Hyperthermic Intraperitoneal Chemoperfusion in Combined Treatment of Locally Advanced and Disseminated Gastric Cancer

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Abstract. Results of using hyperthermic intraperitoneal chemoperfusion (HIPEC) in combined modality treatment of 49 advanced gastric cancer patients are analyzed. Post-surgery complications occurred in 26.5% of the cases, whereas operative mortality constituted 4.1%. The combined modality treatment of serosa-invasive gastric cancer patients allowed reducing the level of metachronous peritoneal carcinomatosis from 73.7% to 11.1% ($p<0.001$) and increasing the median survival from 12 months to 22.5 months ($p=0.001$). The median and 1-year survival of intraperitoneal disseminated gastric cancer patients undergoing combination therapy with the use of HIPEC were 12 months and 68.8% and those of control group patients (palliative chemotherapy) – 8 months and 25% respectively ($p=0.004$). The symptomatic use of HIPEC allows effectively eliminating recurrent ascites in diffuse peritoneal carcinomatosis patients.

Key words: gastric cancer, peritoneal carcinomatosis, cytoreductive operation, hyperthermic intraperitoneal chemoperfusion.

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INTRODUCTION

During the last two decades the paradigm of the treatment of intraperitoneal disseminated tumors has been changing in oncology with the introduction of new active ways of combined modality treatment of such patients, namely those based on cytoreductive operations and hyperthermic intraperitoneal chemotherapy (HIPEC). This approach to treatment has been proved effective for patients suffering from colorectal cancer with peritoneal carcinomatosis (PC), peritoneal pseudomyxoma and peritoneal mesothelioma, which accounts for its inclusion in the national standards of some EU countries [1, 2]. However, the results of using the combination therapy based on HIPEC for gastric cancer (GC) still remain limited by the clinical experience of separate clinics in Japan and Europe, therefore the issue of advisability and effectiveness of using HIPEC in the treatment of GC patients remains urgent and discussible [3, 4, 5].

Peritoneal dissemination is the most common way of GC metastasis [6] and is diagnosed in 30% of all GC patients [7]. Intraperitoneal progression of the disease after radical interventions (metachronous carcinomatosis) develops in 34 – 60 % of patients and is the main cause of GC [8]. Systemic palliative chemotherapy in GC patients with peritoneal implants is ineffective [9]. The use of target medications is in most cases restricted to intestinal type GC characterized by hematogenous cancer spread [10].

Cytoreductive operations (in cases of GC with peritoneal implants: gastrectomy + lymphadenectomy D2 + partial peritonectomy) are based on the principle of maximum excision of tumor mass from the patient's body in order to minimize the intraperitoneal tumor cell pool level and ensure that the subsequent chemohyperthermic treatment of

residual microscopic tumor elements is effective. The fundamental difference between cytoreductive operations and palliative ones is the excision of not only the loco-regional segment of a disseminated tumor, but also of distant metastases. On completion of the main stage of the surgery and in order to carry out a HIPEC treatment, a closed sterile circuit is created by connecting major catheters positioned in the peritoneum with automatic thermostatic equipment, which allows perfusing the peritoneum with a solution of cytostatic drugs in the hyperthermic mode with permanent thermal monitoring of the patient's body at different levels.

The classification suggested by the Japanese Gastric Cancer Association (JGCA) is a reliable method of evaluating the degree of intraperitoneal spread of the metastatic process [11]: P0 – no implants on the peritoneum, P1 – isolated disseminates in the upper peritoneum (above the transverse colon level), P2 – isolated disseminates in all parts of the peritoneum, P3 – diffuse carcinomatosis of the peritoneum, including ascites and CY1 – the presence of malignant cells in peritoneal lavage without macroscopic carcinomatosis.

Another reliable criterion for defining peritoneal carcinomatosis stage is peritoneal cancer index (PCI) that is calculated as follows: the peritoneum is divided into 13 tentative sections, the degree of carcinosis being evaluated in each of them depending on the size of implants (1 to 3 points) with a further summing of points for the whole peritoneum [12].

Completeness of cytoreduction score (CC) is an important prognostic index of cytoreductive operation effectiveness ([12]: CC-0 – no macroscopic residual tumor nodules on the peritoneal after cytoreductive operation, CC-1 – residual nodules less than 2.5 mm in diameter, CC-2 – residual nodules from 2.5 mm to 2.5 cm in diameter and CC-3 – the diameter of residual tumor nodules is larger than 2.5 cm.

The aim of this study was to evaluate the clinical benefit of using combined modality treatment based on HIPEC in locally advanced and disseminated GC patients as

well as to define prognostic factors for advanced GC patients who get combined modality treatment.

STUDY OBJECT AND METHODS

Results of the treatment of 98 advanced GC patients who stayed at the Oncology and Medical Radiology Clinic of Danylo Halytsky Lviv National Medical University and Lviv State Regional Oncology Medical and Diagnostic Centre in 2008 – 2012 have been analyzed (prospective non-randomized clinical study). 66.3% of the patients were male (65 persons) and 33.7% female (33 persons). The age of the patients was 22 to 74 years old, mean age 56.6 ± 10.2 years old. All patients had GC verified morphologically prior to treatment and gave their informed consent to participation in the study. GC was staged in the patients according to the criteria of TNM classification, edition 7 (2009).

The patients under study were divided into three groups. Group 1 consisted of 38 localized or locally advanced GC patients with serosa invasion and consequently high risk of intraperitoneal progression. Group 1 patients were divided into two subgroups: study subgroup – these patients were given standard radical surgery including gastrectomy or subtotal gastrectomy with D2 lymphadenectomy followed by intraoperational HIPEC with adjuvant purposes; and surgical control subgroup – these patients were given only surgical treatment without adjuvant therapy.

Group 2 consisted of 40 GC patients with manifested peritoneal dissemination. Group 2 patients were divided into two subgroups: study subgroup – the patients were given cytoreductive surgery including gastrectomy or subtotal gastrectomy with D2 lymphadenectomy and partial peritonectomy of peritoneal sections affected by implants followed by intraoperational HIPEC and systemic post-operative chemotherapy; and control subgroup – the patients were given only systemic palliative chemotherapy.

Group 3 consisted of disseminated intraperitoneal GC patients with diffuse peritoneal carcinomatosis complicated by tense ascites. Group 3 patients were divided into two subgroups: study subgroup – the patients were given symptomatic surgery including laparotomy, ascites evacuation and symptomatic HIPEC in order to eliminate recurrent ascites; and control subgroup – the patients were given best supportive care. The patients of the given group were not given cytoreductive surgery because of the massive character of peritoneal dissemination and the impossibility to achieve complete cytoreduction (Fig. 1).

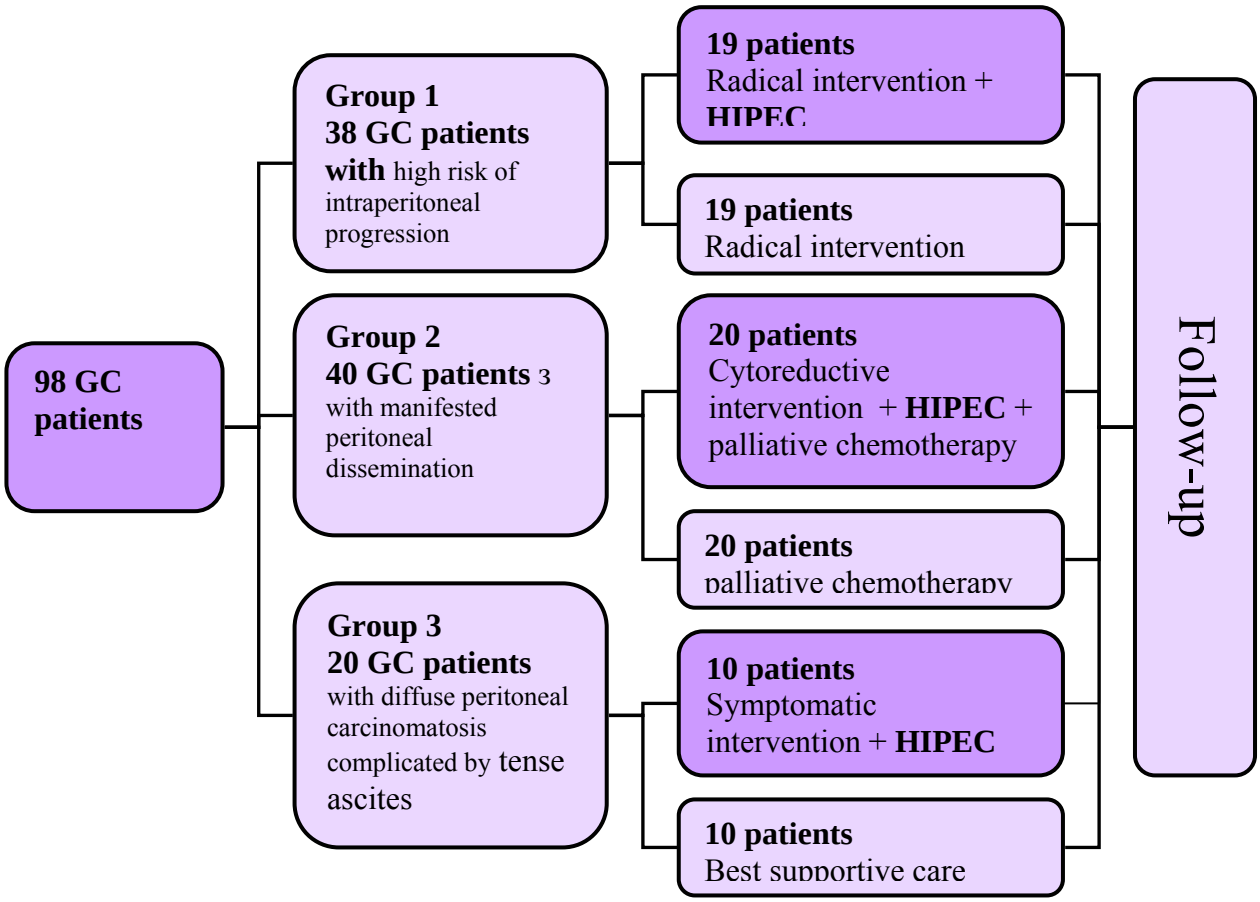

Fig. 1. Study design

The HIPEC procedure lasted 90 min at the medium intra-abdominal temperature of 42,3 ± 1,3 0 C (from 39 to 44) using mitomycin C (MMC) at a dose of 12.5 mg/m2 and cisplatin at a dose of 75 mg/m2. Three patients of trial were given bidirectional chemotherapy (HIPEC plus intraoperative intravenous 5-FU).

The patients (group I) were compared in accordance with the main clinicopathologic parameters (Table 1).

Table 1

	Radical intervention + HIPEC (n=19)	Radical intervention (n=19)
Men Woman	15 (79%) 4 (21%)	13 (68%) 6 (32%)
Localisation: antral corpus antral part + corpus subtotal	 4 (21%) 9 (47%) - 6 (32%)	 7 (37%) 5 (26%) 1 (5%) 6 (32%)
Structure: G2 G3 G4 Signet ring cell	 2 (11%) 9 (47%) 7 (37%) 1 (5%)	 1 (5%) 6 (32%) 10 (52%) 2 (11%)
pT (TNM 7, 2010) pT4a pT4b	 15 (79%) 4 (21%)	 18 (95%) 1 (5%)
Area of serosa's infiltration Less than 20 см^2 More than 20 см^2 Subtotal infiltration	 7 (36%) 6 (32%) 6 (32%)	 7 (36%) 6 (32%) 6 (32%)
Stage (TNM 7, 2010) IIB IIIA IIIB IIIC	 8 (43%) 1 (5%) 5 (26%) 5 (26%)	 11 (58%) 2 (10%) 3 (16%) 3 (16%)
Lymphodissection D1 D2	 8 (42%) 11 (58%)	 10 (52%) 9 (48%)

The Table 2 shows the main clinicopathologic parameters of the patients (group II).

Table 2

	Cytoreductive intervention + HIPEC + chemo (n=20)	Palliative chemo (n=20)
Man Woman	10 (50%) 10 (50%)	16 (80%) 4 (20%)
Localisation: antral corpus antral + corpus subtotal	 2 (10%) 5 (25%) 6 (30%) 7 (35%)	 7 (35%) 4 (20%) 5 (25%) 4 (20%)
Structure: G2 G3 G4 Signet ring cell Mucinosis	 1 (5%) 2 (10%) 14 (70%) 2 (10%) 1 (5%)	 1 (5%) 10 (50%) 6 (30%) 3 (15%) -
Stage of dissemination (JGCA): P0 (CY1) P1 P2 P3	 2 (10%) 10 (50%) 7 (35%) 1 (5%)	 2 (10%) 11 (55%) 6 (30%) 1 (5%)
Mean PCI	3,4 (0-14)	4,2 (0-18)
Lymphodissection D1 D2	 14 (70%) 6 (30%)	 - -

The dissemination degree among the patients assigned to the control subgroup has been determined according to the results of the diagnostic laparoscopy or explorative laparotomy.

The scores of cytoreduction completeness among 20 patients (group II) were as follows: 15 patients (75%) CC-0, 3 patients (15%) - CC-1 and 2 patients (10%) - CC-2.

12 (60%) out of 20 patients (group II) receiving HIPEC in combined modality treatment, at the postoperative stage underwent palliative chemotherapy according to the following schemes: ECF - 4 patients (20%), CF - 4 (20%), CAF - 2 (10%), 5-FU - 1 (5%) and tegafur - 1 (5%). 17 patients (85%) from the control subgroup II underwent systemic palliative chemotherapy according to the following schemes: XELOX - 1 patient (5%), CF - 6 (30%), CAF - 4 (20%), 5-FU - 4 (20%), tegafur - 2 (10%), 3 (15%) patients received symptomatic therapy.

An average amount of peritoneal fluid in the abdominal cavity among patients from the group III equaled to 5,5 ± 1,4 liters (from 3.5 to 8 liters).

Source data were processed using the Statistica program. The Kaplan-Meier method was used to estimate the cumulative survival. The log-rank significance test was applied to determine the difference in survival between various groups. Multivariate analysis was conducted by means of discriminative research.

RESULTS

The average hospital stay was 24,3 ± 5,7 days (from 16 to 48 days).

At the completion of a best surgical effort at cytoreduction using HIPEC 13 (26.5%) out of 49 patients (group III) developed postoperative complications. Among them 7 (14.3%) patients developed surgical implications, 6 (12.2%) patients - complications related to HIPEC and 1 (2%) patient - somatic complications. Surgical complications included: 2 (4.1%) patients - subhepatic abscess, 2 (4.1%) - infected pancreatic necrosis with purulent-septic complications, 1 (2%) - anastomositis, 1 (2%) - mesenteric thrombosis and 1 (2%) - gastrointestinal anastomotic leak. The complications related to HIPEC included: 1 (2.6%) patients - grade III-IV nephrotoxicity (according to the Clinical Toxicity Criteria of the National Cancer Institute of Canada - CTC NCIC), 1 (2.6%) - grade III leukopenia, 1 (2.6%) - significant intestinal distention, 1 (2.6%) tendency to systemic increase in body temperature during the HIPEC procedure, 1 (2.6%) - acute

enterocolitis, 1 (2, 6%) patients - combination of grade III nephrotoxicity and long-term enterocolitis. As for the general somatic complications nosocomial pneumonia was seen in 1 patient (2.6%).

Side effects and mild, barely noticeable effects related to the disease course as well as to the surgery type and the use of HIPEC were diagnosed in 46 (93.9%) patients (Table 3).

Table 3

Adverse events	Number of patients (%)
Hypoproteinemia grade I-III	41 (83,7 %)
Anemia grade I-III	33 (67,3 %)
Leucopenia grade I-II	3 (6,1 %)
Thrombocytopenia grade I	1 (2 %)
Hyperamilasemia grade I-III	17 (34,7 %)
Hyperaminotransferasemia grade I-II	19 (38,8 %)
Renal toxicity grade I-II	14 (28,6 %)
Microhematuria grade I	8 (16,3 %)
Proteinuria grade I-II	14 (28,6 %)
Elevated levels of exudation from drainages	7 (14,3 %)

After combined modality treatment with HIPEC postoperative mortality was occured in 2 (4.1%) out of 49 patients: mesenteric thrombosis and generalized atherosclerosis were seen in 1 patient and necrotic pancreatitis with purulent-septic complications was seen in 1 patient as well.

Minimal follow-up time in patients receiving CRS and HIPEC was 12 months.

In 19 patients (group I) diagnosed a high risk of intraperitoneal progression, undergoing HIPEC with adjuvant purposes a median and 1-year survival comprised 22,5 ±

6,5 months (95% CI 9,7-35,3) and 100 %, respectively; and in 19 patients from the surgical control subgroup - 12 ± 1,3 months (95% CI 9,4-14,6) (p = 0.002) and 52.6% respectively (p = 0.001) (Fig. 2).

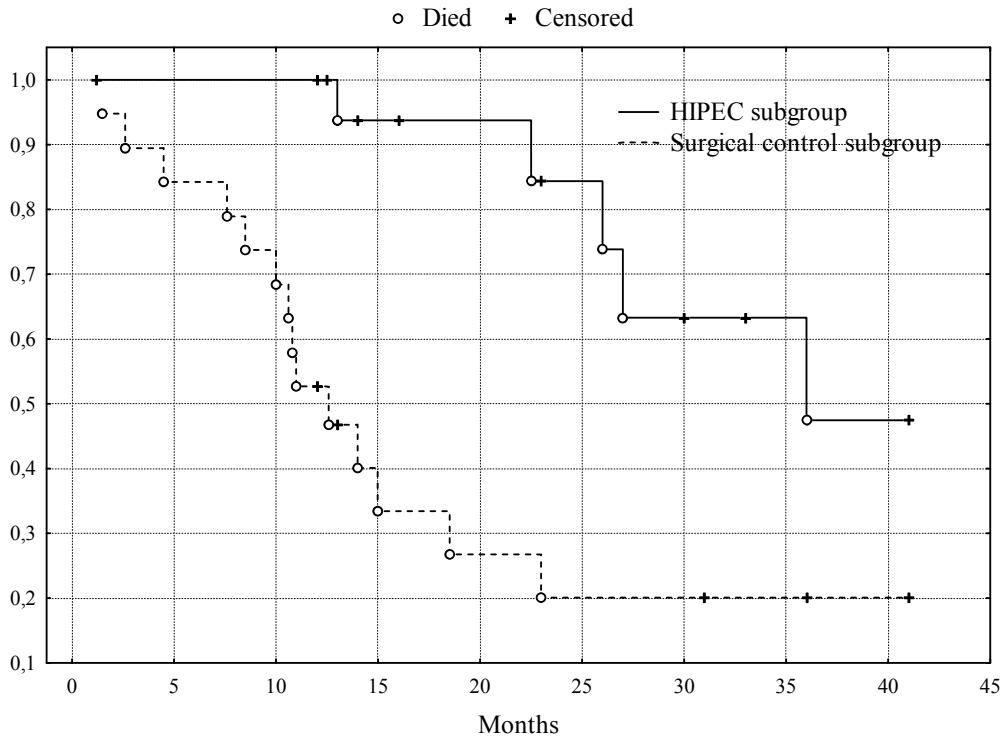

Fig. 2 Cumulative censored overall survival in gastric cancer patients with a high risk of intraperitoneal disease progression after the HIPEC procedure in adjuvant regime and in the surgical control subgroup.

The intraperitoneal recurrence rate in patients (group I) receiving combined treatment with HIPEC equaled to 11.1% and in patients assigned to the surgical control subgroup - 73.7% (p <0.001).

In 20 patients from the II group (with implant associated manifestation), after combined treatment with HIPEC, a median and 1-year survival comprised 12 ± 1,6 months (95% CI 8,9-15,1) and 68.8% respectively, in 20 patients from the control group receiving palliative chemotherapy - 8 ± 2,6 months (95% CI 2,99-13) (p = 0.004) and 25% (p = 0.004) respectively (Fig. 3).

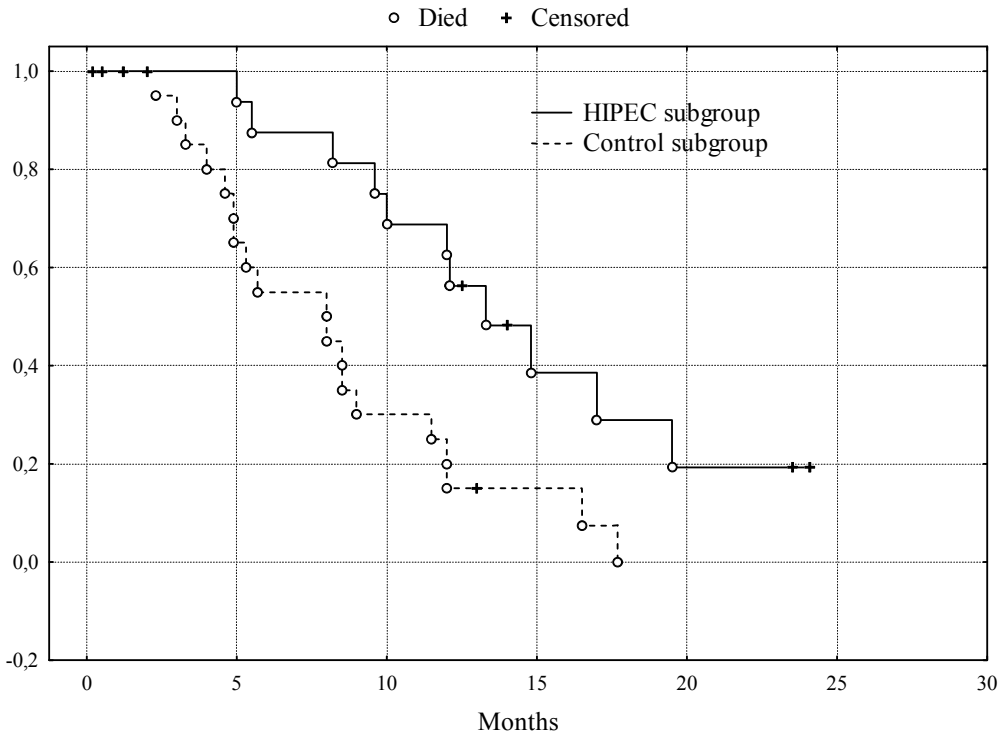

Fig. 3. Cumulative censored overall survival in gastric cancer patients with peritoneal dissemination after combined therapy with HIPEC and in the control subgroup.

In 10 patients with tense malignant ascites from (group III) undergoing combination therapy with the use of HIPEC median survival comprised 3.5 months, and in 10 patients from the control group - 2.4 months, the difference in survival was not estimated as probable ($p = 0.49$) (Fig. 4).

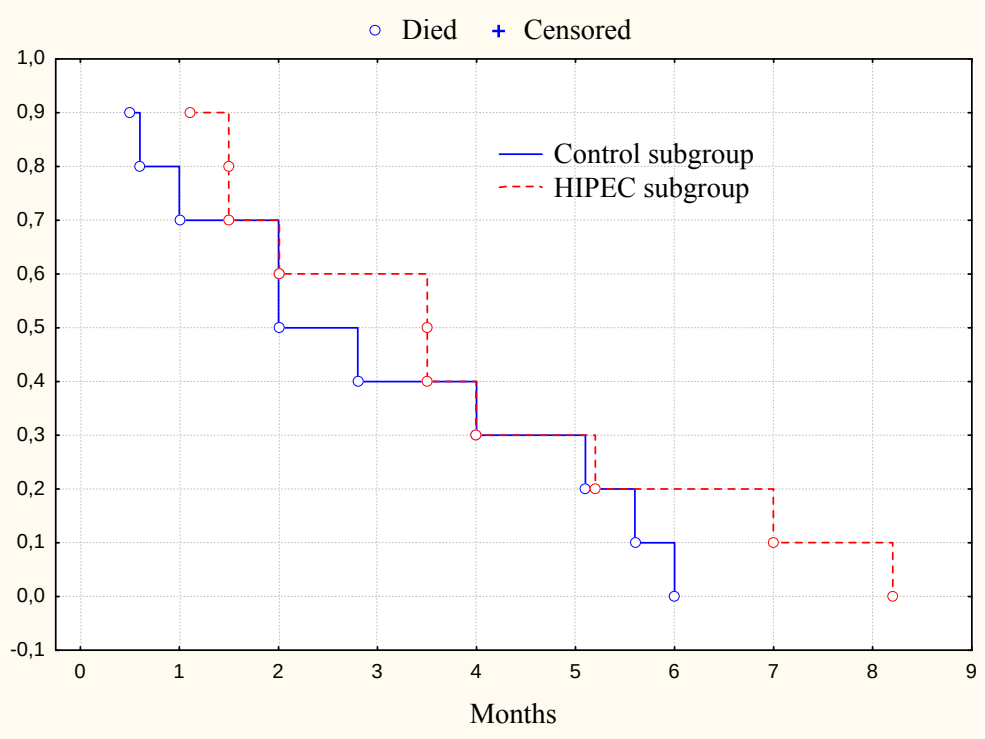

Fig. 4. Cumulative censored overall survival in gastric cancer patients with diffuse peritoneal carcinomatosis with symptomatic ascites after use of HIPEC and after best supportive care

The repetitive procedures (from 1 to 9) of laparocentesis and ascites evacuation were conducted in order to improve the life quality of all patients of the control subgroup. The average amount of laparocentesis procedures was 3,6 ± 2,1. In the HIPEC subgroup only 2 (20%) patients had to undergo laparocentesis procedure due to ascites recurrence.

The independent prognostic factors in patients with disseminated intraperitoneal gastric cancer after aggressive surgical cytoreduction and HIPEC were identified by means of multivariate analysis: according to the classification of the Japanese Gastric Cancer Association a degree of peritoneal dissemination ($p = 0,004$), and a score of cytoreduction completeness ($p = 0,031$).

DESCUSSION OF THE RESULTS

Serosa-invasion gastric cancer exhibits poor prognosis and a high risk of metachronous peritoneal carcinosis, which develops as a result of the microscopic intraperitoneal tumor cell pool proliferation during surgery or intraperitoneal dissemination.

For a long time the use of adjuvant chemotherapy in patients with resectable GC was not confirmed by significant results in randomized trials, however, intraperitoneal chemohyperthermia allowed to increase the survival rates in serosa-invasion GC patients. For today the results of two meta-analyses [13, 14] on this issue have been already published. However, this approach was not accepted as a standard treatment used in daily practice of oncology surgeons. Our study results show double increase in survival rate in patients undergoing adjuvant chemotherapy in combination with HIPEC and reduction of peritoneal recurrence from 73.7% to 11.1%. In the study subgroup intraperitoneal progression was seen in 2 patients. Considering that one of them had surgery 3 years ago, after intraperitoneal chemohyperthermia some changes in intraperitoneal carcinogenesis processes were observed.

Cytoreduction surgery involves maximum excision of tumor mass from the patient's body as well as metastatic lesions in order to minimize the intraperitoneal tumor cell pool level and ensure that the subsequent treatment of residual microscopic tumor cell proliferation with the use of cytotoxic agents is effective. HIPEC therapy aims at destruction of residual microscopic intraperitoneal tumor cell pool by means of loco-regional application of two synergistic antitumor factors - chemotherapy and hyperthermia.

In 1996 Y. Yonemura in collaboration with his colleagues published the results of the first large clinical trial [15] on the efficacy of HIPEC (mitomycin 30 mg + cisplatin 300 mg + etoposide 150 mg, 60 min at 42 - 43 C) in combination with aggressive cytoreductive surgery, including gastrectomy, extended regional lymphadenectomy and partial or subtotal peritonectomy in GC patients with peritoneal carcinosis. As a result we

achieved 1-year survival in 43% of patients and for the first time 5-year survival was seen in 11% of patients with poor prognosis.

In 2010 O. Glehen in collaboration with his colleagues from the Cancer research center of Lyon published the summarized retrospective results of the French national clinical study [16] held on the grounds of the results gained from the treatment of 159 patients from 15 surgery centers. Median overall survival was 9.2 months and 1-year, 3-year and 5-year survival was 43%, 18% and 13%, respectively. The score of cytoreduction completeness was considered to be the only independent prognostic factor identified by means of multivariate analysis. Those patients with CC-0 had better results: the median was 15.0 months, 1-, 3- and 5-year survival time - 61%, 30% and 23% respectively.

Study results also showed an advantage in term of survival in GC patients with peritoneal metastases after aggressive CRS in combination with HIPEC and achievements in long-term survival among selected patients. Two our patients stay alive more than 2 years after treatment and one of them has no sign of disease.

Despite the failure to improve an advantage in survival of symptomatic ascites patients, HIPEC with symptomatic purposes allows effectively eliminating of recurrent ascites.

CONCLUSIONS

1. The use of combination therapy with HIPEC in advanced GC patients is considered to be a safe treatment with the acceptable levels of postoperative complications and mortality.
2. HIPEC in adjuvant regime used to treat GC patients with a high risk of intraperitoneal progression allows reducing peritoneal metachronous carcinomatosis from 73.7% in the surgical control subgroup to 11.1% ($p < 0.001$), and significantly improves patients' survival advantage.

3. CRS, HIPEC and systemic palliative chemotherapy used to treat gastric cancer patients with limited extent of peritoneal carcinomatosis allows achieving median and 1-year survival time equal to 12 months and 68.8%, whereas palliative chemotherapy applied to those of control group patients - 8 months and 25% respectively ($p = 0.004$).
4. However the symptomatic use of HIPEC in GC patients with diffuse peritoneal carcinomatosis complicated by symptomatic ascites does not significantly increase the survival, it allows effectively eliminating recurrent ascites.
5. The independent prognostic factors in GC patients with peritoneal metastases undergoing combined treatment with HIPEC are the stage of peritoneal dissemination in compliance with the classification of the Japanese Gastric Cancer Association and the score of cytoreduction completeness.

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