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Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy in Elderly Patients

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Abstract. *Background: The treatment of peritoneal malignancies in elderly patients with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is an ongoing question due to the high associated surgical risk. Patients and Methods: Thirty patients, 11 (36.7%) older than 65 years, were submitted to CRS plus HIPEC. Criteria of patient eligibility were: peritoneal carcinomatosis of different origin, T3-4 gastric cancer, ECOG performance status ≤2, no extra-abdominal extension and no evidence of bowel obstruction. The median follow-up was 21.5 months (range: 1-63). The purpose of this retrospective study, was to evaluate the feasibility of this approach in elderly patients, with special reference to postoperative morbidity, mortality and survival. Results: We have recorded, in elderly patients, higher grade 3 and 4 morbidity and mortality, similar mean duration of cytoreductive surgery, of postoperative hospital stay, of median survival and of overall survival rates. Conclusion: Since there no statistical differences, in terms of morbidity and mortality, CRS with HIPEC may also be suitable for elderly patients.*

Peritoneal carcinomatosis (PC) is a frequent evolution of gastrointestinal and gynecological malignancy and it has been regarded as a lethal clinical entity (1). Treatment options for these patients have improved significantly in the past few years. Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is an aggressive and promising treatment for this group of patients, with favorable results in terms of quality of life and outcome (2). This type of approach has been established as the standard therapy for pseudomyxoma peritonei as shown by Gonzàlez-Moreno and Sugarbaker in 501 patients with a mean survival of 156 months and 5- and 10-year survival of 72% and 55%, respectively (3). In diffuse malignant peritoneal mesothelioma, which accounts for 10-20% of all forms of malignant mesothelioma (4), the mean survival after aggressive surgery combined with HIPEC has approached 5 years and seems to have improved with subsequent reports (5, 6). In PC of colorectal origin, which occurs in approximately 10-30% of patients with this type of cancer, this treatment has been showed to be superior to systemic chemotherapy in one randomized trial and in one multi-institutional study (7, 8); at present, in the literature, the mean survival varies considerably from 12 to 32 months, with 1-, 2-, 3- and, when reported, 5-year survival rates range from 65% to 90%, 25% to 60%, 18% to 47%, and 17% to 30%, respectively (9). For patients with peritoneal diffusion of gastric cancer, the mean survival range from 8 to 11 months and the 5-year survival from 6% to 16%, respectively (10, 11). Finally, for ovarian cancer, the CRS plus HIPEC showed a significant increase in median progression-free and overall survival from 18 to 23 months and 49 to 66 months, respectively (12, 13).

This type of procedure carries a high postoperative morbidity from 14% to 55% and a treatment-related mortality from 0% to 19% which seem related to the extent of surgery rather than to the HIPEC (14). With the general increase of lifespan, many older patients should be expected to undergo this type of major cancer surgery. However, the suitability of procedure for this group of patients is an ongoing question due to the high surgical risks related to their older age and to the presence of chronic comorbidities, resulting in poor performance status (PS) (15). To our knowledge, at the present time, there is only one report (15) that analyzes the feasibility of HIPEC in elderly patients. The purpose of this retrospective study, the first article in literature that compares two groups of patients with different age class submitted to CRS plus HIPEC, was to evaluate the feasibility of this approach in elderly patients, defined as such according the World Health Organization, with special reference to postoperative morbidity, mortality and survival.

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Patients and Methods

Thirty patients, 19 (63.3%) younger than 65 years (group 1), and 11 (36.7%) older than 65 years (group 2) were submitted, over a period of 4 years, to CRS plus HIPEC in the General Surgery Unit of the University of Messina, Italy,. Criteria of eligibility were PC of any origin, T3-4 gastric cancer, ECOG performance status ≤2, no extra-abdominal extension and no evidence of bowel obstruction. Twenty-two patients were submitted to CRS plus HIPEC for the presence of PC, while in two patients affected by gastric cancer, one by colon cancer and one by ovarian cancer, HIPEC was performed for positive peritoneal cytology. In four patients, affected by gastric cancer of diffuse type, the procedure was performed with prophylactic aim, as intraoperative staging documented two T3 and two T4 tumors. In one patient with colon cancer, and in two with ovarian cancer, for the onset of a local recurrence, the treatment was repeated after 15, 29 and 8 months respectively. Six patients affected by ovarian cancer had undergone neoadjuvant chemotherapy with carboplatin and taxol; all patients were submitted to adjuvant chemotherapy.

A careful abdominal examination was made through a laparotomy from the xyphoid to the pubic area; the intraoperative diagnosis of PC was made by frozen section and the extent of PC was scored according to the Peritoneal Cancer Index (PCI) (16). CRS was carried out according to the technique described by Sugarbaker (17), while to assess the entity of cytoreduction we used the Completeness of Cytoreduction Score (CC score) (18). All patients were submitted to HIPEC with the closed-abdomen technique which foresees the positioning of five abdominal drainages, two inflows on the right (subhepatic sheath and pelvic pouch) and three outflows on the left (subhepatic, left subdiaphragmatic, shallow pelvis) and of six thermometric probes (upper and lower abdomen, inflow, outflow, rectum, and esophagus), the temporary suture of the skin and the perfusion with a preheated solution for peritoneal dialysis. Peritoneal temperature was kept between 41-43˚C and the drugs were administered according to the following schedules: i) cisplatin (CDDP) at 25 mg/m^2/l plus mitomycin C (MMC) at 3.3 mg/m^2/l for 60 min for the treatment of gastric and colonic carcinomatosis; ii) CDDP at 43 mg/l and doxorubicin at 15.25 mg/l for 90 min for ovarian carcinomatosis. Afterward, the cytostatic solution was completely evacuated and the abdominal cavity was revisited. The median follow-up was 21.5 months (range: 1-63). The purpose of this retrospective study, was to evaluate the feasibility of this approach in elderly patients, with special reference to postoperative morbidity, mortality and survival.

Statistical analysis. Survival curves were estimated using the Kaplan-Meier method and compared by log-rank test. Chi-square test was used for categorical data. A value of $p<0.05$ was considered statistically significant.

Results

Thirty CRS plus HIPEC procedures were carried out in 30 patients with a median age of 60 years (range: 30-77 years); 19 (63.3%) were younger than 65 years (median age: 57; range: 30-63 years) (group 1) and 11 (36.7%) older than 65 years (median age: 69; range: 66-77) (group 2). In elderly patients compared to younger patients, we recorded higher, but not statistically significantly so, rates of morbidity (27.3% *vs*. 21.1%) ($p=0.698$) and mortality (18.2% *vs*. 5.3%) ($p=0.256$), probably correlated to the presence of comorbidities (100% *vs*. 36.8%) ($p<0.01$) and, a lower mean postoperative hospital stay (15.6 days *vs*. 19.1) ($p=0.622$). A complete cytoreduction was achieved in 29 out of 30 operations, with 26 CC-0 resections and 3 CC-1 (optimal cytoreductive rate: 96.6%), while one sub-optimal cytoreduction was recorded in one young patient (CC-2 resection). All data are summarized in Tables I and II.

Survival analysis. The 1-, 3- and 4-year survival rates were 90%, 49% and 39% for the patients of group 1 and 100%, 76% and 25% for group 2, with a median survival of 33 and 38.5 months respectively, without significant difference between the two groups ($p=0.75$) (Figure 1).

Discussion

For a long time, PC has been considered as a terminal condition, with no curative options. Over the past decade however, new therapeutic approaches have emerged. Locoregional therapies including cytoreductive surgery with peritonectomy procedures for macroscopic disease and perioperative HIPEC to eradicate the microscopic residual disease have been developed (19). The peritoneal-plasma barrier delays the clearance of high molecular weight chemotherapy from the peritoneal cavity and allows a large exposure of residual small cancer nodules. Tissue penetration of intraperitoneal chemotherapy is improved by moderate hyperthermia (41-42˚C). This promising approach is, however, associated with high postoperative morbidity (14% to 55%) and mortality (0% to 19%), which seem to be related to the extent of surgery as a function of peritoneal involvement rather than to the HIPEC itself (14). With the general increase of lifespan, there are many older patients that can be submitted to this type of major cancer surgery albeit with an higher surgical risk, as these people suffer from frequent comorbidities, resulting in a poorer PS (15). To our knowledge, the present investigation, even if performed on a small heterogeneous sample of cases, is the first that compares two groups of patients with different age class (younger and older than 65 years) submitted to CRS plus HIPEC. In fact, the report of Mueller *et al*. (15), which is the only report that analyzes the HIPEC in elderly patients, considered only patients older than 65 years. In our experience, for elderly patients, we have recorded higher, but not statistically significantly so, rates of morbidity (27.3% *vs*. 21.1%) and mortality (18.2% *vs*. 5.3%), probably correlated to the presence of comorbidities (100% *vs*. 36.8%), a lower mean postoperative hospital stay (15.6 days *vs*. 19.1), and similar median (38.5 months *vs*. 33) and overall survival rates (1-, 3- and 4-year survival: 100%, 76% and 25% *vs*. 90%, 49% and 39%). Comparing the data of our

Table I. *Characteristics of patients and results.*

	N	Procedure	Median age (range) (years)	Chronic comorbidities	Mean duration of surgery (min)	Mean PCI	CC-Score 0/1/2	Mean postop. hospital stay (days)	Grade morbidity 3/4	Mortality
Total	30	30	60 (30-77)	18/30 (60%)	575.3	8.96	26/0 3/1 1/2	17.8	7/30 (23%)	3/30 (10%)
Aged <65 years	19	19	57 (30-63)	7/19 (36.8%)	559.4	8.58	16/0 2/1 1/2	19.1	4/19 (21.1%)	1/19 (5.3 %)
Aged >65 years	11	11	69 (66-77)	11/11 (100%)	602.7	9.64	10/0 1/1 0/0	15.6	3/11 (27.3%)	2/11 (18.2%)

Table II. *Grade of postoperative morbidity.*

Morbidity	Grade 3	Grade 4
Intestinal fistula	3	
Anastomotic leakage		2
Bowel perforation		2

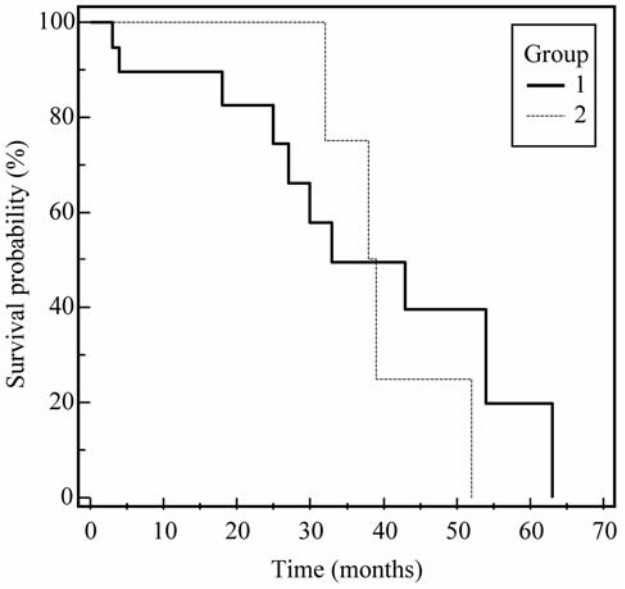

Figure 1. *Kaplan-Meier estimates of survival probability of 30 patients submitted to CRS plus HIPEC (group 1: <65 years; group 2: >65 years).*

elderly patients with those of Mueller, we recorded higher grade 3/4 morbidity (27.3% *vs*. 17%), although two different postoperative morbidity classifications (CTCAE Version 3.0 *vs*. Feldman's classification) were utilized, and a higher mortality (18.2% *vs*. 0%). These differences are probably due to the fact that all our older patients presented chronic comorbidities and that we have reached a better rate of complete cytoreduction (96.6% *vs*. 74.4%). Hence we maintain, on the basis of our experience and of the data of the literature, that CRS plus HIPEC can also be performed in elderly patients with PC with acceptable morbidity and mortality.

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