotherapy), is associated, according to significant statistics, to a better survival ($p = 0.03$; < 0.0001; $p = 0.006$; n.a.; respectively) and a better quality of life (disappearance of the ascites, if any). Therefore, from the exam of the literature and our experience we can assure that a rationale exists for the selection-use of the intraoperative chemotherapy. It is necessary to underline that: the patients must be in good health and biologically young; it must be possible to resect the tumour; an almost complete cytoreduction must be foreseeable (CC0-1).

Conclusions

Nowadays the surgical resection alone appears not a sufficient treatment for patients suffering from an advanced gastrointestinal tumour with evident peritoneal carcinosis or high risk to develop it[1,13-16]. Peritonectomy procedures and HIPEC should be part of the experience of the oncological surgical center to assure to selected patients the best treatment. The data of the present study, according to careful examination of the previous literature, make it possible to hypothesize that there is a rationale for the use of the intraoperative chemotherapy in well selected patients. We need further chemosensitivity studies to achieve an appropriate therapy in biological aggressive tumors.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon's role. Langenbeck's Ann Surg 1999; 384: 576-587.
2) Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum: clinicopathologic correlation and implications for adjuvant therapy. Cancer 1974; 34: 1278-1292.
3) Sugarbaker PH: Surgical management of locally recurrent and metastatic colorectal cancer. In: Karakousis CP, Copeland EM, Bland QUI (eds) Atlas of surgical oncology. Saunders, Philadelphia, 1995; pp. 671-692.
4) Sugarbaker PH. Peritoneal carcinomatosis: drugs and diseases. Kluwer, Boston, 1996
5) Sugarbaker PH. Peritoneal carcinomatosis from appendiceal cancer: a paradigm for treatment of abdominal-pelvic dissemination of gastrointestinal malignancy. Acta Chirurgica Austriaca 1996; 28: 4-8.
6) Di Miceli D, Alfieri S, Caprino P, Menghi R, Quero G, Cina C, Pericoli Ridolfini M, Doglietto GB. Complications related to hyperthermia during hypertermic intraoperative intraperitoneal chemiotherapy (HIPEC) treatment. Do they exist? Eur Rev Med Pharmacol Sci 2012; 16: 737-742.
7) Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. Cancer Treat Rev 2001; 27: 365-374.
8) Ceelen WP, Flessner MF. Intraperitoneal therapy for peritoneal tumors: biophysics and clinical evidence. Nat Rev Clin Oncol 2010; 7: 108-115.
9) Sugarbaker PH, Yonemura Y. Clinical Pathway for the management of respectable gastric cancer with peritoneal seeding: best palliation with a ray of hope for cure. Oncology 2000; 58: 96-107.
10) Cotte E, Glehen O, Mohamed F, Lamy F, Falandry C, Golfier F, Gilly FN. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. World J Surg 2007; 31: 1821.
11) Issels RD. Hyperthermia adds to chemotherapy. Eur J Cancer 2008; 44: 2546-2554.
12) Yano M, Yasuda T, Fujiwara Y, Takiguchi S, Miyata H, Monden M. Preoperative intraperitoneal chemotherapy for patients with serosa-infiltrating gastric cancer. J Surg Oncol 2004; 88: 39-43
13) Yonemura Y, Fujimura T Nishimura G, Falla R, Sawa T, Katayama K, Tsugawa K, Fushida S, Miyazaki I, Tanaka M, Endou Y, Sasaki T. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery 1996; 119: 437- 444.
14) Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T, Kondoh K, Ohkubo H. Survival time and prevention of side effects of intraperitoneal hyperthermic perfusion with mitomycin C combined with surgery for patients with advanced gastric cancer. Cancer Treat Res 1996; 81: 169-176.
15) Hirose K, Katayama K, Iida A, Yamaguchi A, Nakagawara G, Umeda S, Kusuka Y. Efficancy of continuos hyperthemic peritoneal perfusion for prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer: evaluation by multivariate regression analysis. Oncology 1999; 57: 106-114.
16) Yoo CH, Noh SH, Shin DW, Chung HC, Kim JH, Roh JK, Min JS. Early postoperative intraperitoneal chemotherapy for advanced gastric cancer. In proceeding of Third International Gastric Cancer Congress. Seoul, Korea, 1999; p. 103.