Original Article

Intraoperative hyperthermic intraperitoneal chemotherapy as adjuvant chemotherapy for advanced gastric cancer patients with serosal invasion

Lung-Yun Kang, King-Tong Mok, Shiuh-Inn Liu, Cheng-Chong Tsai, Being-Whey Wang, I-Shu Chen, Yu-Chia Chen, Bo-Min Chang, Nan-Hua Chou*

Division of General Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC

Abstract

Background: To evaluate hyperthermic intraperitoneal chemotherapy (HIPEC) as an adjuvant chemotherapy in advanced gastric cancer (AGC) patients with serosal invasion.
Methods: Patients who received radical surgery and palliative surgery between January 2002 and December 2010 were retrospectively examined. Patients were divided into two groups, namely, one group that underwent surgery and another group that underwent surgery with HIPEC. All patients who received HIPEC had suspected serosal invasion on an abdominal computed tomography or by the surgeon's assessment during the operation.
Results: The prophylactic groups included 83 patients who underwent gastrectomy alone. A total of 29 patients underwent gastrectomy with HIPEC. The 5-year survival rates were 10.7% and 43.9%, respectively. The 5-year mean survival times were 22.66 (17.55−25.78) and 34.81 (24.97−44.66) months ($p = 0.029$), respectively. There were 52 patients who had a recurrence of carcinomatosis among 133 patients who had resections (52/133, 39.1%). The 3-year disease-free survival rate for carcinomatosis was 28.87% in the group that received surgery alone, whereas it was 66.03% in the group that received HIPEC. There was no significant difference in the rate of complication between the two groups in the prophylactic group ($p = 0.542$). Thus, curative surgery with HIPEC had a better prognosis for AGC with serosal invasion. The carcinomatosis recurrence time was longer in patients who underwent gastrectomy with HIPEC and received R0 resection.
Conclusion: The survival benefit of HIPEC as an adjuvant therapy for gastric cancer patients with serosal invasion should be validated in a large cohort.
Copyright © 2013 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

Keywords: adjuvant chemotherapy; intraperitoneal chemotherapy; serosal invasion; stomach neoplasm

1. Introduction

Gastric cancer is one of the most frequent causes of cancer-related mortality worldwide.[1] The most favorable treatment is curative surgery and adjuvant chemotherapy.[2] However, the prognosis is poor after tumor recurrence. Typically, peritoneal carcinomatosis (PC) is the main recurrent form of gastric cancer. Previous research has suggested that cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) can be an effective treatment option for PC in many intra-abdominal cancers.[3]

However, other reports have shown HIPEC to be effective in preventing PC,[4−8] and can extend the time before peritoneal recurrence. HIPEC is still not a standard adjuvant therapy for advanced gastric cancer (AGC) because of the timing of drug delivery and the choice of drug. Although there are more complications associated with HIPEC, its safety and efficacy has been well proven in other studies.

We therefore reviewed records for patients in our hospital who had AGC with serosal invasion to demonstrate the efficacy and safety of HIPEC.

* Corresponding author. Dr. Nan-Hua Chou, Division of General Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan, ROC.
E-mail address: vghksc@gmail.com (N.-H. Chou).

2. Methods

Patients who received radical surgery and palliative surgery between January 2002 and December 2010 were included in this study. However, those patients without serosal invasion in their pathologic report were excluded. Patients were divided into two groups, namely, group A (included patients who underwent surgery) and group B (included patients who underwent surgery with HIPEC). The two groups were divided further into two subgroups based on the objective of prophylaxis (group C and group G) and therapeutic treatment (group D and group H).

The prophylaxis group excluded palliative surgeries, stump cancer, and distant metastases. The patients in the gastrectomy-only group were designated as group C, and the gastrectomy with HIPEC patients were noted as group D.

The therapeutic group included patients who underwent palliative surgery without or with HIPEC, which emphasized the therapeutic effect of HIPEC. In the therapeutic groups (group G and H), group G was the surgery-only group and group H included patients who underwent surgery with HIPEC. None of the patients received peritonectomies, but rather palliative gastrectomy combined with other resections without peritonectomy in the therapeutic groups.

The PC recurrence refers to patients, initially without PC grossly, who received curative surgery that was followed by PC recurrence. Another episode of PC recurrence was limited in patients and was noted as resected in the postoperative pathology report. The patients were divided into two groups, namely, the surgery-only group (group E) and the surgery with HIPEC group (group F). Some of the patients had distant metastases and lymph node metastasis. For all affected patients, the duration of carcinomatosis was calculated.

A preoperative survey was arranged for patients in this study. In some cases, endoscopy was performed to prove gastric cancer. In addition, abdominal computed tomography (CT) and chest radiography were performed. All patients who received HIPEC had suspected serosal invasion on abdominal CT or by the surgeon's assessment during the operation, and PC recurrence was assessed by CT. We applied Cox multivariate analysis to control for confounding factors.

2.1. Procedure

HIPEC was performed after gastrectomy and lymph node dissection, and before closure of the abdominal cavity. One inflow tube was placed in a Douglas pouch, following which the skin of the abdomen was attached to a retractor ring, and a plastic sheet covered the open wound to keep the temperature stable. Approximately 3−4 L of lactated Ringer solution containing cisplatin (30 mg/L), mitomycin (10 mg/L), and etoposide (20 mg/L) was circulated for 60 minutes. The temperature was maintained at 41−43°C. After HIPEC, the wound was closed.

Statistical analyses were performed using SPSS (version 12.0; SPSS Inc., Chicago, IL, USA). Between-group comparisons of clinical data were performed using independent sample t tests, and postoperative survival curves were generated according to the Kaplan−Meier method and compared using the log-rank test. Independent prognostic factors were analyzed with a Cox proportional hazards regression method. Statistical significance was assessed for $p < 0.05$.

Informed content was obtained from all patients before operation. The study complied with institutional review board protocols.

3. Results

A total of 172 patients were included in the study (Fig. 1). Of these, 121 patients received surgery alone (group A).
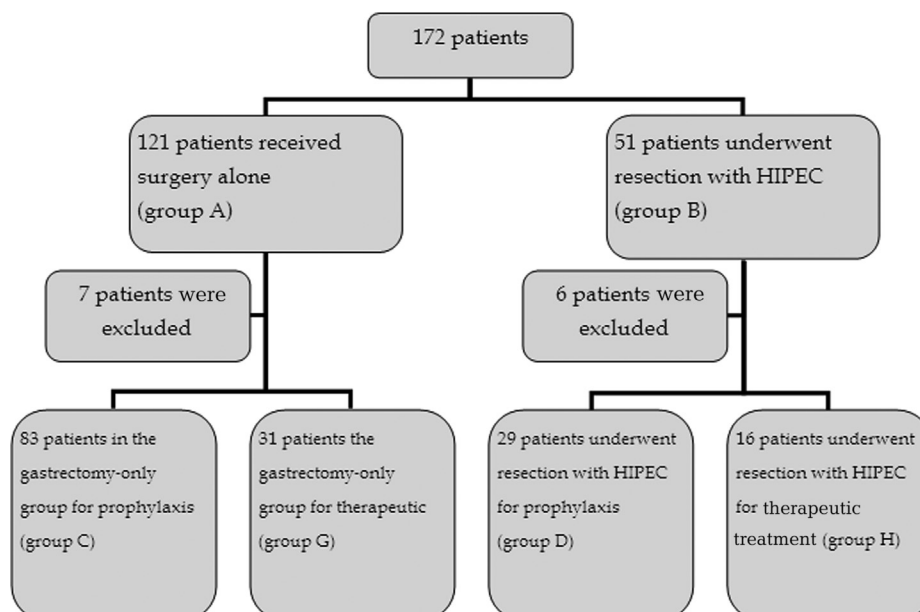

Fig. 1. Patient groups. Group E is the surgery-only group in PC patients. Group F is the surgery with HIPEC in PC group.

Eighty-three patients were group C and 31 patients were designated as group G. Seven patients were excluded due to stump cancer.
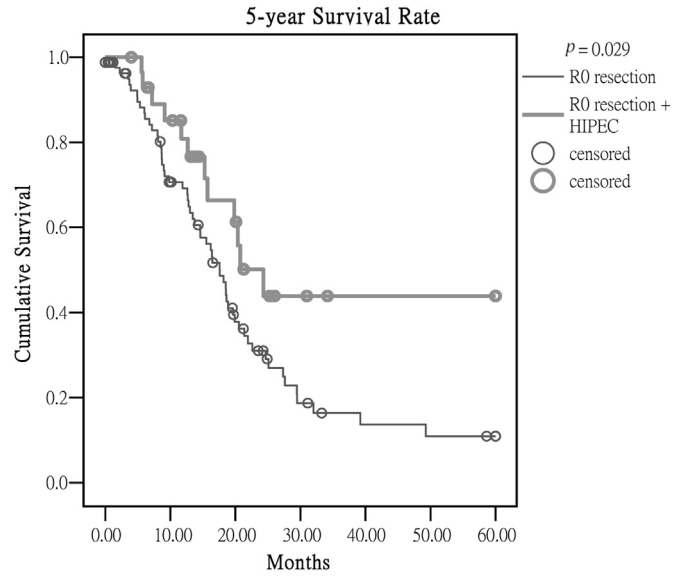
Fifty-one patients underwent resection with HIPEC (group B; Table 1). Twenty-nine patients were in group D, and 16 patients were deemed as group H. Six patients were excluded due to stump cancer (three patients) and recurrence from previous gastric cancer (three patients).

The prophylaxis group excluded palliative surgeries, stump cancer, and distant metastases. There were 83 patients in the gastrectomy-only group (group C). The gastrectomy with HIPEC group comprised 29 patients (group D). The 5-year survival rate was 10.7% in group C and 43.9% in group D. The 5-year mean survival times were 21.66 (range: 17.55–25.78 months) and 34.81 months (range: 24.97–44.66 months), respectively ($p = 0.029$; Fig. 2).

The survival analysis for gastric cancer is shown in Table 2. The T-stage and HIPEC procedure were independent prognostic factors.

A total of 52 patients (44 in group A and eight in group B) had a recurrence of carcinomatosis out of 133 patients who had resections (52/133; 39.1%), including 99 patients in group A and 34 patients in group B. The 3-year disease-free survival rate for carcinomatosis recurrence was 28.87% in the surgery-only group (group E) and 66.03% in the surgery with HIPEC group (group F). The mean recurrence time of PC was 20.55 months (range: 17.62–23.47 months) in the surgery-only group and 27.29 months (range: 22.30–32.39 months) in the group that received surgery with HIPEC ($p = 0.0451$; Table 3; Fig. 3). The only factor leading to a significant difference was HIPEC. Combined resection did not influence recurrence.

In the therapeutic group, 31 patients comprised the surgery-only group (group G) and 16 patients underwent surgery with

Fig. 2. Survival curves in the prophylactic group for advanced gastric cancer with serosal invasion ($p = 0.029$). HIPEC = hyperthermic intraperitoneal chemotherapy.

R0	83	50	23	9	5	4	3
R0+ hi	29	22	12	5	3	3	3

patient at risk

R0: R0 resection

R0+hi: R0 resection + HIPEC

HIPEC (group H). The mean survival time was 8.04 months (range: 6.14–9.93 months) in the surgery-only group and 14.63 months (range: 2.70–26.57 months) in patients who underwent surgery with HIPEC ($p = 0.486$).

Table 1

Comparison of data between hyperthermic intraperitoneal chemotherapy and control patients.

	Gastrectomy ($n = 121$)	Gastrectomy + HIPEC ($n = 51$)	p
Age	66.36 ($\pm$14.54)	64.00 ($\pm$15.20)	0.339
Gender, M/F	85/36 (70%/30%)	34/17 (67%/33%)	0.645
Location			
U/M/L/U + M or M + L/U + M + L/S	20/18/59/13/4/7	8/8/18/10/4/3	0.278
Size	6.59 ($\pm$3.85)	6.38 ($\pm$3.77)	0.747
Histological diagnosis			
Well/intermediately versus Poorly/undifferentiated	25/96 (21%/79%)	13/38 (25%/75%)	0.595
T stage, 4A/4B	90/31 (74%/26%)	38/13 (75%/25%)	0.559
LN stage, 0/1/2/3	12/21/25/63	7/6/11/27	0.836
Distant metastasis, M0/M1	110/11 (91%/9%)	42/9 (82%/18%)	0.111
Carcinomatosis, P0 versus P1	95/26 (78%/22%)	34/17 (67%/33%)	0.132
Stage, 2B/3A/3B/3C/4	8/13/15/45/40	6/1/10/17/17	0.897
Gastrectomy, Sub./Tot.	53/68 (44%/56%)	21/30 (41%/59%)	0.753
LND, D1/D2/D3	5/112/4	3/48/0	0.227
Combined resection			
With/without	27/84 (22%/78%)	24/27 (47%/53%)	0.001
Residual tumor			
R0/R1or R2	83/38 (69%/31%)	30/21 (59%/41%)	0.181
Perioperative mortality	12 (10%)	7 (14%)	0.155
Complication	23 (19%)	17 (33%)	<0.001
Chemotherapy	25 (21%)	11 (22%)	0.981

HIPEC = hyperthermic intraperitoneal chemotherapy; LN = lymph node; LND = lymph node dissection.

Table 2
Survival analysis in the prophylactic group.

Variables	p (Univariate)	p (Multivariate)
Age, ≥65 versus <65	0.742	—
Gender, M/F	0.115	—
Size, ≥6 cm versus <6 cm	0.805	—
Lymph node metastasis, yes versus no	0.114	—
HIPEC, yes versus no	0.032	0.043
T stage, 4B versus 4A	0.003	0.005
Chemotherapy, yes versus no	0.434	—
Complication, yes versus no	0.855	—
Histology		
Well/intermediately versus Poorly/undifferentiated	0.888	—
Gastrectomy, total versus partial	0.323	—
Combine resection, yes versus no	0.305	—

HIPEC = hyperthermic intraperitoneal chemotherapy.

During study period, a total of 58 patients received the HIPEC procedure for prophylactic purposes during the operation, including all T stages of gastric cancer: two patients were designated as T2, 27 patients were T3, and only 29 patients (group D) had genuine serosal invasion (T4a or T4b) in their pathology report. The rate of accuracy of clinical impressions of serosal invasion was 50%.

Among the patients treated by surgery, resection was considered curative by the operating surgeon in 29 of 51 patients (56.9%) in the HIPEC group, compared with 83 of 121 patients (68.6%) in the surgery-only group ($p = 0.018$).

The most common complications were intra-abdominal abscesses, pulmonary complications, and anastomosis leakages (Table 4). The total number of operative mortalities were 12 (10%) in group A and seven in group B (15%; $p = 0.155$). Additional complications were discovered in cases involving operative mortality. There was no significant difference in the rate of complications between the two prophylactic groups ($p = 0.542$), though there was a significant difference between the therapeutic groups ($p = 0.023$).

More lymph node-positive patients had abnormal preoperative serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels compared with lymph node-negative patients (CEA: 40%/14%, $p < 0.001$; CA 19-9: 27%/11%, $p = 0.01$).

Table 3
Univariate analysis for disease-free survival in the peritoneal carcinomatosis group.

Variables	Risk ratio	95% CI	p
Age, ≥65 versus <65	0.841	0.485−1.459	0.538
Gender, M/F	0.852	0.486−1.492	0.575
Size, ≥6 cm versus < 6 cm	1.185	0.657−2.137	0.573
Lymph node metastasis, yes versus no	1.351	0.608−3.001	0.460
HIPEC, yes versus no	0.445	0.209−0.947	0.036
T stage, 4B versus 4A	1.804	0.956−3.403	0.068
Chemotherapy, yes versus no	1.380	0.751−2.538	0.300
Complication, yes versus no	0.875	0.411−1.864	0.729
Combine resection, yes versus no	0.930	0.494−1.751	0.823

CI = confidence interval; HIPEC = hyperthermic intraperitoneal chemotherapy.

3-year Disease Free Survival for Carcinomatosis
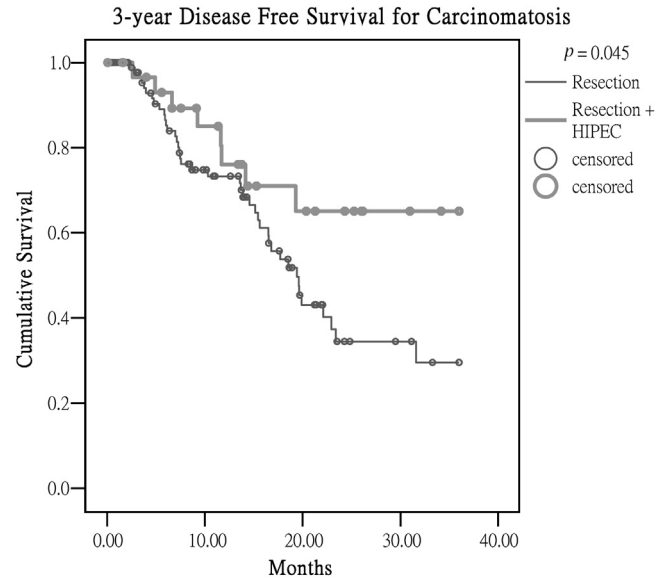
R0	99	52	19	8	5
R0+ hi	29	22	12	5	3

patient at risk
R0: R0 resection
R0+hi: R0 resection + HIPEC

Fig. 3. Three-year disease-free survival rate for carcinomatosis recurrence ($p = 0.0451$). HIPEC = hyperthermic intraperitoneal chemotherapy.

Thirty-seven patients (21.5%) received systemic chemotherapy in our study. There was no significant difference ($p = 0.434$).

Cytology of ascites was performed in 15 patients who received HIPEC. The cytology results of three patients were positive, of which two patients (66.67%) had PC, whereas the results were negative for the remaining 12 patients, of which two (17%) patients had PC. Of the 10 patients who were cytology negative without PC, PC recurred in four of them (40%). The sole patient who was cytology positive without PC had no PC recurrence.

4. Discussion

It had been reported in several other reports that radical gastrectomy with HIPEC is effective for prophylaxis.[4−11] There are two possible sources of PC: serosal invasion increases the chance of tumor seeding to the peritoneal cavity, and surgical trauma also spreads tumor cells to the peritoneal cavity while lymph node dissection is performed. Marutsuka et al reported that free cancer cells were found in the lavage

Table 4
Complications in all patients.

	Gastrectomy ($n = 121$)	Gastrectomy + HIPEC ($n = 51$)	p
Complication	23 (19%)	17 (33%)	<0.001
Intra-abdominal abscess	6 (5%)	13 (25%)	<0.001
Anastomosis leakage	3 (2.5%)	6 (11.8%)	<0.001
Pulmonary complication	7 (5.7%)	7 (13.7%)	0.001

HIPEC = hyperthermic intraperitoneal chemotherapy.

fluid after lymph node dissection of 14.3% and 26.7% of patients with submucosal and muscularis propria tumors, respectively.[12−15] Adjuvant chemotherapy was required for these patients with AGC, and HIPEC is one such choice. HIPEC can eradicate the spread of tumor cells in the peritoneal cavity.[15] Extensive intraoperative peritoneal lavage, followed by intraperitoneal chemotherapy, had a significantly lower incidence of peritoneal recurrence than intraperitoneal chemotherapy alone.[16]

PC was the most common recurrent form of gastric cancer after curative surgery[17,18]; in our study, 39.1% patients experienced peritoneal recurrence. It has been demonstrated that HIPEC can decrease the rate of peritoneal recurrence.[4−8,19] Decreasing peritoneal recurrence and delaying the time until peritoneal recurrence can lead to longer patient survival. In our study, the 3-year disease-free survival rate for PC recurrence was elevated after surgery with HIPEC. In the prophylaxis group, the HIPEC group had a better survival rate, consistent with other studies.[4−8] In the multivariate survival analysis, HIPEC and T stage were the two factors that affected survival, and multivariate analysis showed significant differences resulting from both factors. Thus, HIPEC is an independent prognostic factor in the prophylactic group and it can be effectively used as an adjuvant chemotherapy.

There are many effective drugs for chemotherapy, such as oxaliplatin,[20] paclitaxel,[21] and docetaxel.[22] In our study, we used a drug mixture of cisplatin,[6,23] mitomycin C,[24] and etoposide,[25] which has been reported to be effective.

Preoperative staging can be performed using many methods, such as positron emission tomography-CT, abdominal CT, laparoscopic staging, and tumor markers. If PC was suspected, cytoreductive surgery should be considered before HIPEC. Laparoscopic staging is a useful tool for the diagnosis of PC.[26,27] Once PC was discovered, HIPEC was performed with cytoreductive surgery therapeutically.

In our opinion, HIPEC is effective as prophylactic therapy, and palliative surgery with HIPEC is not useful because of insufficient tumor resection, which is supported by our research data. Many reports have revealed that cytoreductive surgery plus HIPEC is effective for AGC.[28−30] The effect of HIPEC is limited to a depth of less than 3 mm, and PC has a barrier that can protect tumor cells from the antitoxic agents. Therefore, its therapeutic effect for PC is limited. No peritonectomy surgery was performed in our patients. Thus, the outcomes in our therapeutic cohort were not different between the two groups.

Abdominal CT was used to determine clinical stage. This method has been reported to have moderate accuracy.[31,32] Many other factors were discussed for predicting serosal invasion, including elevated neutrophil-to-lymphocyte ratio, decreased hemoglobin (Hb), and poorly differentiated histology.[33] Abnormal preoperative serum tumor markers, such as CEA and CA 19-9, were found in patients who had positive lymph nodes (CEA: $p = 0.029$; CA 19-9: $p = 0.218$), but were not related to the recurrence of carcinomatosis and carcinomatosis.[34] Tumor markers cannot be an indicator for the performance of HIPEC. The sensitivity and specificity of positive peritoneal washing cytology in predicting peritoneal recurrence

were 61% and 100%, respectively.[35] The sensitivity and specificity of positive peritoneal washing cytology for predicting peritoneal seeding were 52% and 89.6%, respectively. In our study, the sensitivity and specificity of positive cytology for predicting peritoneal seeding were 50% and 90.9%, respectively. Cytology had high specificity for predicting PC.[16] Positive cytology without PC could be used an indicator for HIPEC if the false-negative rate can be improved.[36] We therefore used abdominal CT and the surgeon's assessment to predict serosal invasion and perform HIPEC. Consequently, reduced accuracy was a limitation. Only 50% of patients truly had serosal invasion, as demonstrated by pathological study results. Kuramoto et al reported that 59% (35/59) of patients who received intraperitoneal chemotherapy had serosal invasion.[16] Yu et al reported 80% accuracy for predicting serosal invasion.[37] The accuracy of predicting serosal invasion is low. However, preoperative CT and the surgeon's assessment during surgery are now an indicator for HIPEC. More tools, such as laparoscopic staging, endoscopic ultrasonography, intraperitoneal washing cytology, and intraoperative frozen section reports, are available.[38−41] Cytology and intraoperative frozen section reports may help to ascertain which patients should receive adjuvant HIPEC.

Hyperthermia can potentiate cytostatic effects. The pharmacological basis for using heat to supplement chemotherapy effects is related to the increased penetration of chemotherapeutic agents into tumors with hyperthermia, the delayed clearance of chemotherapeutic agents from the peritoneal cavity after direct instillation, and an increased cytotoxicity that has been documented with selected chemotherapy agents.[37,42−44] However, the effects of heat and drug toxicity may lead to more complications. The most common complications were anastomotic leakage, intra-abdominal abscess, and wound infection (Table 4). There were more complications in the HIPEC group, particularly intra-abdominal abscesses, as seen in other studies.[37,43] The rate of complication of anastomosis leakage was higher in the HIPEC group. Pulmonary complications are related to fluid overload and inflammatory status; HIPEC can induce dehydration that shifts fluid to the third space, and fluid supply is important. However, fluid overload and the inflammatory process can induce pulmonary edema and acute respiratory distress syndrome. HIPEC may maximize this effect in the peritoneal cavity and minimize the systemic effect.[7,19,25,45] No neutropenia was noted in our study. Operative mortality was higher in the HIPEC group, but no significant difference between groups was found. Operative mortality refers to death within 30 days of the operation, or within the same admission. In the prophylactic group, there was no significant difference in complications between the two groups. The highest rate of complications was found in the therapeutic group that received HIPEC. The overall condition of patients in this group was relatively poor, and HIPEC can impose a massive systemic stress that results in more complications and mortality. However, HIPEC for prophylaxis was relatively safe and efficacious.

Our patient group was older, with a mean age of 65.66 (±14.77) years. Notwithstanding this elevated age

representation, HIPEC still appeared to be safe for older patients. Curative surgery with HIPEC had a better prognosis for AGC with serosal invasion. The duration before carcinomatosis recurrence was longer in patients who received gastrectomy with HIPEC and R0 resection, even though HIPEC was accompanied by more complications. The survival benefit of this strategy as an adjuvant therapy for gastric cancer patients with serosal invasion should be validated by prospective clinical trials in a large cohort.

Acknowledgments

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;**24**:2137—50.
2. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;**14**:113—23.
3. Al-Shammaa HA, Li Y, Yonemura Y. Current status and future strategies of cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *World J Gastroenterol* 2008;**14**:1159—66.
4. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 1994;**73**:2048—52.
5. Yonemura Y, de Aretxabala X, Fujimura T, Fushida S, Katayama K, Bandou E, et al. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. *Hepatogastroenterology* 2001;**48**:1776—82.
6. Yonemura Y, Ninomiya I, Kaji M, Sugiyama K, Fujimura K, Sawa T, et al. Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. *World J Surg* 1995;**19**:450—4. discussion 455.
7. Hirose K, Katayama K, Iida A, Yamaguchi A, Nakagawara G, Umeda S, et al. Efficacy of continuous hyperthermic peritoneal perfusion for the prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer: evaluation by multivariate regression analysis. *Oncology* 1999;**57**:106—14.
8. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 1999;**85**:529—34.
9. Sugarbaker PH. Adjuvant intraperitoneal chemotherapy for advanced primary gastric cancer. *Scand J Surg* 2006;**95**:270—3.
10. Zhu ZG, Tang R, Yan M, Chen J, Yang QM, Li C, et al. Efficacy and safety of intraoperative peritoneal hyperthermic chemotherapy for advanced gastric cancer patients with serosal invasion. A long-term follow-up study. *Dig Surg* 2006;**23**:93—102.
11. Xu DZ, Zhan YQ, Sun XW, Cao SM, Geng QR. Meta-analysis of intraperitoneal chemotherapy for gastric cancer. *World J Gastroenterol* 2004;**10**:2727—30.
12. Lejeune FJ. Is surgical trauma prometastatic? *Anticancer Res* 2012;**32**:947—51.
13. Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, et al. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg* 2003;**90**:1113—9.
14. Eggermont AM, Steller EP, Sugarbaker PH. Laparotomy enhances intraperitoneal tumor growth and abrogates the antitumor effects of interleukin-2 and lymphokine-activated killer cells. *Surgery* 1987;**102**:71—8.
15. Marutsuka T, Shimada S, Shiomori K, Hayashi N, Yagi Y, Yamane T, et al. Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: an ultrarapid detection system for intraperitoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. *Clin Cancer Res* 2003;**9**:678—85.
16. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. *Ann Surg* 2009;**250**:242—6.
17. Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, et al. Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. *Am J Surg* 1999;**178**:256—62.
18. Wu CW, Lo SS, Shen KH, Hsieh MC, Chen JH, Chiang JH, et al. Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. *World J Surg* 2003;**27**:153—8.
19. Fujimura T, Yonemura Y, Muraoka K, Takamura H, Hirono Y, Sahara H, et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. *World J Surg* 1994;**18**:150—5.
20. Elias D, Matsuhisa T, Sideris L, Liberale G, Drouard-Troalen L, Raynard B, et al. Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: pharmacokinetics, tissue distribution and tolerance. *Ann Oncol* 2004;**15**:1558—65.
21. Imano M, Imamoto H, Itoh T, Satou T, Peng YF, Yasuda A, et al. Impact of intraperitoneal chemotherapy after gastrectomy with positive cytological findings in peritoneal washings. *Eur Surg Res* 2011;**47**:254—9.
22. Fujiwara Y, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, et al. Intraperitoneal docetaxel combined with S-1 for advanced gastric cancer with peritoneal dissemination. *J Surg Oncol* 2012;**105**:38—42.
23. Kuo SC, Chao Y, Luo JC, Lee KC, Wu CW, Li AF, et al. Primary small cell carcinoma of the stomach successfully treated with cisplatin and etoposide. *J Chin Med Assoc* 2009;**72**:598—602.
24. Sugarbaker PH, Stuart OA, Carmignani CP. Pharmacokinetic changes induced by the volume of chemotherapy solution in patients treated with hyperthermic intraperitoneal mitomycin C. *Cancer Chemother Pharmacol* 2006;**57**:703—8.
25. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. *J Natl Cancer Inst* 1997;**89**:480—7.
26. Valle M, Garofalo A. Laparoscopic staging of peritoneal surface malignancies. *Eur J Surg Oncol* 2006;**32**:625—7.
27. Facchiano E, Scaringi S, Kianmanesh R, Sabate JM, Castel B, Flamant Y, et al. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of malignant ascites secondary to unresectable peritoneal carcinomatosis from advanced gastric cancer. *Eur J Surg Oncol* 2008;**34**:154—8.
28. Yonemura Y, Endou Y, Sasaki T, Hirano M, Mizumoto A, Matsuda T, et al. Surgical treatment for peritoneal carcinomatosis from gastric cancer. *Eur J Surg Oncol* 2010;**36**:1131—8.
29. Li C, Yan M, Chen J, Xiang M, Zhu ZG, Yin HR, et al. Surgical resection with hyperthermic intraperitoneal chemotherapy for gastric cancer patients with peritoneal dissemination. *J Surg Oncol* 2010;**102**:361—5.
30. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer Treat Rev* 2001;**27**:365—74.
31. Venkataraman I, Rao HK, Singh P, Elangovan S, Kate V. Efficacy of hydrogastric sonography and spiral computed tomography in staging of gastric carcinoma—a comparative study. *J Clin Ultrasound* 2010;**38**:480—5.
32. Yan C, Zhu ZG, Yan M, Chen KM, Chen J, Xiang M, et al. Value of multidetector-row CT in the preoperative prediction of peritoneal metastasis from gastric cancer: a single-center and large-scale study. *Zhonghua Wei Chang Wai Ke Za Zhi* 2010;**13**:106—10. [Article in Chinese].
33. Aizawa M, Gotohda N, Takahashi S, Konishi M, Kinoshita T. Predictive value of baseline neutrophil/lymphocyte ratio for T4 disease in wall-penetrating gastric cancer. *World J Surg* 2011;**35**:2717—22.

34. Liu X, Cai H, Wang Y. Prognostic significance of tumor markers in T4a gastric cancer. *World J Surg Oncol* 2012;**10**:68.

35. Euanorasetr C, Lertsithichai P. Prognostic significance of peritoneal washing cytology in Thai patients with gastric adenocarcinoma undergoing curative D2 gastrectomy. *Gastric Cancer* 2007;**10**:18–23.

36. Benevolo M, Mottolese M, Cosimelli M, Tedesco M, Giannarelli D, Vasselli S, et al. Diagnostic and prognostic value of peritoneal immunocytology in gastric cancer. *J Clin Oncol* 1998;**16**:3406–11.

37. Yu W, Whang I, Chung HY, Averbach A, Sugarbaker PH. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. *World J Surg* 2001;**25**:985–90.

38. Tsendsuren T, Jun SM, Mian XH. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. *World J Gastroenterol* 2006;**12**:43–7.

39. Shimoyama S, Yasuda H, Hashimoto M, Tatsutomi Y, Aoki F, Mafune K, et al. Accuracy of linear-array EUS for preoperative staging of gastric cardia cancer. *Gastrointest Endosc* 2004;**60**:50–5.

40. Xi WD, Zhao C, Ren GS. Endoscopic ultrasonography in preoperative staging of gastric cancer: determination of tumor invasion depth, nodal involvement and surgical resectability. *World J Gastroenterol* 2003;**9**:254–7.

41. Nakagawa S, Nashimoto A, Yabusaki H. Role of staging laparoscopy with peritoneal lavage cytology in the treatment of locally advanced gastric cancer. *Gastric Cancer* 2007;**10**:29–34.

42. Sugarbaker PH. Laboratory and clinical basis for hyperthermia as a component of intracavitary chemotherapy. *Int J Hyperthermia* 2007;**23**:431–42.

43. Yan TD, Black D, Sugarbaker PH, Zhu J, Yonemura Y, Petrou G, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. *Ann Surg Oncol* 2007;**14**:2702–13.

44. Mohamed F, Marchettini P, Stuart OA, Urano M, Sugarbaker PH. Thermal enhancement of new chemotherapeutic agents at moderate hyperthermia. *Ann Surg Oncol* 2003;**10**:463–8.

45. Cattel L, De Simone M, Passera R, Verlengo MC, Delprino L. Pharmacokinetics of cisplatin in semi-closed hyperthermic peritoneal perfusion (HPP) for treatment of peritoneal carcinomatosis. *Anticancer Res* 2004;**24**:2041–5.