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Hyperthermic intraperitoneal chemotherapy in serosa-invasive gastric cancer patients

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ABSTRACT

Background: Evaluation of hyperthermic intraperitoneal chemotherapy (HIPEC) in reducing metachronous peritoneal metastases (MPM) risks in patients with resectable serosa-invasive gastric cancer.
Materials & methods: Between 2008 and 2016, 154 patients with gastric cancer (stage IIB-IIIC) were randomly assigned to two groups: 76 patients underwent HIPEC (cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2, 42 °C, 1 h) combined with radical surgery (HIPEC group) and 78 patients underwent only radical surgery (control group).
Results: Evaluation of HIPEC toxicity showed neither toxic complications of IV-V degree nor haematological toxicity (according to CTCAE *v.* 4.03). There was no significant difference in the rate of complications between the two groups ($p = 0.254$). There was a more frequent disease progression in the control group than in the HIPEC group: 42/55 patients (76.4%) *vs.* 36/68 patients (52.9%), respectively ($p = 0.009$). At the same time a significant decrease in the rate of MPM was observed after HIPEC administration as compared with surgery alone – 16/68 (12.8%) *vs.* 39/55 (27.6%) ($p < 0.001$). 3-year progression-free survival was 47% (95% CI 36–61)) in the HIPEC group and 27% (95% CI 17–43) in the control group – $p = 0.0024$.
The N-stage, HIPEC procedure, type of surgery and interaction between HIPEC treatment and age were independent prognostic factors.
Conclusions: HIPEC appears to be helpful in improving treatment results in radically operated gastric cancer patients.

Introduction

Survey of studies of the efficacy of improving survival in gastric carcinoma patients by applying radical surgery in combination with HIPEC shows that some researchers find such an approach to be effective in preventing MPM and extending time before disease progression [1–3], while others report little if any HIPEC efficacy in preventing peritoneal relapses [4–7]. Most of the HIPEC efficacy studies published so far have been carried out in the Eastern Pacific countries and that gives grounds for uncertainty over the reproducibility of these findings with regard to the European population [1–8]. These considerations – a lack of consensus on the benefits of HIPEC in treating patients with resectable gastric cancer and a geographically narrow focus of the relevant studies conducted to date – justify the need to further evaluate the effectiveness of this method in preventing MPM after radical gastric cancer surgery.

In our prospective randomized study undertaken at the National Cancer Center in Belarus we attempted to assess the preventive efficacy of HIPEC with regard to the peritoneal recurrence of gastric carcinoma in patients from across Belarus.

Patients and methods

Patient selection and treatment

The study involved patients with histologically confirmed gastric cancer, aged 18–70, T4a-bN0-3M0, stage IIB–IIIC, with preoperative ECOG status of 0-I, without esophagus involvement, who underwent a potentially curative operation (i.e. R0 resection). Resectable serosa-invasive gastric cancer, Borrmann type III–IV,

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was used as an inclusion criteria. Resectability was established according to the results of a pre-operative CT and ultrasonographic examination. The decision to include patients in the study was made only after intraoperatively obtaining morphological confirmation of serosal invasion (pT4) by employing a frozen section procedure performed by an experienced pathologist. Serosal invasion was then postoperatively confirmed by performing a regular morphological examination. Borrmann type identification was based on intraoperative evaluation results and then checked by performing a postoperative morphological examination of excised specimens by the Center's pathologists. Exclusion criteria included metastatic disease (M1), New York Heart Association class III-IV, history of active infectious disease or myocardial infarction over the previous 6 months, and history of significant ventricular arrhythmia.

The trial was approved by the Ethics Committee of the N.N. Alexandrov National Cancer Center. Written informed consent was obtained from all patients before trial entry.

The patients were randomized to two groups at the time of surgery after an *intraoperative morphological confirmation* of serosal invasion by means of a frozen section procedure. Surgical treatment consisted of total or partial (distal subtotal resection) gastrectomy with free margins (R0 resection) and D2 lymph node dissection, in case of necessity supplemented by liver, distal pancreatic or transverse colon resections.

HIPEC technique. HIPEC was performed after gastrectomy/alimentary tract reconstruction and wound closure. One inflow catheter (32F) was positioned beneath the left hemidiaphragm. Three outflow catheters (32F) were placed in both the true and false pelvises in the subhepatic area. Temperature probes were placed on the inflow and outflow catheter tips. HIPEC was administered for 1 h with an automatic HIPEC device (Thermochem HT-1000 (ThermaSolutions, Inc., USA)). Perfusate used was Ringer's solution (5–6L) mixed with cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2 warmed to an inflow temperature of 42 °C. Patients over the age of 70 were not considered suitable for HIPEC because of the anticipated incidence of serious complications. Neither pre- nor postoperative systemic chemotherapy was administered to the patients.

Toxicities were assessed according to the CTCAE version 4.03 expanded common toxicity criteria. The evaluation of toxic complications was conducted during 90 days from administering combined therapy. Follow-up consisted of detailed clinical examinations, laboratory tests (blood count, hepatic function), and periodic diagnostic imaging (chest radiography, ultrasonography, CT) performed every 3 months during the first year after the treatment and every 6 months during the second and subsequent years. MPM such as massive ascites, enhanced nodules located in the abdominal or pelvic cavity, abnormal wall thickness of the intestine were monitored by performing CT and ultrasonography and also by second-look laparoscopy and peritoneal biopsy every year after the treatment or where there was a suspicion of gastric cancer progression. Hematogenous and distant lymph node metastases (paraaortic, mesenteric, and extraabdominal lymph nodes) were classified as distant metastases (DM).

As the study spanned the period from 2008 to 2016, the disease staging was initially based on the then applied 6th and subsequently 7th editions of TNM staging system. Before evaluating final treatment outcomes, tumors were restaged in accordance with the 8th pTNM edition.

End Points. Progression-free survival (PFS) was measured from random assignment to the date of gastric cancer progression. All same cancer recurrences (MPM, DM) and deaths from the same cancer were accounted for as events.

Statistical analysis

The study was designed as a randomized trial to compare 3-year progression free survival (PFS) in patients with advanced gastric carcinoma with a hypothesis that the 3-year PFS would be about 25% in the control group and about 50% in the HIPEC group. With a two-sided type I error of 0.05 and a power of 80% and a 30% dropout rate taken into account, the intended number of randomly assigned patients was determined to be not less than 150 (75 per arm).

Initial patients' characteristics in the two groups were compared using Fisher's exact test for categorical data while the Mann-Whitney test was used to compare the age variable. Median follow-up was calculated according to Schemper and Smith method (1996) [9].

The survival rate was assessed applying the Kaplan-Meier estimator. Multifactor Cox-model was implemented to establish risk factors for PFS. Preliminary model was reduced with a backward elimination based on the Bayesian information criterion to prevent overfitting. A competing risks analysis was carried out for a more detailed study of MPM and DM. We fitted Fine & Gray proportional subdistribution hazards regression models [10]. For each subpopulation, we established the most important factors associated with MPM and DM progression. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using an exponential transformation of the respective parameters of the models.

A P value < .05 was considered statistically significant for final inferences.

Statistical analysis was conducted with R-software, version 3.4.2 (R Project for Statistical Computing, http://www.r-project.org). We also used the *survival* package [11] to perform a survival and competing risks analysis.

Results

Patient characteristics. Between April 2008 and August 2016, a total of 478 patients were enrolled in the trial. Subsequently, 27 patients withdrew their consent to participate at the pre-operative phase. Based on the frozen section procedure, 281 patients were not intraoperatively confirmed to have serosal invasion (pT2N0-3M0 – 163; pT3N0-3M0 – 135) and were excluded from further participation in the trial as not meeting the eligibility criteria. A further 16 patients were disqualified from the trial as not meeting the inclusion criteria on account of the presence of co-morbidities that led to the reduction of the volume of lymph node dissection to D1. These patients were not randomized despite the intraoperative morphological confirmation of serosal invasion.

As a consequence, the study covered only 154 patients – 95 male and 59 female patients aged between 24 and 70 who were randomized after intraoperative morphological confirmation of serosal invasion (pT4) based on frozen section procedure (Fig. 1).

After randomization the two groups were well balanced (Table 1).

Postoperative complications. 20 complications were observed in 13 patients in the HIPEC group (17.1%) and 12 complications in 11 patients in the control group (14.1%) – the difference in complications was not statistically significant (p = 0.254). Surgery-related complications (postoperative pancreatitis, pancreatic fistula, intraabdominal abscesses, leakage, etc.) in the HIPEC and control groups were observed in 9 (12%) and 5 (6%) cases, respectively, non-surgical complications (pneumonia, myocardial infarction, etc.) – in 11 (14.5%) and 7 (9%) cases, respectively. Esophagojejunal anastomotic leak with a lethal outcome occurred in 2 patients (2.6%) from the HIPEC group. 90-days postoperative mortality rate in the cohort was 1.3%.

HIPEC-related complications. Evaluation of HIPEC toxicity showed neither toxic complications of IV-V degree nor

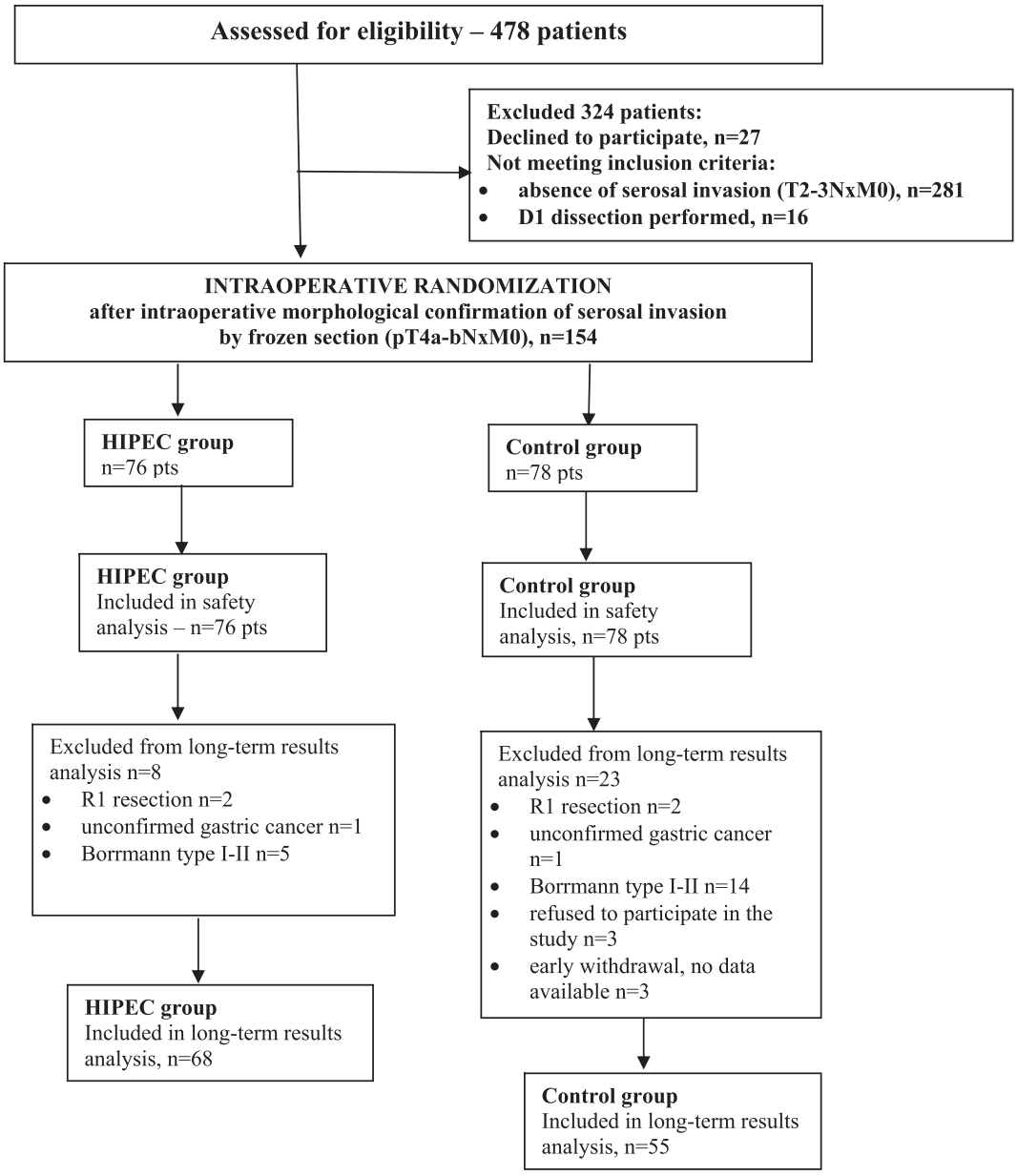

Fig. 1. Disposition of patients.

Table 1
Patient characteristics.

Variable	HIPEC group n = 76 (%)	Control group n = 78 (%)	p
Age (yrs), mean ± SD	56 ± 8	56 ± 9	0.756
Gender (male/female)	50/26	45/33	0.324
pT			0.155
pT4a	63 (83)	71 (91)	
pT4b	13 (17)	7 (9)	
pN			0.994
pN0	23 (30)	22 (28)	
pN1	13 (17)	14 (18)	
pN2	16 (21)	17 (22)	
pN3	24 (32)	25 (32)	
G			0.440
GI	6 (8)	5 (6)	
GII	17 (22)	16 (20)	
GIII	44 (58)	40 (51)	
GIV	9 (12)	17 (22)	

haematological toxicity (according to CTCAE *v.* 4.03). No chemotherapy-related death occurred.

3-Year follow-up results

After the final postoperative morphological confirmation of serosa invasion and Borrmann type III–IV only 123 patients were available for the estimation of long-term results. Excluded from the analysis were: (1) non-radically operated patients with R1 resection margins (HIPEC group – 2, control group – 2); (2) patients with an unconfirmed diagnosis of gastric adenocarcinoma (HIPEC group – 1, control group – 1); (3) Borrmann type I-II patients according to the final morphological study results (HIPEC group – 5, control group – 14); (4) early withdrawals with no data available (control group – 3); and (5) patients who refused to participate in the study (control group – 3).

As a result, the HIPEC group comprised 68 patients available for the estimation of long-term results while the control group included 55 patients.

The median follow-up was 41 months (HIPEC group – 47 months, control group 38 months). 3-year PFS survival was higher in the HIPEC group (47% (95% CI 36–61)) as compared with the control group (27% (95% CI 17–43)) – $p = 0.0024$. Median PFS time was 28 months in the HIPEC group and 13 months in the control group.

We observed a more frequent disease progression in the control group than in the HIPEC group: 42/55 patients (76.4%) *vs.* 36/68 patients (52.9%) – $p = 0.009$.

Our multivariate analysis using the Cox model showed an increased risk of disease progression: (a) in cases of regional lymph node metastases; (b) in cases requiring gastrectomy or combined gastrectomy; (c) in the control group (Table 2).

We also observed interaction between HIPEC treatment and age in the Cox model. The risk of progression decreased with age in the HIPEC group – 0.93 (95% CI 0.89–0.98), $p = 0.004$. For a more detailed analysis of gastric cancer progression types an analysis of competing risks was carried out. The cumulative incidence of MPM and DM is shown in Table 3. MPM were observed in 55 patients (median 12 months), and DM – in 23 patients (median 12.7 months). It was established that the combined treatment (surgery + HIPEC) resulted in a statistically significant decrease in the MPM rate compared with surgery alone – 16/68 (12.8%) *vs.* 39/55 (27.6%), $p < 0{,}001$ and a significant decrease in the MPM cumulative incidence with a simultaneous increase in the cumulative incidence of DM (Table 3, Fig. 2).

The cumulative incidence of disease progression in patients with signet ring GC subtype was similar to that of the rest of the patient cohort (Table 3).

Variables from the final Cox model were employed in the multivariate competing risks analysis (Table 4).

The multivariate analysis showed that the pN3 stage affected both MPM ($p = 0.003$) and DM ($p = 0.025$); pN1-2 also affected DM ($p = 0.038$) (Table 4).

As noted earlier, the application of gastrectomy and combined gastrectomy led to a higher risk of developing various types of disease progression than in the case of subtotal gastric resection – HR 1.9 (95% CI 1.1–3.1), $p = 0.018$ (Table 2). However, no link was observed between the applied surgical procedures and the types of post-surgery gastric cancer progression (Table 4).

Interaction between age and HIPEC treatment showed that the risk of MPM decreases with age in the HIPEC group (0.91 (95% CI 0.86–0.97) per year) ($p = 0.002$). However, no association between age and DM was observed in either of the groups. HIPEC treatment was statistically significant in decreasing the MPM cumulative incidence – RR = 0.2 (95% CI 0.11–0.37), $p < 0.001$. At the same time the HIPEC group patients remained at risk of developing DM 7.5 (95% CI 2.2–25), $p = 0.001$ (Table 4).

Discussion

According to conclusions of many researchers, MPM progression is virtually unavoidable after performing radical GC surgery [12,13]. The prime cause is tumor cell seeding in the peritoneal cavity from the serosal surface, lymph nodes and/or vessels occurring at the time of performing lymph node dissection as, for example, reported by *T. Marutsuka* et al. [14]. With these givens the administration of adjuvant therapy to this cohort of patients is an obvious method of choice to prevent GC progression. Indeed, the results of administering systemic chemotherapy to these patients have given some ground for optimism. For example, *S.E. Al-Batran* et al. [15] report that the administration of FLOT chemotherapy was associated with significantly higher proportions of patients achieving pathological complete regression than was ECF/ECX (20 [16%; 95% CI 10–23] of 128 patients vs. 8 [6%; 95% CI 3–11] of 137 patients; $p = 0.02$). The study included resectable GC patients who had clinical stage cT2 or higher, nodal positive (cN+) disease, or both. Regrettably, this study did not provide any subgroup analysis, especially with regard to pT3-4 GC patients that are most susceptible to the MPM development.

It is obvious that in view of the peritoneal-plasma barrier only locoregional therapy aimed at blocking the diffusion of free tumor cells and their total eradication in the peritoneal cavity is potentially capable of improving long-term results of treating such patients. Extensive intraoperative peritoneal lavage is one of such treatment strategies. The promising results of its application have proved it to be a viable treatment option. Thus, Kuramoto M. et al. (2009) [16] report that the combination of extensive intraopertive peritoneal lavage (EIPL) and intraperitoneal chemotherapy (IPC) was associated with a 5-year survival of 43.8% that was a lot higher

Table 2
Factors associated with gastric cancer progression (Cox model).

Variables	Preliminary model		Final model		
	β	p	β	HR (95% CI HR)	p
Age in control group	0.03	0.084	0.03	1.03 (1.0–1.07)	0.073
Gender M *vs.* F	0.06	0.801	–	–	–
GIII-IV *vs.* GI-II	0.13	0.655	–	–	–
pN1-2 *vs.* pN0	0.80	0.035	0.84	2.3 (1.1–4.7)	0.022
pN3 *vs.* pN0	1.67	<0.001	1.67	5.3 (2.7–10.7)	<0.001
pT4b *vs.*pT4a	0.13	0.683	–	–	–
Gastrectomy + Combined Gastrectomy *vs.* Subtotal gastric resection	0.63	0.024	0.64	1.9 (1.1–3.1)	0.018
Surgery *vs.* Surgery + HIPEC	0.69	0.004	0.68	2.0 (1.3–3.3)	0.003
Interaction between HIPEC treatment and age	−0.07	0.005	−0.07	0.93 (0.89–0.98)	0.004

Table 3
Cumulative incidence (CI) of gastric cancer progression events.

Cumulative incidence	HIPEC group, CI ± se		Control Group, CI ± se		*p*
	1-year	3-year	1-year	3-year	
Cumulative incidence of MPM[a]	4.8 ± 2.7	24.0 ± 5.46	41.8 ± 6.7	67.6 ± 6.8	<0.001
Cumulative incidence of DM **	11.1 ± 4.0	29.1 ± 5.9	3.6 ± 2.6	5.5 ± 3.1	0.001
G1-2					
Cumulative incidence of MPM[a]	0	4.8 ± 4.8	46.2 ± 14.6	53.8 ± 14.7	<0.001
Cumulative incidence of DM **	0	34.6 ± 11.1	0	7.7 ± 8.1	0.092
G3-4					
Cumulative incidence of MPM[a]	3.6 ± 3.6	29.3 ± 9.0	40.7 ± 9.7	65.7 ± 10.0	0.003
Cumulative incidence of DM **	21.4 ± 7.9	28.8 ± 8.8	7.4 ± 5.2	7.4 ± 5.2	0.047
Signet Ring Cell Carcinoma					
Cumulative incidence of MPM[a]	14.3 ± 9.7	42.9 ± 14.0	40.0 ± 13.2	80.0 ± 11.4	0.036
Cumulative incidence of DM **	7.1 ± 7.2	21.4 ± 11.7	0	0	0.045

[a] – MPM progression was considered as a competing event regardless of any other type of disease progression when they were detected simultaneously; ** – any progression in the absence of MPM was considered to be an event.

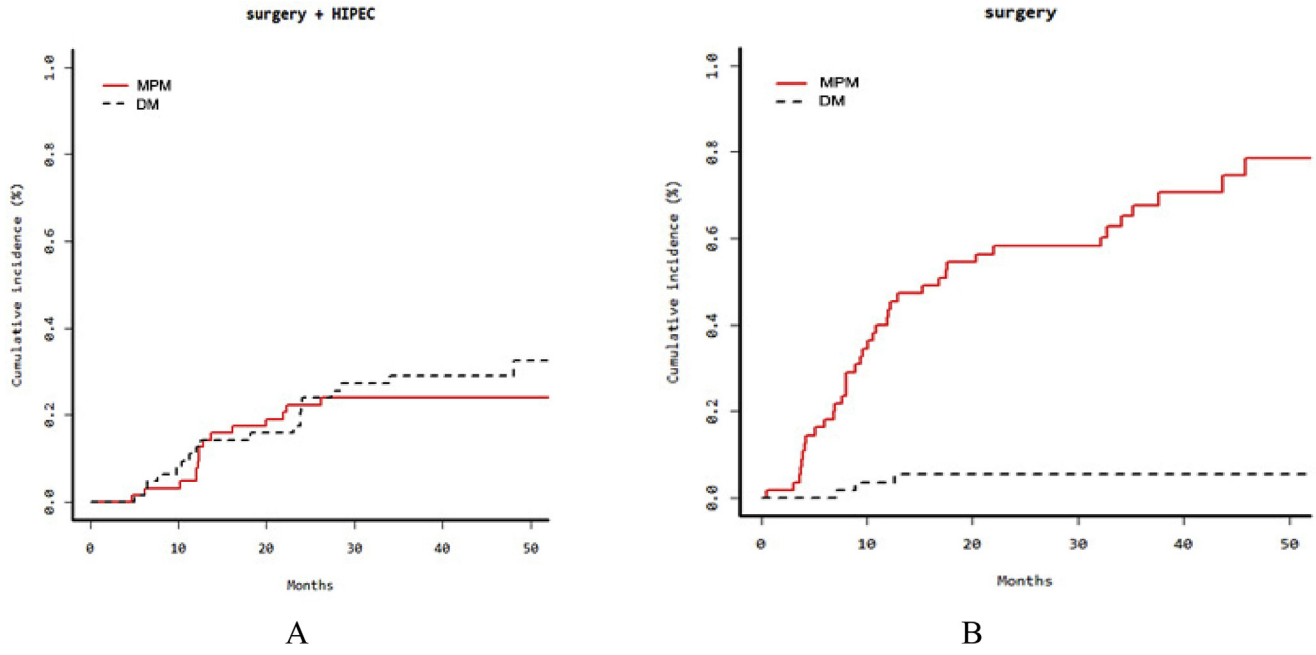

Fig. 2. Cumulative incidence of gastric cancer progression types in the HIPEC group (A) and the control group (B).

Table 4
Relative risk of metachronous peritoneal metastases and distant metastases in competing risks (Fine & Gray model).

Variables	*Metachronous peritoneal metastases*			*Distant metastases*		
	β	RR (95% CI)	*p*	*β*	RR (95% CI)	*p*
Age in control group	0.02	1.02 (0.99–1.06)	0.215	0.03	1.03 (0.91–1.16)	0.677
pN1-2 *vs.* pN0	0.44	1.5 (0.7–3.5)	0.290	1.63	5.2 (1.1–24.2)	0.038
pN3 *vs.* pN0	1.19	3.3(1.5–4.4)	0.003	1.74	5.7 (1.2–26.1)	0.025
Gastrectomy+ Combined Gastrectomy *vs.* Subtotal gastric resection	0.27	1.3 (0.7–2.4)	0.391	0.73	2.1 (0.75–5.7)	0.158
Surgery + HIPEC *vs.* Surgery	−1.60	0.2 (0.11–0.37)	<0.001	2.0	7.5 (2.2–25)	0.001
Interaction between HIPEC treatment and age	0.09	0.91 (0.86–0.97)	0.002	−0.01	0.99 (0.86–1.12)	0.827

than in the patients who underwent only the IPC treatment (4.6%, $p < 0.0001$) or in the patients who underwent only surgical treatment (0%, $p < 0.0001$).

At the same time, according to the data of a randomized phase III trial exploring the significance of EIPL in addition to standard treatment for ≥ T3 resectable gastric cancer (CCOG 1102) the administration of EIPL without IPC follow-up therapy showed no significant difference in the 3-year disease-free survival (DFS) for pT4a-b patients - 63.9% in the EIPL group and 59.7% in the non-EIPL group – $p = 0.25$. As regards OS, it was 75.0% and 73.7%, respectively, $p = 0.65$ [17].

We believe that HIPEC offers certain advantages over the

currently used treatment methods of preventing MPM development owing to the possibility of potentiating the antitumor effect of chemotherapeutic drugs by increasing their penetration into the peritoneal tissue and also owing to the direct destruction of tumor cells and an increased permeability of the cytoplasmic membrane that leads to a selective accumulation of therapeutic drugs in tumor cells.

Koga S. et al. [4] were among the first to use HIPEC as a prophylactic treatment for peritoneal recurrence after gastric cancer surgery. Since they released their data, a fairly large number of reports have been published demonstrating a successful application of HIPEC in preventing MPM in gastric cancer patients. For example, *Yonemura Y.* et al. [1] found that applying mitomycin C-based HIPEC in combination with cisplatin (30 mg of mytomicin C (MMC)+300 mg of cisplatin, 42-43^{0}C, 60 min) helped to increase the 5-year survival in gastric cancer patients to 61% as compared with 42% in the control group. Our trial results are generally in agreement with the studies conducted by researchers in Europe and Asia that have shown a positive effect of HIPEC on MPM rates [1–3,12,18]. The incidence of MPM in our trial was comparable with some earlier studies [8]. However, the cumulative incidence of MPM in our case was strikingly high (1 year–41.8 ± 0.50%; 3-year – 67.6 ± 0.50%), exceeding that mentioned in the literature [13]. No III-IV grade toxicities according to CTCAE version 4.03 criteria were recorded in our trial as a result of using the combination of cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2. Nor were there any instances of clinical manifestations of peritoneal adhesions during follow-up patient monitoring or any pronounced adhesion processes when performing second-look laparoscopy. Our findings do not accord with the data published by Kusamura S. et al. (2007) [19]. These researchers report that the application of a similar combination of cisplatin 43 mg/L + doxorubicin 15.25 mg/L increased the risk of III-IV grade toxicities 2.36 times compared with a cisplatin + mitomycin C combination. Given the fact that the average perfusate volume is 5–6 L, this could possibly be associated with a high dose of cisplastin exceeding 240 mg. According to the same researchers the application of the same cisplastin dosage increased the risk of developing HIPEC-related toxicities 2.78 times.

In our study we observed an increase in the cumulative incidence of DM from 5.4 ± 0.10% (in the control group) to 26.6 ± 0.30% after HIPEC ($p = 0.001$) despite the reduction in the MPM cumulative incidence. Our results are partly in agreement with *Coccolini* et al. (2014) [12], who found no difference in lymph-nodal recurrence rate between the intraperitoneal chemotherapy group and the control group. The mismatch between the MPM and DM incidences in our study may presumably be attributed to the fact that the development of the MPM is the earliest-occurring event among all possible scenarios of gastric cancer progression. Apparently, while blocking the MPM implantation we failed to block the DM development. This probably explains why we observed a low MPM and a high DM cumulative incidence in the HIPEC group. Alternatively, the MPM development in the control group was the earliest and fairly frequent scenario of gastric cancer progression leading to the death of patients with the absolute majority of them passing away before the DM progression set in.

The above findings highlight the need to combine HIPEC treatment with systemic chemotherapy as emphasized in a number of cited studies [18,20].

Although our study was focused on pT4, we see a potential benefit in administering HIPEC to pT3 patients in view of their risk of MPM development as evident from our and other studies [21]. Our analysis of treating 125 patients with pT3 whose data were available for treatment evaluation (87 male patients (70%) and 38 female patients (30%), mean age±SD 61 ± 10) who were excluded from the study as not meeting the inclusion criteria, and therefore were not randomized, and, as a consequence, not administered HIPEC, showed that their 3-year MPM cumulative incidence was 23.6 ± 4.1%, i.e. lower than in the pT4 patients (Table 3). That explains statistically significant PFS differences in this group of patients in comparison with the pT4 patients - 65.4 ± 4.6% ($p < 0.001$). Yet the fact that a quarter of these patients were diagnosed to develop MPM shows that the administration of HIPEC therapy to this cohort of patients could potentially improve treatment results. The importance of assessing HIPEC administration to pT3 patients is a topical issue as evidenced by various studies conducted in Asia and Europe. Of special interest is the GASTRICHIP multicenter study now under way in France that is focused on this cohort of patients and is aimed at evaluating the potentiality of adjuvant hyperthermic intraperitoneal chemotherapy within European or Caucasian demographic and at validating the results observed in similar trials performed in Asia [22]. As distinct from previously published reports [1,2,12,18], our study revealed that the risk of MPM decreases with age in the HIPEC group – HR 0.91 (95% CI 0.86–0.97), $p = 0.002$. As a result, this finding necessitates a reappraisal of approaches to the management of patients aged 20 to 50 after a combined treatment to ensure a timely detection of gastric cancer progression including the development of MPM.

In conclusion, our analysis indicates that HIPEC may have a positive role in advanced gastric cancer treatment improving the prognosis for patients. At the same time, our findings point to a need for combining HIPEC with systemic chemotherapy. But further studies are warranted to assess the possible benefits that could be gained from using this promising complex adjuvant treatment modality.

Conflicts of interest

The authors have declared no conflicts of interest.

Disclosure

The authors have declared no conflicts of interest.

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