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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of hyperthermic intraperitoneal chemotherapy on gastric cancer survival: Peritoneal metastasis and cytology perspectives

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Abstract

BACKGROUND

Gastric cancer presenting with peritoneal metastasis is notably associated with diminished survival prospects. The use of cytoreductive surgery in conjunction with hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to increase survival rates in these patients. Despite these advancements, debates persist regarding the magnitude of survival improvement attributed to this treatment modality. The present investigation examined survival outcomes following HIPEC in individuals diagnosed with gastric cancer and peritoneal metastasis, and it took a comparative analysis of patients exhibiting positive and negative cytological findings.

AIM

To compare the impact of HIPEC on survival in gastric cancer patients with peritoneal metastasis and positive or negative cytology.

METHODS

Between April 2013 and March 2020, 84 patients with advanced gastric cancer treated at our institution were categorized into three cohorts: HIPEC (20 patients with peritoneal metastasis), cytology-positive (23 patients without peritoneal nodules but with positive wash cytology), and cytology-negative (41 patients with advanced gastric cancer, no peritoneal nodules, and negative wash cytology). The HIPEC cohort underwent gastrectomy with HIPEC, while the cytology-positive and cytology-negative groups received gastrectomy alone. The demographic, pathological, and survival data of the groups were compared.

RESULTS
The HIPEC cohort-predominantly younger females-exhibited relatively extended surgical durations and high blood loss. Nevertheless, the complication rates were consistent across all three groups. Median survival in the HIPEC group was 20.00 ± 4.89 months, with 1-year, 2-year, and 3-year overall survival rates of 73.90%, 28.70%, and 9.60%, respectively. These figures paralleled the survival rates of the cytology-positive group (52.20% at 1 year, 28.50% at 2 years, and 19.00% at 3 years). Notably, 47% of patients experienced peritoneal recurrence.

CONCLUSION
HIPEC may offer a modest improvement in short-term survival for patients with gastric cancer and peritoneal metastasis, mirroring the outcomes in cytology-positive patients. However, peritoneal recurrence remained high.

Key Words: Cytoreductive surgery; Gastric cancer; Hyperthermic intraperitoneal chemotherapy; Peritoneal metastasis; Positive cytology

Core Tip: This investigation evaluated the survival outcomes of 84 advanced gastric cancer patients from 2013 to 2020. Among them, the hyperthermic intraperitoneal chemotherapy (HIPEC) cohort, characterized by peritoneal nodules, underwent longer surgeries and experienced greater blood loss; however, the rate of complications did not significantly differ among groups. The HIPEC group's median survival was 20.00 ± 4.89 mo, with 1-year, 2-year, and 3-year survival rates of 73.90%, 28.70%, and 9.60%, respectively. These rates were akin to those of the cytology-positive group. While HIPEC appears to offer a survival benefit, particularly in the short term, the incidence of peritoneal recurrence remains high.

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INTRODUCTION

Although the global incidence and mortality rates of gastric cancer are declining[1], Thailand is experiencing an increase in mortality related to this malignancy[2]. This discrepancy may stem from the disease's advanced stage at the time of diagnosis within the Thai population, with peritoneal carcinomatosis found in the majority of Thai gastric cancer patients [3]. Despite being managed by multidisciplinary teams[4], these patients have historically survived for only 3 to 4 months [5]. Even though systemic chemotherapy offers only marginal benefits, the combination of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is recognized as an effective strategy for managing gastric cancer accompanied by carcinomatosis, demonstrating an acceptable complication profile. Rau's *et al* findings[6], alongside additional research, corroborate the survival advantages conferred by CRS and HIPEC, with some patients achieving long-term survival[7-9]. However, the extent of survival improvement with this approach remains variable. Our study endeavored to compare the outcomes of a CRS and HIPEC cohort against those of patients exhibiting positive cytology who were treated solely with systemic chemotherapy.

MATERIALS AND METHODS

Study design

This research was conducted at the Minimally Invasive Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, from April 2013 to March 2020. Patients diagnosed with gastric cancer manifesting either peritoneal carcinomatosis or positive cytology were included. The study population was divided into two primary groups: those who received CRS with HIPEC (referred to as the "HIPEC group") and those who underwent D2 gastrectomy followed by postoperative systemic chemotherapy (termed the "cytology-positive group"). Additionally, the study included a cohort of advanced gastric cancer patients characterized by negative cytology (the "cytology-negative group"). Patients under the age of 18 years were excluded.

Comprehensive demographic data, including age, sex, operative time, duration of hospital stay, blood loss, instances of combined resection, and complications, were collected. The following pathological parameters were meticulously documented: tumor size, histology, anatomical location, margin status, presence of lymphovascular invasion, and number of lymph nodes retrieved. Tumor staging was performed in accordance with the guidelines in the 8th edition of the staging manual of the American Joint Committee on Cancer.

The preoperative evaluation included gastroscopy and abdominal computed tomography scans for all patients. Diagnostic laparoscopy and wash cytology were uniformly conducted to ascertain the extent of disease spread. In the absence of discernible gross peritoneal nodules, patients underwent gastrectomy accompanied by D2 lymph node dissection. For individuals with positive cytology findings, a regimen of postoperative systemic chemotherapy comprising fluoropyrimidines and platinum-based drugs was initiated. When peritoneal nodules were identified during diagnostic laparoscopy, the treatment approach varied by period: CRS with HIPEC was the choice for patients identified before 2017, while those diagnosed from 2017 onward received preoperative chemotherapy.

During diagnostic laparoscopy for CRS with HIPEC, the peritoneal cancer index (PCI) was determined following established protocols[10]. Subsequent to this assessment, gastrectomy with D2 lymph node dissection was performed. In cases where complete (R0) resection was needed, gastrectomy was accompanied by resection of the adjacent involved organs. A comprehensive peritonectomy, involving the removal of the entire abdominal peritoneum, was conducted in every patient to minimize residual disease. After completing the surgical anastomosis, extensive intraperitoneal lavage was carried out using 10 liters of tepid saline, followed by HIPEC at 42 °C for 60 min, utilizing either 100 mg/m^2 cisplatin or 120 mg/m^2 oxaliplatin. The application of CRS combined with HIPEC was contraindicated in patients who presented with distant metastases, para-aortic nodal metastases, or a poor preoperative functional state.

Statistical analyses

We performed the statistical analyses using IBM SPSS Statistics, version 29 (IBM Corp, Armonk, NY, United States). Continuous variables were analyzed by calculating means and standard deviations, whereas categorical variables were expressed as percentages. When the data deviated from a normal distribution, we utilized medians and interquartile ranges. We determined differences in means using either Student's *t* test or the Mann-Whitney *U* test, depending on the parametric nature of the data. Differences among groups were assessed using one-way analysis of variance. The Tukey test was applied for homogeneity of variances, while the Games-Howell test was employed when variances were unequal. Categorical variables across groups were compared using the χ^2 test. Survival durations and their curves were estimated through the Kaplan-Meier method, with intergroup differences evaluated *via* the log-rank test. All *P* values were computed as two-tailed, with the significance threshold set at $P < 0.05$.

RESULTS

Our study included 84 individuals who were diagnosed with gastric cancer. Specifically, the HIPEC cohort included 20 patients who exhibited peritoneal carcinomatosis. The cytology-positive category comprised 23 participants without peritoneal nodules but with affirmative wash cytology results. Conversely, the cytology-negative group consisted of 41 patients with advanced gastric cancer who lacked peritoneal nodules and had negative wash cytology findings. The demographic characteristics are detailed in Table 1. Notably, the mean age within the HIPEC group was significantly younger (45.10 ± 11.34 years) than those in the cytology-positive or cytology-negative cohort. Females predominated in the HIPEC group, constituting 85% of its demographic data. The surgical duration in the HIPEC group averaged 534.60 ± 112.76 min, and blood loss was 1056.50 ± 128.03 mL, with both values notably surpassing those of the other groups. The frequency of combined organ resections, apart from splenectomy, was greater in the HIPEC group, occurring in 90% of patients. This group also experienced a 35% rate of complications, which was higher than the rates of the other two groups, although the differences did not reach statistical significance. The study reported zero mortality.

The HIPEC group exhibited significantly larger tumor sizes than did the cytology-negative group, as detailed in Table 2. Histological analysis revealed that 70% of patients in the HIPEC group presented with poorly differentiated adenocarcinoma or signet ring cell adenocarcinoma. Regarding tumor staging, 50% of these patients were at primary tumor stage IVa, while 30% were at stage IVb. Sixty percent of the patients were classified as having lymph node stage III disease. In addition, 25% of the patients in the HIPEC group exhibited positive resection margins, indicating the presence of tumor cells at the cut edge of the removed tissue. Moreover, 80% of patients demonstrated angiolymphatic invasion, reflecting aggressive tumor behavior. The PCI ranged from 0 to 18, with a median score of 3.0. Complete cytoreduction, indicating no visible residual disease, was achieved in 95% of the patients (19 individuals) with a complete cytoreduction score of zero, while a score of one was recorded in 5% of the patients (1 individual).

All patients underwent follow-up for a median of 88 months (range: 1-179 months). The HIPEC group exhibited a median survival duration of 20.00 ± 4.89 months. The 1-year overall survival rate was 73.90%, declining to 28.70% by the second year and 9.60% by the third year. In comparison, the cytology-positive group had a 1-year survival rate of 52.20%, which decreased slightly to 28.50% by the second year and increased to 19.00% by the third year. The cytology-negative group demonstrated more favorable survival rates of 76.70% at 1 year, 50.10% at 2 years, and 38.90% at 3 years. These survival trends are depicted in Figure 1, which shows that while the survival rate of the HIPEC group aligned with that of the cytology-positive group, it remained substantially lower than that of the cytology-negative group.

Recurrent disease was observed in 80% (16 of 20) of the patients in the HIPEC group. Specifically, peritoneal recurrence was noted in 47% of these patients, with 35% presenting with isolated peritoneal carcinomatosis and 12% showing combined organ and peritoneal metastases. Additionally, 41% of patients experienced distant organ metastasis, and 12% experienced local or lymph node recurrence (Figure 2).

Univariate analysis of prognostic factors revealed a significant association between the PCI score and survival outcomes ($P = 0.041$), underscoring the prognostic relevance of the PCI score in this context.

Table 1 Comparative demographic characteristics of hyperthermic intraperitoneal chemotherapy, cytology-positive, and cytology-negative patient groups

Feature	Cytology-negative group, *n* = 41	Cytology-positive group, *n* = 23	HIPEC group, *n* = 20	*P* value
Age	59.87 ± 10.25	63.17 ± 13.57	45.10 ± 11.34	< 0.0001
Sex				
Male	23 (56.1)	15 (62.5)	3 (15)	0.002
Female	18 (43.9)	8 (34.8)	17 (85)	
Operative time	269.27 ± 98.42	326.43 ± 135.39	534.60 ± 112.76	< 0.0001
Length of stay	14.88 ± 7.76	14.69 ± 6.48	19.05 ± 9.63	0.120
Blood loss	437.56 ± 69.04	616.09 ± 134.64	1056.50 ± 128.03	< 0.0001
Combined resection (other than splenectomy)				
No	37 (90)	18 (78.3)	2 (10)	< 0.0001
Yes	4 (9.8)	5 (21.7)	18 (90)	
Complication				
No	33 (80.5)	17 (73.90)	13 (65.0)	0.419
Yes	8 (19.5)	6 (26.10)	7 (35.0)	

Data are *n* (%). HIPEC: Hyperthermic intraperitoneal chemotherapy.

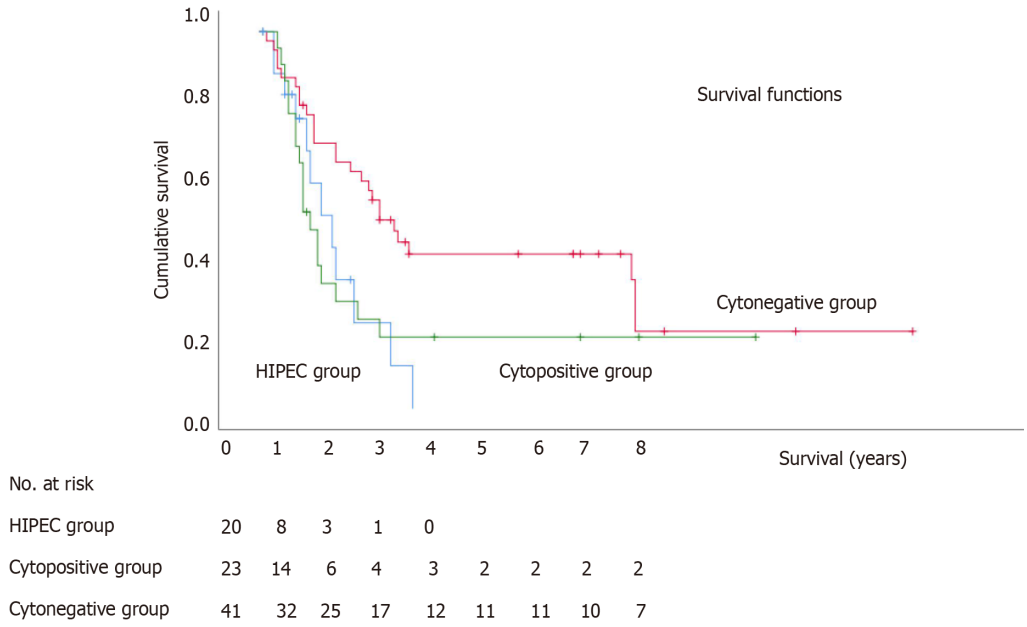

Figure 1 Comparative survival analysis of hyperthermic intraperitoneal chemotherapy *vs* cytology-positive and cytology-negative groups. HIPEC: Hyperthermic intraperitoneal chemotherapy.

DISCUSSION

Our analysis suggested that CRS combined with HIPEC may enhance short-term survival in patients, with 2-year and 3-year survival rates of 28.70% and 9.60%, respectively. The median survival duration for individuals in the HIPEC cohort was 20.00 ± 4.89 months, consistent with the findings of Smith *et al*[11]. Liu's *et al* meta-analysis of 21 randomized controlled trials, encompassing 1674 participants, demonstrated a significantly greater 3-year survival rate in patients receiving HIPEC than in those who did not[12]. Chia's *et al* systematic review also revealed a 5-year survival rate ranging from 6% to 31% for CRS patients within the HIPEC group[13]. Brandl *et al*[14] identified 28 long-term survivors with a median survival exceeding 5 years among 448 patients treated with HIPEC. Despite these encouraging results, our study did not record any 5-year survivors, suggesting the presence of more advanced peritoneal metastases in our patient cohort.

Table 2 Pathological profile comparison among hyperthermic intraperitoneal chemotherapy, cytology-positive, and cytology-negative groups

Feature	Cytology-negative group, *n* = 41	Cytology-positive group, *n* = 23	HIPEC group, *n* = 20	*P* value
Size	6.34 ± 3.40	7.49 ± 3.66	9.13 ± 4.25	0.025
Histology				
Well/moderately differentiated	15 (36.6)	6 (26.1)	6 (30.0)	0.670
Poorly differentiated/Signet ring cell adenocarcinoma	26 (63.4)	17 (73.9)	14 (70.0)	
Location				
Upper	19 (46.3)	8 (34.8)	4 (20.0)	0.548
Middle	6 (14.6)	4 (17.4)	6 (30.0)	
Distal	11 (26.8)	7 (30.4)	6 (30.0)	
Entire	5 (12.2)	4 (17.4)	4 (20.0)	
pT-stage				
Stage I	2 (4.9)	0 (0)	1 (5.0)	0.154
Stage II	6 (14.6)	2 (8.7)	0 (0)	
Stage III	13 (31.7)	3 (13.0)	3 (15)	
Stage IVa	16 (39)	14 (60.9)	10 (50)	
Stage IVb	4 (9.8)	4 (17.4)	6 (30)	
pN-stage				
Stage 0	8 (19.5)	1 (4.3)	2 (10)	0.132
Stage I	8 (19.5)	4 (17.4)	2 (10)	
Stage II	6 (14.6)	2 (8.7)	4 (20)	
Stage IIIa	12 (29.3)	6 (26.1)	2 (10)	
Stage IIIb	7 (17.1)	10 (43.5)	10 (50)	
Margin				
Negative	36 (87.8)	20 (87)	15 (75)	0.401
Positive	5 (12.2)	3 (13)	5 (25)	
Angiolymphatic invasion				
Negative	19 (46.3)	5 (21.7)	4 (20)	0.047
Positive	22 (53.7)	18 (78.3)	16 (80)	
Lymph node retrieval	34.20 ± 15.17	36.74 ± 14.88	39.50 ± 15.74	0.436

Data are *n* (%). HIPEC: Hyperthermic intraperitoneal chemotherapy.

Gastric cancer patients with positive cytology typically have poor prognoses[15]. Individuals with positive cytology generally exhibit superior survival rates to those with visible peritoneal metastases[16]. Mezhir *et al*[17] reported that cytology-positive patients achieved a considerably longer median survival (1.5 years) than patients with macroscopic peritoneal nodules (0.8 years). A study by Jamel *et al*[18] corroborated these findings, demonstrating enhanced survival in cytology-positive patients compared with patients with palpable nodules. In our analysis, HIPEC treatment elevated survival rates for patients with macroscopic nodules to levels comparable to those observed in cytology-positive patients. To the best of our knowledge, this is the first study to present survival data of such a nature. Further research is imperative to discern whether the observed survival benefits stem from HIPEC treatment itself or from concomitant peritonectomy performed during CRS.

The HIPEC group experienced a complication rate of 35%, which, while higher than that of the non-HIPEC group, did not reach statistical significance. This finding aligns with prior research confirming the acceptable safety profile of the HIPEC procedure. A meta-analysis by Patel *et al*[19] encompassing 10 randomized controlled trials concluded that HIPEC does not increase complication rates. Similarly, Marano *et al*[20] reported a complication rate of 29.7% among 91 HIPEC-

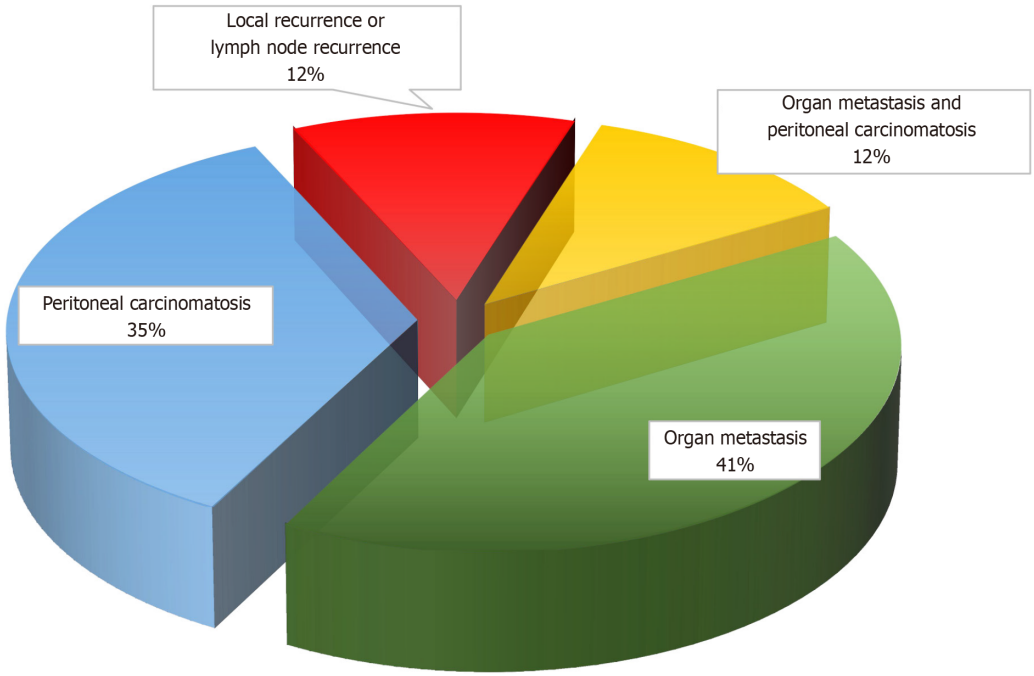

Figure 2 Recurrence patterns post-gastrectomy with and without hyperthermic intraperitoneal chemotherapy adjunct.

treated patients, and Merboth noted a rate of 26.7%[21], further supporting the relative safety of the procedure. Notably, our study recorded no mortality. Comprehensive peritonectomy was performed in all patients, with a high rate of combined organ resection of 90%. These outcomes suggest that CRS with HIPEC can be safely conducted, provided that patients are carefully selected for the procedure.

The application of CRS and HIPEC for treating gastric cancer involves various techniques and remains controversial [22]. Given the prevalent advanced stage of gastric cancer in our region, we opted for total peritonectomy, which, when combined with gastrectomy in patients with peritoneal metastasis, has been shown to be beneficial[23]. Nevertheless, the precise role and scope of peritonectomy within the HIPEC protocol for gastric cancer remain to be explored. Our institution employs an open technique utilizing a cisplatin-based chemotherapy regimen for HIPEC, aligning with findings that underscore the efficacy of cisplatin in such treatments[24]. Although we did not establish a PCI threshold for determining resectability, the median PCI observed in our cohort was 3.0. This value is consistent with recommendations for HIPEC in cases where the PCI is low (< 6)[25], as higher PCIs often correlate with widespread mesenteric nodules that preclude the possibility of achieving complete (R0) resection. Our findings from a multivariate analysis of pathological factors identified the PCI as the only significant predictor of patient survival, thus highlighting its critical role in selecting suitable candidates for HIPEC.

Previous studies have indicated the efficacy of HIPEC in reducing peritoneal recurrence rates[26]. However, our findings show a high overall recurrence rate of 80%, with the peritoneum being the predominant site of recurrence (47%). These results align with the observations by Yu *et al*[27], which noted a decrease in recurrence from 40.3% to 20.9% with HIPEC, yet peritoneal recurrence remained the most common. These outcomes suggest that HIPEC, while beneficial, may not be sufficient as a standalone intervention for controlling peritoneal cancer cell dissemination.

Other modalities aimed at eradicating intraperitoneal cancer cells should be considered. Pressurized intraperitoneal aerosol chemotherapy could produce high intraperitoneal concentrations of chemotherapeutic drugs with low systemic absorption, leading to observed regression of peritoneal metastasis[28]. Meta-analyses have also demonstrated tumor regression, albeit with some heterogeneity across studies[29]. Intraperitoneal chemotherapy, when used in combination with systemic chemotherapy, has shown improved survival rates in patients who underwent surgery after responding to treatment[30]. A combination of these modalities, along with standardization of the HIPEC procedure itself, can help reduce the tumor burden in the peritoneal cavity, thereby lowering the risk of peritoneal recurrence.

CONCLUSION

This study demonstrated that HIPEC can enhance survival rates for patients with gastric cancer and peritoneal metastasis. However, given the advanced stage of the disease at presentation, long-term survival remains elusive for most patients. Although the survival outcomes observed in the HIPEC cohort were comparable to those in the cytology-positive cohort, the difference in the peritoneal recurrence rate continued to be significant.

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FOOTNOTES

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