

# Postoperative intraperitoneal hyperthermic perfusion improve survival for advanced gastric cancer

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## Abstract

To evaluate the value of intraperitoneal hyperthermic perfusion (IPHP) in the treatment of gastric cancer.

Gastric cancer (GC) is a malignancy with poor prognosis, recent years have demonstrated advances in the use of IPHP for the treatment of advanced gastric cancer (AGC), but the outcome is controversial.

Between January 2015 and January 2017, 134 patients with GC were treated with IPHP in our surgery department, 130 of them were advanced GC patients, and other 1439 cases were treated without IPHP for comparison. In this retrospective cohort study, demographic, perioperative data, and follow-up data were analyzed by univariate analysis, Kaplan–Meier and Cox regression survival analysis.

We found the 1-year survival in IPHP group was significantly longer than it in non-IPHP group (85.5% vs 73.8%,  $P = .027$ ). and IPHP decreased mortality 1.8 times in 2-year course (OR = 0.556,  $P = .004$ ). The incidence rate of total complications in IPHP group was similar to that in the Non-IPHP group (6.67% vs 7.46%, respectively;  $P = .718$ ). We classified all patients into four groups, operation alone, operation+chemotherapy, operation+IPHP, and operation+IPHP+chemotherapy. The 1-year survival in the groups was 70.2%, 77.5%, 83.1%, and 93.5%, respectively ( $P = .001$ ), compared with the group of operation alone, the 2-year mortality risk was decreased 1.76 times (OR = 0.569,  $P = .030$ ) and 2.59 times (OR = 0.385,  $P = .022$ ) in operation+IPHP group and operation+IPHP+chemotherapy group.

Our results suggest that IPHP could contribute to improve survival of patients with gastric cancer. And the modality of operation+IPHP+chemotherapy is the optimal treatment modality for gastric cancer.

**Abbreviations:** AGC = advanced gastric cancer, CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, IPHP = intraperitoneal hyperthermic perfusion, OS = overall survival, PM = peritoneal metastases.

**Keywords:** cytoreductive surgery, gastric cancer, hyperthermic intraperitoneal chemotherapy, peritoneal metastases

## 1. Introduction

Gastric cancer (GC) ranks third morbidity and second mortality in all kinds of cancer worldwide.<sup>[1]</sup> It has reported the median survival of GC is 50, 14 and 3 months for patients who had chemotherapy plus surgery, had chemotherapy alone and best supportive care, respectively.<sup>[2]</sup> Up to 17% patients with gastric cancer are diagnosed with the presence of peritoneal metastases

(PM), these patients have an average survival of 1–3 months.<sup>[3]</sup> Systemic chemotherapy could improve the survival of patients with gastric metastatic cancer about 7–10 months, however, this benefit could not be reproduced in patients with PM.<sup>[4]</sup>

Recent years have demonstrated advances in the use of cytoreductive surgery (CRS) in combination with intraperitoneal hyperthermic perfusion (IPHP) or hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of PM from appendiceal tumors, colorectal cancer, gastric cancer, epithelial ovarian cancer, and rare primary peritoneum based neoplasms.<sup>[5–10]</sup> Hyperthermia as well as intraperitoneal chemotherapy is effective in killing cancer cells, IPHP/HIPEC achieve a better heat delivery and preservation by a better circulation of the perfusion fluid, by which all peritoneal surfaces are exposed equally throughout the duration of the therapy as well as avoid dangerous temperatures or over-exposure to normal tissues.<sup>[11]</sup> IPHP/HIPEC has been shown to be an effective tool whenever a complete or an almost complete resection of the peritoneal implants can be performed.<sup>[12–14]</sup> Together with new therapeutic options such as targeted therapies, IPHP/HIPEC improve the prognosis of these patients, not only by treating clinically manifest carcinomatosis, but also in a prophylactic setting, by eliminating occult peritoneal seeding.<sup>[15]</sup> In China, an expert consensus on CRS-HIPEC has been reached by the leading surgical and medical oncologists under the framework of the China Anti-Cancer Association.<sup>[16]</sup>

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However, the role of IPHP/HIPEC in the treatment of gastric cancer is controversial, some documents has reported, the outcome with this approach is not encouraging and is influenced by patient selection.<sup>[17]</sup> In addition, high procedure-related morbidity and mortality associated with CRS-HIPEC have also been reported, and there is a need clearly to outline the appropriate role of CRS-HIPEC in gastric cancer.<sup>[18]</sup>

In this study, we analyzed IPHP performed in earlier stage after gastric resection, the safety and outcome of this method were evaluated, and we aimed to boost up the efficiency of this approach.

## 2. Methods

### 2.1. Patient enrollment

Between January 2015 and January 2017, 4433 consecutive patients with gastric cancer underwent gastrectomy by the First Department of Digestive Surgery of Xijing Hospital, Fourth Military Medical University (Xi'an, China). Part of them were also underwent IPHP treatment. The selective standard for IPHP were as follows: firstly, patient with gastric cancer and aged less than 75 years; secondly, patients had no severe basic disease such as hypertension, heart disease, and chronic obstructive pulmonary disease (COPD), and their liver and renal function were normal, and hemoglobin (Hb) was not less than 80 mg/L; thirdly, patients without Hyperthermia after operation, and body temperature less than 38°C; fourthly, patients without severe abdominal pain and distention. For this retrospective cohort study, all patient data were evaluated by two researchers, and to enhance the comparability, the patient inclusion criteria were set as follows: firstly, adult patient aged from 18 to 75 years; secondly, patients were diagnosed as gastric cancer based on pathologic characteristics and underwent gastrectomy or explorative surgery; thirdly, patients had no severe basic disease such as hypertension, heart disease, liver, and renal function were normal by laboratory test, Hb was not less than 80 mg/L, and at the level of I or II according to American Society Anesthesiology Physical Status Classification System; fourthly, patients had complete data of follow-up.

This study was approved by the Ethics Committee of the Fourth Military Medical University (ethics code: XJYYLL-2015276). All patients received verbal and written information regarding the study and provided informed consent prior to surgery.

### 2.2. IPHP method

The perfusion tubes were implanted at the end of operation, and IPHPs were performed from the second day after operation, the procedure consists of 3–5L of saline circulated using an extracorporeal circulation device at an inflow temperature of 43°C and a flow rate of 200–400 mL/minute for 30–120 minute, and perform 2–3 times with a 1–2 days interval.

### 2.3. Demographic and preoperative data

Demographic data, including sex, age, preoperative data, including TNM clinical and pathological staging classification, routine hematological and biochemical tests, and X-rays were collected to enable subsequent analysis of the comparability of the groups. The patients were divided into two groups: with IPHP, and without IPHP.

### 2.4. Perioperative observations

The highest postoperative temperature was recorded. The histological subtype and pathological stage were determined using the Union for International Cancer Control and TNM classification for gastric cancer. Postoperative complications, including anastomotic complication, wound infection, wound rupture, lung infection, bleeding, reoperation, duodenal leak, and intestinal obstruction were observed and evaluated. Anastomotic complication assessment was performed using a water-soluble radiological contrast enema at 6–8 days postoperatively. A clinical leak was defined as the appearance of food material in the abdominal drains, or the development of systemic sepsis associated with local peritoneal signs during the postoperative period. Any extravasation of the contrast medium detected on radiography was considered as a radio-logical leak.

### 2.5. Follow-up data

All patients were followed for two year from the beginning of operation. And at the end of follow-up, the status of patients were recorded, which included survival, death, and lost follow-up.

### 2.6. Statistical analysis

Statistical analysis was performed using SPSS 17 software (SPSS Inc., Chicago, IL). Differences among groups consisted of measurement data were analyzed by students' *t* test, and when unequal variance existed, the adjust-T test was used; differences in expression rate among groups were analyzed by Pearson's Chi-squared ( $\chi^2$ ) test. The Fisher's exact test was used to assess the difference of positive rate when the number of total cases was less than 40. *P* value < .05 was considered statistically significant. Survival analysis was used by Kaplan–Meier and Cox regression. For Cox model, factors previously demonstrated to be prognostically significant or thought to be clinically important, and covariates identified in bivariate analyses as predictors of mortality were considered.

## 3. Results

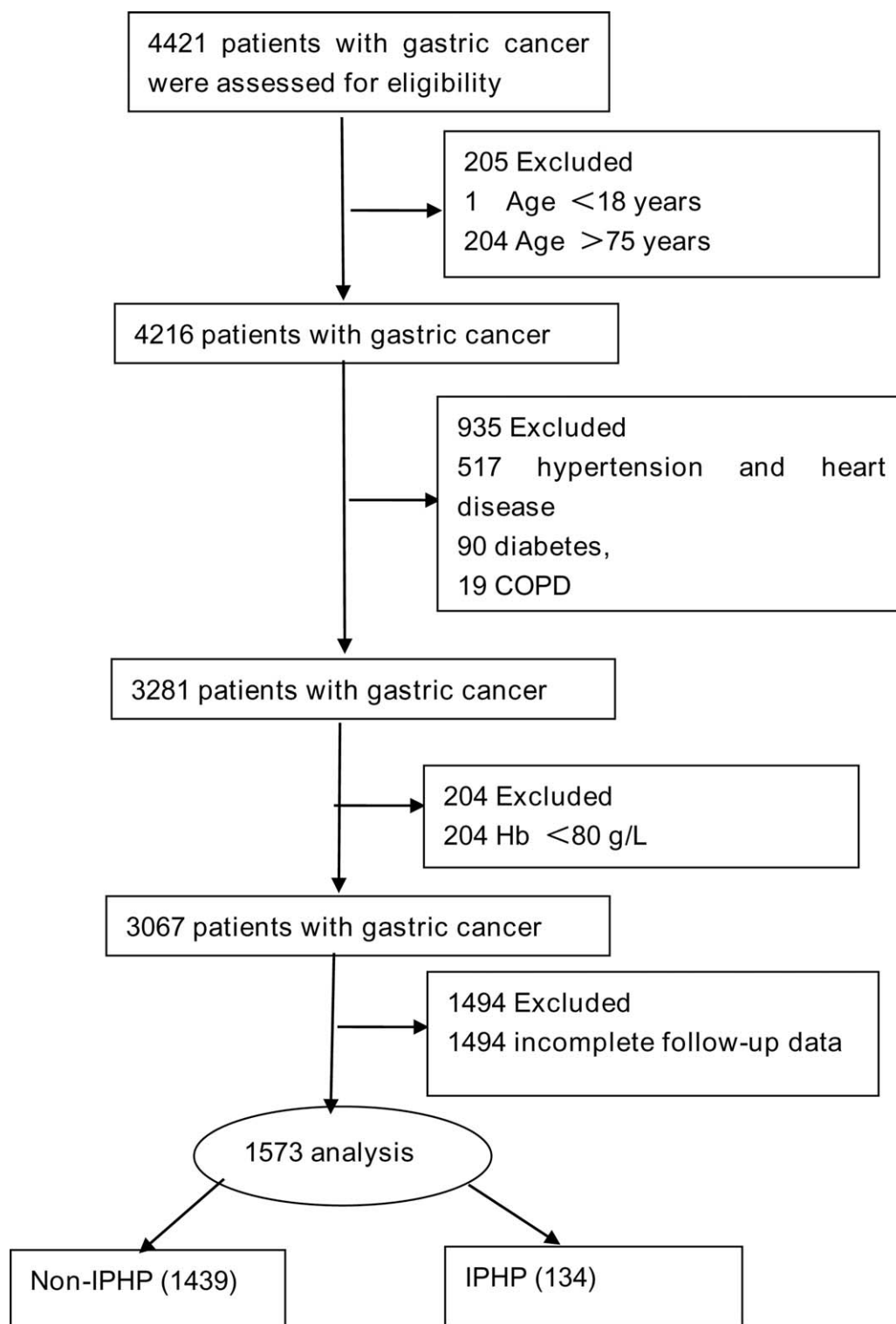
### 3.1. IPHP and baseline characteristics

According to patient inclusion criteria, 2848 cases were excluded from this study. Of them, 205 cases for age <18 years or >75 years; 935 cases for severe basic disease or severe abdominal pain and distention after operations; 204 cases for Hb <80 g/L; and 1494 cases for incomplete follow-up data. And a total of 1573 cases met the inclusion criteria and were analyzed in this cohort study (Fig. 1), of whom 134 cases were treated with IPHP, and other 1439 cases were treated without IPHP for comparison. The comparison of baseline data between the IPHP and Non-IPHP groups was described in Table 1.

There were no significant differences between the two groups regarding preoperative variables, such as age, sex, but the variants of tumor differentiation, pathological stage, histological subtype, and TNM stage in IPHP group were worse than those in non-IPHP group.

### 3.2. IPHP could not increase postoperative complications

The postoperative complications included anastomosis stricture 0.19%, anastomosis leakage 0.38%, wound infection 0.32%, wound rupture 0.76%, lung infection 2.80%, postoperative bleeding 0.38%, intestinal obstruction 0.95%, gastroparesis



**Figure 1.** Flow diagram of patients enrollment. COPD=chronic obstructive pulmonary disease, Hb=hemoglobin, IPHP=intraperitoneal hyperthermic perfusion.

0.19%, pleural effusion 0.32%, leakage of duodenal stump 0.13%, chylous leakage 0.64%, other complication 0.89%, and total complication was 6.74% in all the patients.

Fewer patients developed a fever in the IPHP group compared with the non-IPHP group (34.05 vs 11.19%, respectively;  $P=.003$ ). The incidence rate of total complications in IPHP

group was not statistically different from that in the non-IPHP group (6.67% vs 7.46%, respectively;  $P=.718$ ). In addition, there were no differences regarding lung infection, wound infection, wound rupture, anastomotic leakage, bleeding, duodenal leak, chylous leakage, and intestinal obstruction according to the univariate analysis (Table 2).

**Table 1****Characteristics of patients with intraperitoneal hyperthermic perfusion and without intraperitoneal hyperthermic perfusion.**

Feature	IPHP		P value
	No	Yes	
No.	1439	134	
Male/female	1103/336	107/27	.401
Age (mean ± SD, years)	55.41 ± 11.02	55.53 ± 10.76	.890
Tumor size (mean ± SD, cm)	5.10 ± 2.57	8.31 ± 4.13	.001
Tumor status (T)			
T1	177(12.30%)	4(2.99%)	
T2	195(13.55%)	5 (3.73%)	
T3	622(43.22%)	29(21.64%)	
T4	277(19.24%)	84(62.69%)	.001
Unknown	161(11.19%)	12(8.96%)	
N status (N)			
N0	385(26.75%)	21(15.67%)	
N1	276(19.18%)	18(13.43%)	
N2	224(15.57%)	20(14.93%)	
N3	393(27.31%)	61(45.52%)	.001
Unknown	171(11.88%)	14(10.45%)	
M status(M)			
M0	1085(75.40%)	55(41.04%)	.001
M1	354(24.60%)	78(58.21%)	
TNM stage			
I	238(16.54%)	4(2.99%)	
II	147(10.22%)	6(4.48%)	
III	268(18.62%)	17(12.69%)	
IV	657(45.66%)	107(79.85%)	.001
Unknown	129(8.96%)	0(0%)	
Grade of differentiation			
Well	250(17.37%)	8(5.97%)	
Moderate	461(32.04%)	65(48.51%)	
Poor	664(39.19%)	50(37.31%)	.001
Unknown	162(11.26%)	11(8.21%)	
Advanced GC (Borrmann)			
I	70(5.19%)	2(1.53%)	
II+III	1077(79.9%)	97(74.05%)	
IV	78(5.79%)	17(12.98%)	.002
Unknown	133(9.87%)	15(11.45%)	
Pathological type			
Adenocarcinoma	1291(89.72%)	120(89.55%)	
Non-adenocarcinoma	46(3.2%)	0(0%)	.039
Unknown	102(7.09%)	14(10.45%)	

Differences among groups consisted of measurement data were analyzed by students' *t* test; differences in expression rate among groups were analyzed by Pearson's Chi-squared ( $\chi^2$ ) test. cm = centimeter, GC = gastric cancer, IPHP = intraperitoneal hyperthermic perfusion, M = metastasis, M0 = no organ metastasis, M1 = with organ metastasis, N = lymph node, N0 = no nodal metastasis, N1 = 1–3 perirectal lymph nodes involved, N2 = 4 or more perirectal lymph nodes involved, SD = standard deviation, T = tumor, T1 = tumor invades submucosa, T2 = tumor invades muscularis propria, T3 = penetration through muscularis propria into subserosa, T4 = invasion of other organs or involvement of free peritoneal cavity.

### 3.3. IPHP contribute to improve 1-, 2-year survive

We found the 1-year survival in IPHP group was significantly longer than it in non-IPHP group (85.5% vs 73.8%,  $P = .027$ ) and 2-year survival in IPHP group was also longer than it in non-IPHP group, but the difference was not significant statically (60.6% vs 73.1%,  $P = .851$ ) (Fig. 2A–C). to further investigate the role of IPHP in gastric cancer, multivariable including sex, age, tumor size, operation mode, differentiation, TNM stage, neoadjuvant chemotherapy, postoperative chemotherapy, was considered by Cox regression analysis, and operation mode and Borrmann classification were assigned as dummy variables, We

**Table 2****Comparison of complication between group with intraperitoneal hyperthermic perfusion and without intraperitoneal hyperthermic perfusion.**

	IPHP		P value
	No	Yes	
Operation mode			
Total gastrectomy	660(45.87%)	59(44.03%)	.203
Distal subtotal gastrectomy	513(35.65%)	38(28.36%)	
Proximal subtotal gastrectomy	150(10.42%)	19(14.18%)	
Palliative and explorative	116(8.06%)	18(13.43%)	
With neoadjuvant chemotherapy	43(2.99%)	11(8.21%)	.004
With postoperative chemotherapy	859(59.69%)	53(39.55%)	.001
Complications			
Fever	490(34.05%)	15(11.19%)	.001
Anastomosis stricture	3(0.21%)	0(0%)	.765
Anastomosis leakage	4(0.28%)	2(1.49%)	.086
Wound infection	3(0.21%)	2(1.49%)	.061
Wound rupture	11(0.76%)	1(0.75%)	.982
Lung infection	42(2.92%)	2(1.49%)	.338
Postoperative bleeding	6(0.42%)	0(0%)	.586
Intestinal obstruction	15(1.04%)	0(0%)	.597
Gastroparesis	2(0.14%)	1(0.75%)	.235
Pleural effusion	3(0.21%)	2(1.49%)	.061
Leakage of duodenal stump	2(0.14%)	0(0%)	.666
Chylous leakage	9(0.63%)	1(0.75%)	.591
Other complication*	13(0.9%)	1(0.75%)	.662
Total complication†	96(6.67%)	10(7.46%)	.718

Data was shown as No. (percentage), differences between the two groups were analyzed by Pearson's Chi-squared ( $\chi^2$ ) test, the Fisher's exact test was used to assess the difference of positive rate when the number of total cases was less than 40.

IPHP = intraperitoneal hyperthermic perfusion.

\* Other complication included hiccup, arrhythmia, urinary retention, pneumothorax, pulmonary embolism.

† Total complications did not contain the cases of fever.

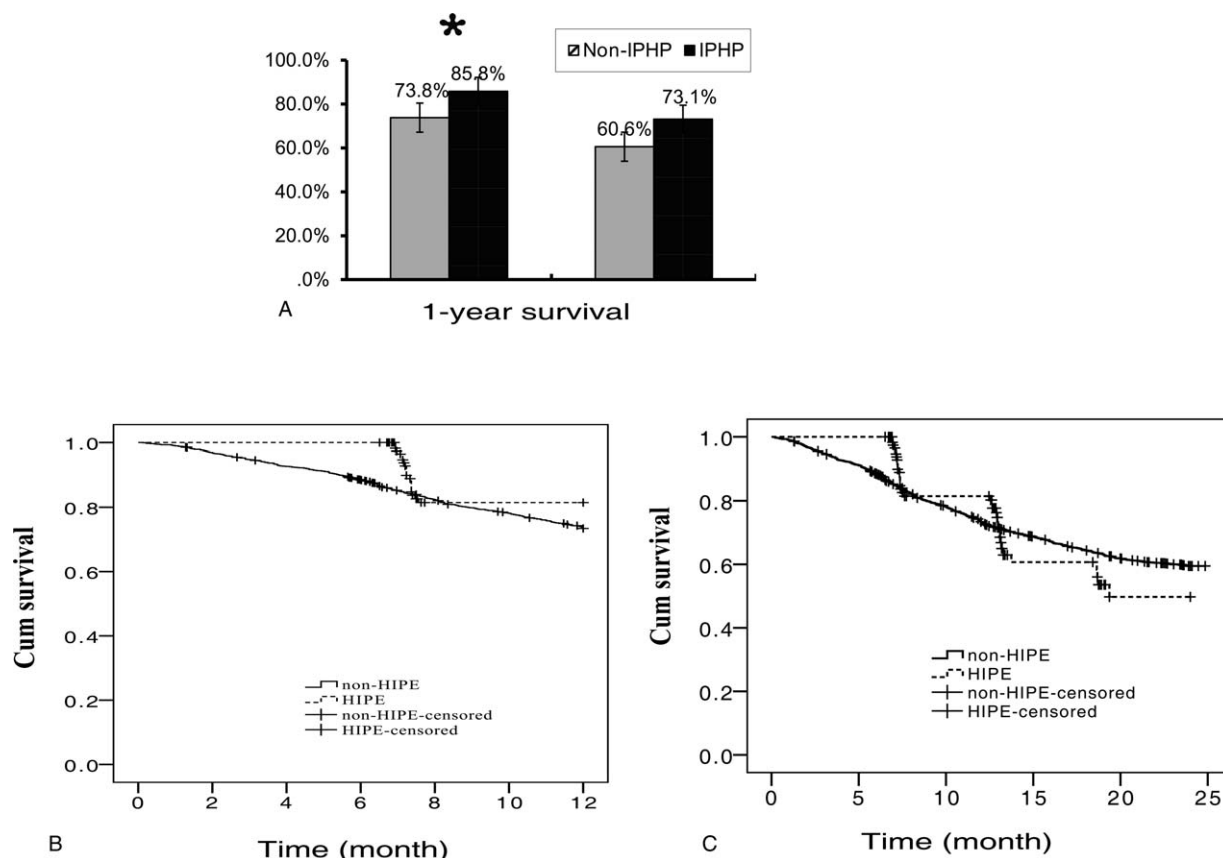
found IPHP decreased mortality 1.8 times in 2-year course (OR = 0.556,  $P = .004$ ), and the factors of, operation mode, IV type of Borrmann classification, differentiation, TNM stage, neoadjuvant chemotherapy and postoperative chemotherapy play a role in the survival of patients with gastric cancer (Table 3).

### 3.4. The optimal treatment combined with IPHP

Based on the previous study,<sup>[19]</sup> treatment modal could influence the therapeutic outcome, we classified all patients into four groups, operation alone, operation + chemotherapy, operation + IPHP, and operation + IPHP + chemotherapy. The 1-year survival in the groups was 70.2%, 77.5%, 83.1%, and 93.5%, respectively ( $P = .001$ ), and 2-year survival in the groups was 60.6%, 62.2%, 70.1%, and 80.4% ( $P = .332$ ) (Fig. 3A–C). Compared with the reference group (operation alone), the 2-year mortality risk was decreased 1.76 times (OR = 0.569,  $P = .030$ ) and 2.59 times (OR = 0.385,  $P = .022$ ) in operation + IPHP group and operation + IPHP + chemotherapy group, respectively. The result demonstrated that the modal of operation + IPHP + chemotherapy was the optimal treatment modal for gastric cancer (Table 4).

## 4. Discussion

The aim of the present study was to investigate the value of IPHP for gastric cancer. Compared with the non-IPHP method, IPHP



**Figure 2.** The survival difference between groups with intraperitoneal hyperthermic perfusion and without intraperitoneal hyperthermic perfusion in patients with gastric cancer. (A) The outcome of IPHP in the 1-, 2-survival of patients with gastric cancer. \* denoted there was a statistically difference between the two groups, *P* value < .05. (B) 1-year survival curve of patients with or without IPHP. (C) 2-year survival curve of patients with or without IPHP. IPHP = intraperitoneal hyperthermic perfusion. Solid line = non-IPHP, dotted line = IPHP.

**Table 3**  
**Relationship between cancer specific mortality and perioperative variables-Cox multiple-regression analysis.**

Variable	Regression coefficient	Standard error	OR	<i>P</i> value
Sex	-0.042	0.116	0.959	.720
Age	0.008	0.005	1.008	.090
Tumor size	0.001	0.005	1.001	.864
Operation mode*				.020
Total gastrectomy	-0.582	0.290	0.559	.045
Distal subtotal gastrectomy	-0.817	0.298	0.442	.006
Proximal subtotal gastrectomy	-0.915	0.338	0.401	.007
Pathology†				.122
Borrmann I	0.079	0.293	1.082	.788
Borrmann IV	0.358	0.157	1.431	.022
Differentiation	0.219	0.059	1.245	.001
TNM stage	0.789	0.074	2.201	.001
Neoadjuvant chemotherapy	1.105	0.211	3.019	.001
Postoperative chemotherapy	-0.246	0.100	0.782	.013
IPHP	-0.587	0.206	0.556	.004

Sex was coded 1 = male and 2 = female; age and tumor size was recorded according operation record; pathology was categorized and coded as 1 = I, 2 = II + III, 3 = IV according to Borrmann type; differentiation was coded as 1 = well, 2 = moderate, 3 = poor, 4 = no differentiation; TNM stage was coded as 1 = I, 2 = II, 3 = III, 4 = IV; neoadjuvant chemotherapy, postoperative chemotherapy and IPHP was coded as 0 = no, 1 = yes, respectively.

IPHP = intraperitoneal hyperthermic perfusion.

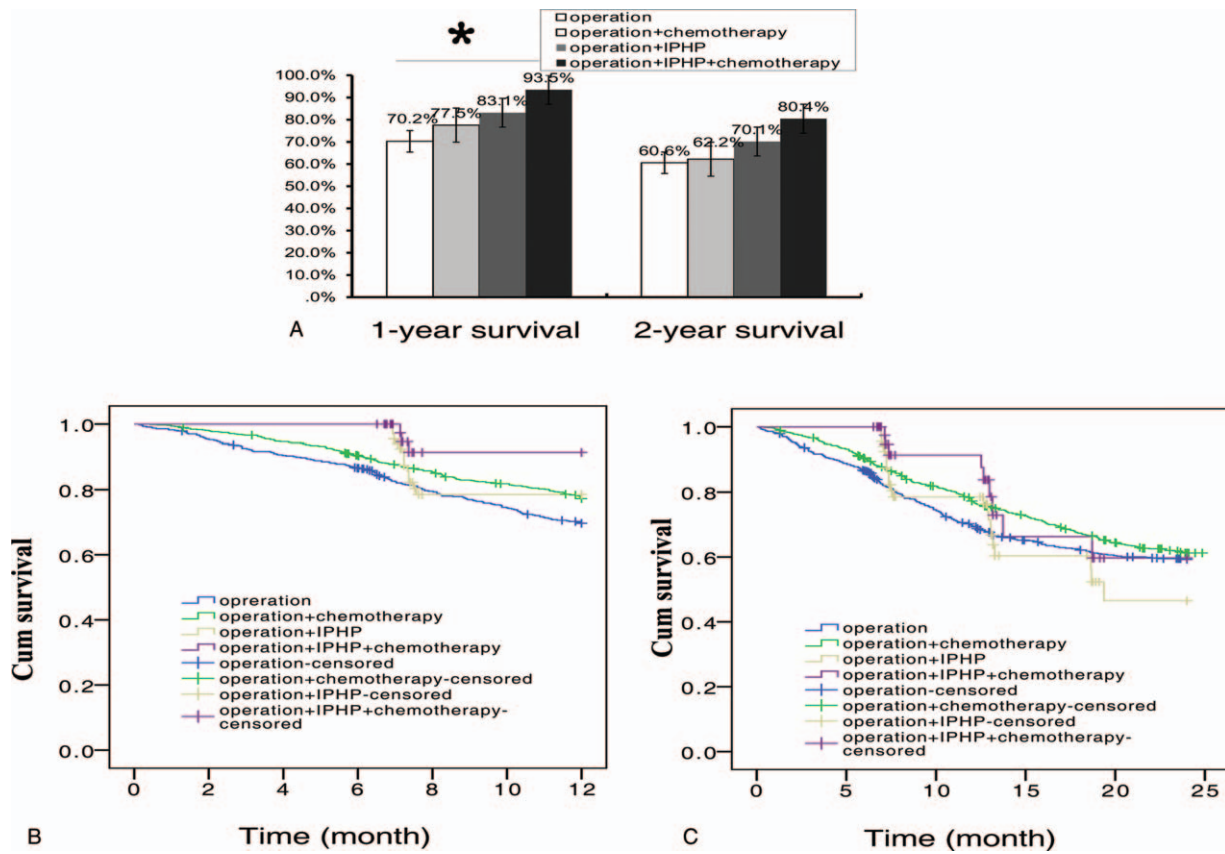
\* Compared with Palliative or explorative operations.

† Compared with Borrmann II + III.

contributed to improve 1-, 2-year survival, moreover, it did not increase the rate of complications.

The first human was subjected to IPHP/HIPEC for locally abdominal malignancy in 1979,<sup>[20]</sup> till now, IPHP/HIPEC has been used in three situations in gastric cancer. Firstly, it has been used in patients with established PM,<sup>[21]</sup> secondly, it has been used as a prophylaxis against peritoneal recurrence after curative surgery,<sup>[22]</sup> thirdly, IPHP/HIPEC contribute to reduce malignant ascites,<sup>[23,24]</sup> palliate symptom, and improve quality of life in AGC patients.<sup>[25]</sup> But there is not a standard procedure for IPHP/HIPEC. We replaced IPHP tubes at the end of operation, and performed the perfusion earlier from the second day after operation, our method contributed to reduce residual tumor cells, which had a chance to implantation and reduced the need for frequent paracentesis.<sup>[26,27]</sup>

In this study, although the baseline data including tumor size, TNM stage and grade of differentiation, in IPHP group were significantly worse than non-IPHP group, we found the 1-year survival in IPHP group was significantly higher than it in non-IPHP group (85.5% vs 73.8%), and we also found IPHP decreased 2-year mortality risk about 1.8 times (OR = 0.556). Our results provided powerful evidence for the therapeutic value of IPHP in gastric cancer. It has reported that CRS and HIPEC could improve the OS to 11 months compared to best supportive care in selected patients.<sup>[3]</sup> Yuan reported the rate of tumor disappear and decrease in the HIPEC + group was 82.60%, which was statistically significantly superior to that of the IPHPC-group



**Figure 3.** The survival difference among four therapeutic modalities in patients with gastric cancer. (A) The modalities with or without IPHP in the 1-, 2-survival of patients with gastric cancer. \* denoted there was a statistically difference among the groups,  $P$  value  $< .05$ . (B) 1 year survival curve of patients treated with four modalities. (C) 2-year survival curve of patients treated with four modalities. IPHP = intraperitoneal hyperthermic perfusion. Blue line = operation alone, green line = operation + chemotherapy, yellow line = operation + IPHP, purple line = operation + IPHP + chemotherapy.

**Table 4**  
Treatment mode could influence the mortality of gastric cancer-Cox multiple-regression analysis.

Variable	Regression coefficient	Standard error	OR	P value
Sex	-0.054	0.120	0.947	.650
Age	0.007	0.005	1.007	.128
Tumor size	0.001	0.005	1.000	.934
Operation mode*				.006
Total gastrectomy	-0.707	0.289	0.493	.014
Distal subtotal gastrectomy	-0.954	0.299	0.385	.001
Proximal subtotal gastrectomy	-1.067	0.340	0.344	.002
Pathology†				.110
Borrmann I	0.001	0.319	1.000	.999
Borrmann IV	0.387	0.162	1.472	.017
Differentiation	0.205	0.060	1.228	.001
TNM stage	0.783	0.075	2.188	.001
Treatment Modal‡				.013
operation + chemotherapy	-0.202	0.104	0.817	.053
operation + IPHP	-0.563	0.260	0.569	.030
operation + IPHP + chemotherapy	-0.954	0.418	0.385	.022

Sex was coded 1 = male and 2 = female; age and tumor size was recorded according operation record; pathology was categorized and coded as 1 = I, 2 = II + III, 3 = IV according to Borrmann type; differentiation was coded as 1 = well, 2 = moderate, 3 = poor, 4 = no differentiation; TNM stage was coded as 1 = I, 2 = II, 3 = III, 4 = IV; treatment modes were categorized and coded as 1 = operation alone, 2 = operation + chemotherapy, 3 = operation + IPHP, 4 = operation + IPHP + chemotherapy. IPHP = intraperitoneal hyperthermic perfusion.

\* Compared with palliative or explorative operations

† Compared with Borrmann II + III

‡ Compared with operation alone

(54.80%).<sup>[28]</sup> And the median OS after CRS+HIPEC was 13.3, the median 1-, 2-, and 5-year survival rates after CRS+HIPEC were 50.0%, 35.8%, and 13.0%, respectively.<sup>[29]</sup> Our results was consistent with those reports, and combined with the above study boomed up the application of IPHP/HIPEC. However, the value of HIPEC in gastric cancer is controversial, It has reported CRS plus HIPEC yield fewer benefits in patients with PM from gastric cancer, and the median OS in GC is shorter than in other malignancies such as colorectal cancer, ovarian cancer, and appendicular cancer.<sup>[30,31]</sup> And clinical usefulness of systemic chemotherapy and HIPEC is judged to be moderate to high for PM of ovarian and colorectal origin but moderate to poor for gastric origin.<sup>[32]</sup> Contrast to these studies, the above studies mainly targeted the advanced gastric cancer with peritoneal metastasis, while, we aimed each stage of gastric cancer, and our IPHP procedure was not combined with chemotherapeutic agent, which may increase morbidity of adverse event.

Fewer patients developed a fever in the IPHP group compared with the non-IPHP group. And the incidence rate of total complications in IPHP group was not statistically significantly different from that in the non-IPHP group. In addition, there were no differences regarding lung infection, wound infection, wound rupture, anastomotic leakage, bleeding, duodenal leak, chylous leakage, and intestinal obstruction between the two groups according to the univariate analysis, therefore, our results proved that IPHP was safety for gastric cancer treatment. The morbidity of complication in our study was lower than others. Which

reported that the morbidity approximate 11%–37.5%, and the mortality is 0%–4.8%.<sup>[33–35]</sup> Some documents reported there is higher incidence of procedure-related morbidity in the HIPEC group, whereby higher incidence of myelotoxicity and renal insufficiency. CRS-HIPEC causes surgery-related morbidity including abscess, fistula, and anastomotic leak, and chemotherapy-related morbidities such as leucopenia, anemia, thrombopenia, and heart, liver or renal toxicity. In addition, it has reported 5.7% develop delayed major complications correlated with IPHP, which included pancreatic pseudocyst/pancreatitis, abdominal wall dehiscence, gastric perforation, and ureteral stricture with associated hydronephrosis.<sup>[36]</sup> The higher morbidity and mortality limit the application of HIPEC. Our lower morbidity of complications were attribute to IPHP procedure, which was not combined with chemotherapeutic agent, moreover, the selection of patients for IPHP was performed strictly, the candidate aged less than 75 years, and no severe basic disease. Repeated evidence demonstrates that incidence of morbidity or mortality is significantly influenced by the institutional experience and selecting candidate patients.<sup>[37,38]</sup> Overall, application of pathogenetic ways of protection from thermal injury, timely control and correction of homeostasis caused by the toxic effects of chemotherapy and burn peritoneum, may reduce the risk of complications.

IPHP/HIPEC is frequently combined with CRS, and IPHP/HIPEC can performed pre-, intra-, and post- CRS or radical resection of gastric cancers.<sup>[26,39]</sup> We investigated four treatment modality in our study, and found the 2-year mortality risk was decreased 1.76 times and 2.59 times in operation + IPHP group and operation + IPHP + chemotherapy group respectively. Moreover, we found the modality of operation + IPHP + chemotherapy was the optimal treatment modality for gastric cancer to increase 2-year survival. Our results were consistent with the study which demonstrate the modality of gastrectomy + chemotherapy + HIPEC showed an optimum survival.<sup>[19]</sup> Using HIPEC and systematic chemotherapy followed by a staged CRS (HIPEC + Chemo + CRS), Wu has reported the tolerance and compliance of the new modality is better than simultaneous CRS and HIPEC, and the mortality and the complications of both modality were similar.<sup>[40]</sup> But some authors hold a opposite view and reported that the morbidity and mortality rates of CRS and HIPEC, in combination with gastrectomy, were significant and the survival rates of this approach may not extend beyond that of treatment with systemic chemotherapy.<sup>[41]</sup>

*Helicobacter pylori* infection is the major cause of gastric cancer. Inducing tolerogenic dendritic cells and inhibiting effector T cell responses, *H. pylori* can successfully evade the strong innate and adaptive immune responses and colonize in the gastric epithelium. The mechanisms related to *H. pylori* persistence involve bacterial virulence factors such as cytotoxin-associated gene A, vacuolating cytotoxin A, or gamma-glutamyltranspeptidase.<sup>[42]</sup> *H. pylori* could against gastric acidity, shape its helical morphology and flagella, and change genetic diversity to facilitate persistent infection.<sup>[43]</sup> In this study, whether IPHP play a role in anti-*H. pylori* treatment and affected the immune evasion of *H. pylori* was unclear. And besides thermal injury, how did IPHP change inhospitable microniche and play a role in molecular pathogenesis and signal transduction of *H. pylori* need further investigate.

Our study have limitations, because of poor prognosis of AGC and a relatively small sample size in IPHP group, we could only analyzed 2-year survival, and we could not evaluate the

preventive role of IPHP in PM. And for the safety, the patients with serious basic disease such as heart disease, hypertension and COPD, or with hyperpyrexia, severe abdominal pain, and distension after operation were unsuitable for IPHP, and were excluded from this study. The quality of life in patients with IPHP and the tolerance of IPHP need further investigate. Therefore, we couldn't extrapolate the value of IPHP to all GC patients. And a prospective randomized controlled study about IPHP should be performed eventually and hopefully to confirm the observation in the future.

In conclusion, our results suggest that IPHP is safety and efficacy in GC treatment, and could become one of important therapeutic strategy for GC. And establishment of standard of IPHP is very necessary in current clinical practice. Moreover, the appropriate selection of patients and modality need further investigate.

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