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ORIGINAL ARTICLE

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal carcinomatosis. Preliminary results and cost from two centers in Greece

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Summary

Purpose: *To report our preliminary experience in the combined treatment of peritoneal carcinomatosis (PC) using cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC).*

Patients and methods: *This prospective study included patients with PC from gynaecological, gastric and colon cancer, treated in two centers. Cytoreductive surgery included the peritonectomy procedures described by Jacquet and Sugarbaker as well as multivisceral resections in order to achieve a complete macroscopical cancer eradication. The HIPEC that followed was performed via the open abdomen technique.*

Results: *Twenty-four patients (3 men and 21 women, mean age 60 years) were treated. Twelve patients had PC from ovarian cancer, 7 from colon, 3 from gastric and 2 from uterine cancer. The mean duration of the procedure was 7.83 h (range 5 -12.30). Macroscopically, complete cytoreduction (CC) was achieved in 18 (75%) patients. Two (8.3%) patients died in the first 30 days. The overall morbidity was 42% and 2 patients were reoperated. The mean follow up was 22 months (range 3-36). The overall 1-year survival was 59.1%; concerning the gynaecological cancers it was 53.8% (mean survival 11.7 months) and for gastrointestinal cancers it was 44.4% (mean survival 9.5 months).*

Conclusion: *Our preliminary data suggest that the combined treatment of cytoreduction plus HIPEC for PC is associated with acceptable mortality and morbidity and offers an improved survival in these patients. An optimal patient selection and establishment of experienced centres are of paramount importance.*

Key words: hyperthermic intraperitoneal chemotherapy, peritoneal carcinomatosis, peritonectomy procedures

Introduction

Peritoneal carcinomatosis from gastrointestinal or gynecologic malignancies represents an end-stage disease and in the past it was a lethal condition associated with a short survival and poor quality of life [1,2].

Peritoneal dissemination is established through a multistep process, via trans-mesothelial and trans-lymphatic metastases which occur with serosal invasion or the surgical maneuvers during the operation. Free cancer cells are established in the peritoneal cavity and are the main cause of peritoneal recurrence even in potentially curable gastrointestinal and gynecological cancers, especially ovarian cancer [3]. The use of HIPEC is reported to be effective for the prevention of recurrence in patients with positive peritoneal lavage.

Recently, management strategies have emerged suggesting that prevention of PC is possible, that treatment of selected patients is a reality, and that strategies for improved palliation should be accepted as a standard of practice [4]. These encouraging results concerning PC with low-volume disease have been achieved

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with a combined treatment including cytoreduction via peritonectomy procedures plus HIPEC [4].

In this study, we present the results and the cost of the above mentioned combined treatment from two Greek centres which perform this method with the same protocol.

Patients and methods

A total of 24 patients with PC arising from colorectal cancer (n=7), gastric cancer (n=3), uterus (n=2) and ovarian cancer (n=12), were treated between January 2004 and May 2007.

All patients were operated by the first two authors. The management of peritoneal surface malignancies was established in both of their institutes in the last 3 years, with standard treatment protocols formulated according to the recommendations of the Washington Cancer Institute program.

The aim of surgery was to remove all macroscopically visible tumor nodules from the visceral and parietal peritoneum. Concerning the preoperative description of PC, we used the peritoneal cancer index (PCI) as described by Jacquet and Sugarbaker [5]. This scoring system has been used to evaluate PC and is a quantitative assessment of both cancer distribution and cancer implant size throughout the abdomen and the pelvis (Figure 1). Patients' evaluation included clinical examination, abdominal and thoracic computed tomography and cardiological examination.

Cytoreductive surgery consisted of a variety of peritonectomy procedures as previously described by Sugarbaker [6]. These include omentectomy, splenectomy, left and right subdiaphragmatic peritonectomy, pelvic peritonectomy and often multivisceral resections in order to achieve complete macroscopic disease clearance.

Concerning the completeness of CC, we used the CC score as described by Sugarbaker and Chang [7]. CC-0: no macroscopic residual cancer; CC-1: no residual nodule greater than 5 mm in diameter; and CC-2: diameter of residual nodules greater than 5 mm.

After resection, we performed the HIPEC using the open abdomen (coliseum) technique (Figure 2). One inflow catheter was placed below the epigastrium between the small bowel loops, and 3 outflow catheters were positioned in the right and left subphrenical area and in the cul-de-sac. Temperature probes were placed next to the outflow catheters. Up to 3 litres of dextrose 5% were used to fill the abdominal cavity before the circulation of the fluid was started. A heater device (Thermochem, ST Medical, Greece) with a pump allowed a continuous distribution of the fluid within the abdominal space at 42° C.

The chemotherapeutic agent depended on the tumor's histology: cisplatin (80 mg/m^2) plus doxorubicin (15 mg/m^2) for ovarian cancer, mitomycin (15 mg/m^2) plus cisplatin (50 mg/m^2) for gastric cancer and mitomycin (10 mg/m^2) or oxaliplatin (360 mg/m^2) plus irinotecan (360 mg/m^2) for colorectal cancer. All these drugs were added in the heated circulation and maintained for 90 min except oxaliplatin and irinotecan protocol in colorectal cancer which were used for 30 min as described by Elias et al. [8].

Intraoperative hydration prior to and during HIPEC (in order to maintain a urine output > 600 ml/h) by appropriate volume expansion with crystalloid and colloid solutions was mandatory. It was crucial for the anaesthesiologist to be aware of the heat stroke syndrome.

Digestive anastomoses were completed after the

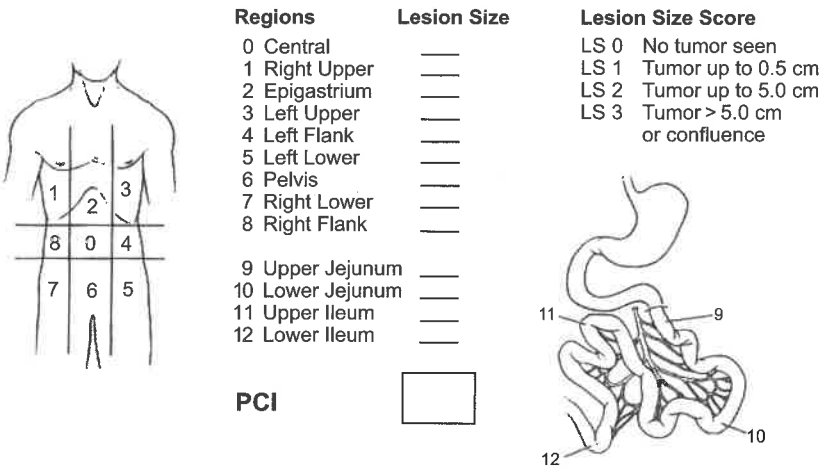


Figure 1. Peritoneal Cancer Index [3].

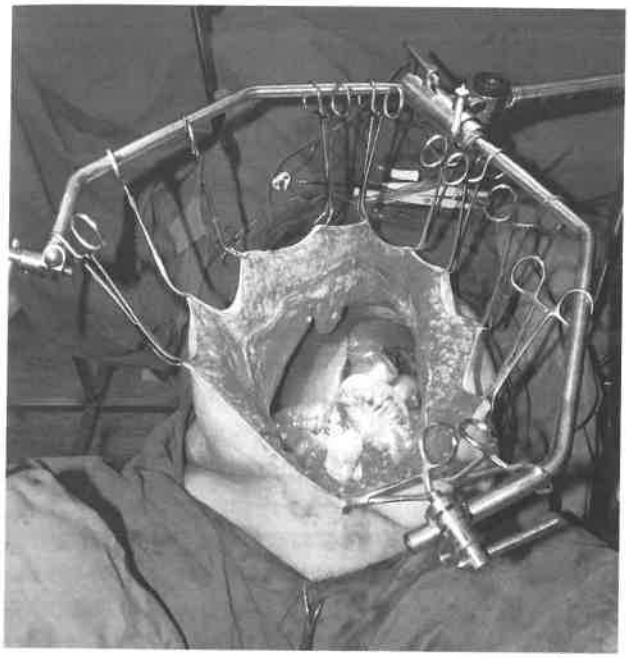


Figure 2. Open abdomen (coliseum) technique.

chemotherapeutic agents had been drained away and the abdominal cavity had been lavaged.

Two problems were encountered during HIPEC. First, the difficulty in attaining the desired temperature of 42° C; and second, the diminished return of the dialysate to the reservoir, usually due to the leakage of intraperitoneal fluid into the chest requiring chest tube(s) insertion. In our patients we inserted chest tubes bilaterally at the end of the operation.

Results

Twenty-four patients (3 men and 21 women) were treated. The mean age of the study group was 60 years (range 24-74).

The mean duration of the operation, including the HIPEC infusion was 7 h and 50 min (range 5-12.30 h). The mean blood product transfusion requirements per patient was 2.2 units of packed red cells (range 0-4) and 4 units of fresh frozen plasma (range 0-8).

Table 1 demonstrates the patient characteristics,

Table 1. Patient characteristics, peritoneal cancer index (PCI), completeness of cytoreduction (CC) and final outcome

Patient no.	*Sex*	*Age (years)*	*Type of cancer*	*PCI*	*CC score*	*Survival (months)*
1	F	71	Ovary	35	CC1	Perioperative death
2	F	74	Ovary	36	CC2	4
3	F	67	Rectal	4	CC0	6*
4	F	70	Ovary	16	CC0	12*
5	F	62	Rectal	7	CC0	10*
6	F	34	Ovary	15	CC1	11
7	F	72	Colon	33	CC2	6
8	F	71	Colon	39	CC2	Perioperative death
9	F	69	Uterus	4	CC0	12*
10	F	71	Ovary	14	CC0	6*
11	F	24	Uterus	15	CC0	12*
12	F	48	Gastric	34	CC0	18
13	F	56	Ovary	32	CC1	6
14	F	62	Ovary	14	CC0	36
15	F	49	Colon	3	CC0	12*
16	F	56	Ovary	3	CC0	10*
17	F	60	Ovary	3	CC0	12*
18	M	64	Gastric	25	CC0	10
19	M	58	Colon	18	CC0	12*
20	F	67	Ovary	16	CC0	6
21	F	62	Ovary	24	CC2	12*
22	F	48	Ovary	19	CC2	14*
23	M	54	Colon	26	CC0	10*
24	F	71	Gastric	36	CC2	2

*still alive
F: female, M: male

PCI, completeness of cytoreduction score, and final outcome.

Macroscopically complete cytoreduction (CC-0 and CC-1) was achieved in 18 (75%) patients. During HIPEC the mean intraabdominal inflow temperature was 41.7° C, the perfusion flow was 1.2 - 2 l/min and the mean perfusate volume was 2.6 l. During HIPEC the mean patient temperature was 38.1° C (range 37.4 - 39.4).

Figure 3 demonstrates the overall survival of patients with gynaecological and gastrointestinal PC. The survival curves between these patients were almost identical in the first 16 months, but after that time the survival of the gastrointestinal cancer patients declined abruptly ($p < 0.02$).

Figure 4 demonstrates the overall survival between patients with PCI < 16 vs. ≥ 16. The mean survival was 36 months vs. 10 months, respectively ($p<0.04$). Figure 5 shows the overall survival between patients with CC-0 + CC-1 vs. patients with CC-2. The mean survival in CC-0 + CC-1 was 19 months, while it was 9.8 months in CC-2 group ($p < 0.04$).

The overall perioperative mortality was 8.3% (2 patients) due to septic complications, one from pancreatitis and the other one from pneumonia.

The overall morbidity was 42%. The most frequent complications were enteric fistulas (3/24 patients, 12.5%), intestinal obstruction (1/24 patients, 4.1%), pulmonary embolism (2/24 patients, 8.2%), pneumonia (5/24 patients, 20.8%), urinary infection (3/24 patients, 12.5%) and wound infection (4/24 patients, 16.6%).

Reoperation was necessary in 2 patients (one with intraabdominal sepsis due to necrotic pancreatitis and the other with intraabdominal hemorrhage). Postoperatively, all patients were admitted in the intensive care unit (ICU) and their mean stay was 2.1 days (range 0-10); the mean hospital stay was 18.9 days (range 12-30).

The mean follow-up time was 22 months (range 3-36). One-year survival rate was 59.1%. Concerning the gynaecological cancers it was 53.8% and in gastrointestinal cancers 44.4%. The mean overall survival in gynaecological cancers was 11.7 months and in gastrointestinal cancers it was 9.5 months. The mean cost of this procedure was 18,500 € per patient.

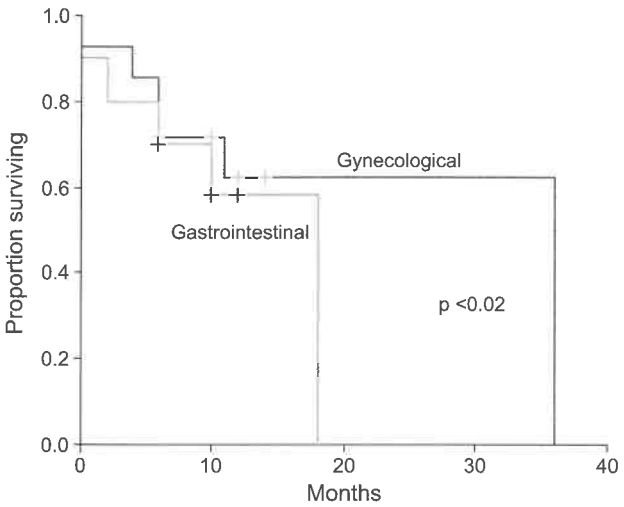


Figure 3. Overall survival: gynaecological vs. gastrointestinal peritoneal carcinomatosis.

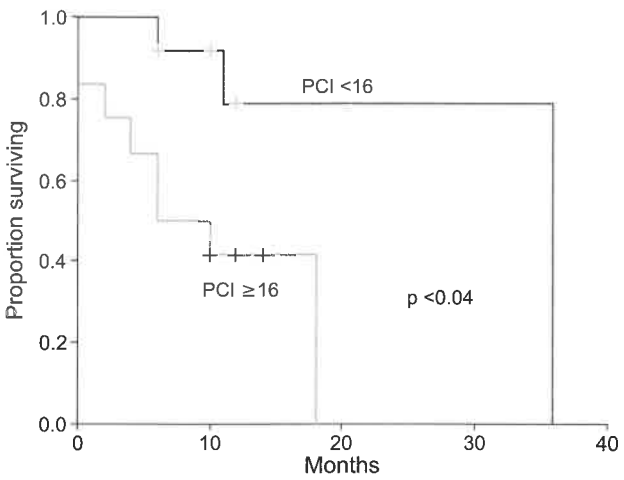


Figure 4. Overall survival between the patients with PCI < 16 vs. PCI ≥ 16.

Discussion

Peritoneal disease is commonly the end-stage of many gastrointestinal and gynaecological cancers and

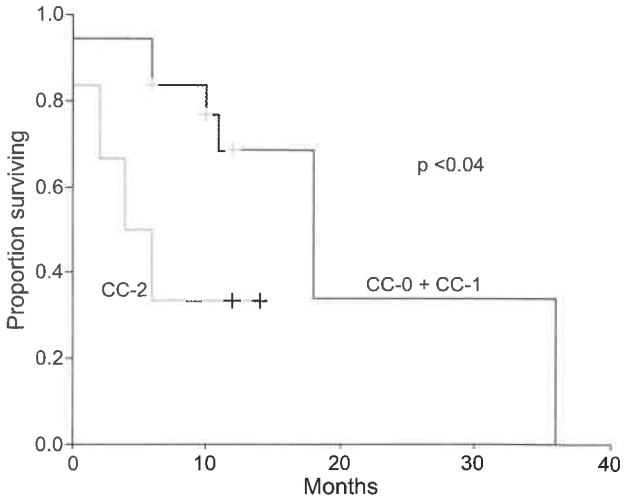


Figure 5. Overall survival between patients with CC-0 + CC-1 vs. patients with CC-2.

is associated with a poor survival of less than 6 months as well as with problems of intestinal obstruction and malignant ascites.

Peritoneum is a complex structure and performs specific functions. It consists of a monolayer of mesothelial cells supported by a basement membrane that rests on a layer of connective tissue. Peritoneal carcinomatosis is a multistep process of local-regional cancer spread [2]. Tumor cells must first gain access to the peritoneal cavity, spread intraabdominally along with the peritoneal fluid, attach to the mesothelial surface and then invade through the peritoneal surface to become vascularized.

Aggressive cytoreductive surgery attempts to eradicate all residual tumor cells and the HIPEC allows a favorable drug distribution to all surfaces at risk, without delay.

There are some important factors concerning the patients' outcome and survival.

In our study, patients with PCI < 16 were benefited from this approach. The mean survival in this subgroup of patients was 10 months vs. 6.8 months in patients with PCI ≥ 16 ($p < 0.04$). These results agree with other studies and suggest a meticulous selection preoperatively with different diagnostic procedures in order to select the candidates for effective intraperitoneal chemotherapy [9,10].

The role of completeness of cytoreduction is another factor that can predict overall survival. In our study, patients who achieved CC-0 had mean survival of 10.3 months vs. 8.5 months of patients in the CC-1 group and 6 months in the CC-2 group ($p < 0.02$). Analogous results regarding the achievement of cytoreduction were reported from other investigators [11,12].

Concerning the mortality and morbidity, our results are similar with the initial experience of other centres in Europe and South America. Perioperative variables, like total blood loss, duration of operation and ICU stay, have been reported as significant prognostic factors for postoperative morbidity and survival [13]. An independent factor which is important to be evaluated is the number of digestive anastomoses performed. This variable has been reported as a significant prognostic factor for postoperative morbidity [14,15]. All trials evaluating the cytoreductive surgery and HIPEC reported 0-10% mortality and 10-60% morbidity rates [14,16].

Among all techniques, the "coliseum" open abdomen technique allows optimal temperatures and diffusion of chemotherapeutic agents to all areas; on the other hand, there are no prospective studies showing higher recurrence rates of open compared to close abdomen technique [17,18].

The cost of this therapy has been evaluated in different countries and it is high [19,20]. In our institutions the cost ranged between 10,000 - 40,000 €, depending on the patient's performance status, the complications, the ICU stay and the total hospital stay. The real cost of the intraperitoneal chemotherapy materials was 3,000 €. In our system of reimbursing, the hospital which offers this type of new therapy to its patients receives back all the amount spent. On the other hand, it is necessary that corrective measures should be taken, first to describe this combined treatment in the official list of medical insurance and second to determine the exact cost of each patient for reimbursing.

In conclusion, our preliminary data suggest that the combination of cytoreductive surgery with HIPEC is associated with acceptable morbidity and mortality and offers an improved survival in patients with peritoneal carcinomatosis. An optimal patient selection, the probability of complete cytoreduction and an experienced centre are the most important factors for a favorable final outcome. Such patients should be treated within the frame of carefully designed trials. The criteria that we used are in line with those adopted by the Peritoneal Surface Malignancy Oncology group in 2006 [21].

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