ORIGINAL ARTICLE

Perioperative intraperitoneal chemotherapy for advanced gastric cancer

A. A. Tentes[1], N. Pallas[1], D. Kyziridis[1], G. Zorbas[1], S. Popidis[1], O. Korakianitis[2], C. Mavroudis[2], A. Spiridonidou[2]

1. Surgical Department, Didimotichon General Hospital, Didimotichon, Greece. 2. Department of Anesthesiology, Didimotichon General Hospital, Didimotichon, Greece

Correspondence: Antonios-Apostolos K. Tentes. Address: Surgical Department, Didimotichon General Hospital, Didimotichon, 68300, Greece. Telephone: 302-553-044-258. Fax: 302-553-024-763. Email: atentes@did-hosp.gr

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Abstract

Background-Aims: Perioperative intraperitoneal chemotherapy either under normothermia during the early postoperative period (EPIC) or intraoperatively combined with heat (HIPEC) has been shown to improve survival after radical resection of advanced gastric cancer. The purpose of the study is to compare the effect of EPIC and HIPEC in patients undergoing D_2 gastrectomy for advanced gastric cancer.

Patients-Methods: Patients that received EPIC after D_2 gastrectomy were retrospectively compared to those that received HIPEC after D_2 gastrectomy. The end point of the study was the assessment of survival, and recurrences.

Results: The groups were comparable for age, gender, performance status, tumor anatomic distribution, stage, degree of differentiation, Lauren classification, hospital mortality, morbidity, and type of surgery. 5-year survival rate for HIPEC group was 68% and for EPIC group was 14% (p=0.0054).The recurrence rate in EPIC group was 57.9% and in HIPEC group 17.4% (p=0.001).

Conclusions: Patients with advanced gastric cancer undergoing D_2 gastrectomy in combination with HIPEC have improved survival and lower recurrence rate as compared to those undergoing D_2 gastrectomy in combination with EPIC.

Key words

Gastric cancer, Hyperthermic intraperitoneal intraoperative chemotherapy, Early postoperative intraperitoneal chemotherapy, Survival, Recurrence

1 Introduction

The rate of loco-regional recurrence after potentially curative resection of gastric adenocarcinoma is approximately 50% [1, 2]. The sites of recurrence after curative gastrectomy combined with adjuvant or neo-adjuvant treatment are the same as those observed with surgery alone [3, 4]. Only extensive surgery with radical lymph node resection has been shown to be associated with lower rate of loco-regional recurrence [5, 6].

Perioperative intraperitoneal chemotherapy has the property to eradicate the microscopic residual tumor after potentially curative resection of gastrointestinal or gynecologic tumors. Hyperthermic intraperitoneal intraoperative chemotherapy

(HIPEC) has been effectively used in the treatment or prevention of peritoneal carcinomatosis from gastric cancer [7-12]. Early postoperative intraperitoneal chemotherapy (EPIC) has also been effectively used as an adjuvant in the treatment of resectable gastric cancer or following cytoreductive surgery in gastric cancer with peritoneal carcinomatosis [13, 14].

The purpose of the study is to compare the effect of EPIC and HIPEC after potentially curative resection in patients with gastric cancer. The end points of the study are the assessment of survival and recurrences.

2 Patients-methods

Table 1. General characteristics of the patients

	EPIC group	**HIPEC group**	***p* value**
Male/female ratio	14/5	19/4	>0.05
Physical activity			
90-100%	18	21	>0.05
70-80%	1	2	
Anatomic distribution			
Fundus	4	6	
Body	6	5	>0.05
Antrum	7	10	
Gastric remnant	2	2	
Age			
<65	6	5	>0.05
>65	13	18	
Surgery			
Subtotal gastrectomy	6	10	>0.05
Total gastrectomy	13	13	
Tumor depth			
T3	17	23	>0.05
T4	2		
Nodal involvement			
N0	2	7	
N1	8	5	>0.05
N2	5	9	
N3	4	2	
pTNM stage			
II	2	8	
IIIA	4	3	>0.05
IIIB	5	8	
IV	8	4	
Lauren classification			
Intestinal	10	17	>0.05
Diffuse	9	6	
Degree of differentiation			
G1	1	2	>0.05
G2	4	8	
G3	14	13	
Systemic chemotherapy	3	1	>0.05
Hospital mortality	0	2	>0.05
Hospital morbidity	7	9	>0.05
Recurrence	12	4	0.001

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From January 2000 until December 2006, patients with locally advanced gastric cancer (T_3 and T_4 tumors), underwent D_2 gastrectomy and received EPIC because the HIPEC technology was not available. From January 2007 until today, patients with locally advanced gastric cancer, underwent D_2 gastrectomy and received HIPEC. The general characteristics of the patients are listed in Table 1.

All patients were assessed with physical examination, hematological-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), abdominal and thoracic CT-scan, and whole body bone scanning. The diagnosis was established by gastroscopy and biopsy. The performance status of the patients was assessed using the Karnofsky performance scale. Patients inclusion criteria were: 1) proven by biopsy gastric carcinoma, 2) age >16 years, 3) no distant metastases (lung, bone, brain), 4) acceptable performance status (Karnofsky performance scale >50%), 5) WBC > 4000, 6) platelet count > 150.000, 7) blood urea level <50mg/dL, 8) creatinine level < 1.5mg/dL, 9) normal liver biochemical examination, 10) no evidence of a second tumor or at risk for recurrence (except for skin basal carcinoma or carcinoma of the cervix adequately treated). Patients with peritoneal carcinomatosis were included in the study. Debilitated patients (Karnofsky performance status <50), age >90 years, pregnant women, patients with recent myocardial infarction, or severe myocardial failure, or chronic obstructive pulmonary disease were excluded from the study. Both protocols (for EPIC or HIPEC) were approved by the hospital's Ethical Committee and patients signed an informed consent.

2.1 Treatments

All patients with tumors of the antrum underwent subtotal D_2 gastrectomy. The reconstruction of the alimentary tract was possible by hand-sewn Roux-en-Y gastro-jejunal anastomosis. Patients with tumors of the body or the fundus underwent total D_2 gastrectomy. The reconstruction of the alimentary tract was possible by Roux-en-Y esophago-jejunal anastomosis. After tumor resection and before the reconstruction of the gastrointestinal tract HIPEC was performed using the Coliseum technique [15] for 90 min with cis-platin (50mg/m^2) and Mitomycin-C (10mg/m^2) at 42.5-43℃. HIPEC was performed via a circuit of 4 drains (2 inflow and 2 outflow) that were connected to an extracorporeal sterile circuit in which a 3 lit perfusate was circulated by two peristaltic pumps (one inflow and one outflow) at a flow rate of 2lit/min. The sterile circuit was heated by a thermal exchanger connected to the heating circuit (Gamida-Tech, Sun-Chip, France). EPIC was performed during the first 5 postoperative days. During day 0 the peritoneal cavity was irrigated continuously with $D_{1.5}W$ via a Tenckhoff catheter until the drains were clear of blood and clots. The Tenckhoff catheter was inserted in the operating theater at the end of the operation.

During day 1 Mitomycin-C (10 mg/m^2) in 1liter of $D_{1.5}W$ was instilled rapidly with the drains closed, and dwelled in the abdominal cavity for 23 hours. Then the drains were opened for one hour. During days 2-5, 5-FU (650mg/kg. b. w) in 1 liter of $D_{1.5}W$ was instilled rapidly with the drains closed and dwelled for 23 hours.

The patients remained in the ICU for at least one day. Patients of the EPIC group remained in the ICU during treatment with EPIC.

Patients surviving surgery who were found to be pTNM stage IV received systemic chemotherapy.

2.2 Histopathology

All specimens were examined histopathologically and were staged according to TNM system. The location of the tumors and the lymph node stations were described according to the Japanese Classification of Gastric Carcinoma [16]. Examination of the specimens included evaluation of the lymph nodes in each station by number of resected lymph nodes and number of positive lymph nodes.

The age, gender, tumor location, type of surgery, tumor depth, nodal infiltration, stage, degree of differentiation, Lauren classification, hospital mortality and morbidity, recurrences and the anatomic sites of recurrence were all analyzed. Toxicity related to intraperitoneal chemotherapy was also recorded.

2.3 Follow-up

All patients were followed-up in 3-6 months intervals with physical examination, hematological and biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), abdominal and thoracic CT-scan, and gastroscopy after the first year. Recurrences and the sites of recurrence were recorded.

2.4 Statistical analysis

The proportions of patients with a given characteristic were compared by chi-square analysis. Differences in the means of continuous measurement were tested by the Student's-t-test. The survival curves were obtained using the Kaplan-Meier method and comparison of survival was calculated using the log-rank test. Multivariate analysis of survival was possible using Cox regression analysis. Multivariate analysis of recurrence was possible using logistic regression analysis. A two-tailed p value < 0.05 was considered statistically significant.

3 Results

Nineteen patients, mean age 70±8.5 (54-82) years comprised the EPIC group, and 23 patients, mean age 70.7±10.4 (35-83) years the HIPEC group (p>0.05). As shown in Table 1 the two groups were comparable except for recurrence. Three patients in the EPIC group and 4 patients in the HIPEC group had limited peritoneal carcinomatosis and underwent complete cytoreduction.

3.1 Morbidity and hospital mortality

During the immediate postoperative period 7 patients in the EPIC group and 9 patients in the HIPEC group were complicated (Table 2). No patient developed chemotherapy toxicity either in EPIC or in HIPEC group. As listed in Table 1, two patients in the HIPEC group died during the postoperative period. By univariate analysis no variable was found to be related either to morbidity or to hospital mortality.

Table 2. Complications

	EPIC group	HIPEC group
Respiratory infection	1	2
Postoperative bleeding	0	1
Anastomotic failure	1	4
Wound infection	3	2
Intra-abdmoninal abscess	2	0

3.2 Survival

Table 3. Survival analysis-univariate

Factor	*p* value
Gender	>0.05
Physical activity	>0.05
Systemic chemotherapy	>0.05
p TNM stage	0.0259
Tumor depth	>0.05
Nodal involvement	>0.05
Type of surgery	>0.05
Tumor anatomic distribution	>0.05
Age	>0.05
HIPEC	0.0054

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Table 3. Survival analysis- multivariate

Factor	HR	*p* value	95% CI
HIPEC	5.703	0.017	0.071-0.77
pTNM	4.823	0.028	1.091-4.636

The mean and median survival for EPIC group was 26±11 and 10 months respectively. The mean survival for HIPEC group was 38±6 months. The median survival for HIPEC group was not reached. The 5-year survival rate for HIPEC and EPIC group was 68% and 14% respectively (p=0.0054) (Figure 1). By univariate analysis the p TNM stage, the degree of differentiation, and the use of HIPEC were the factors that correlated to survival (Table 3). Multivariate analysis showed that HIPEC (HR=5.703, p=0.017, 95% CI=0.071-0.77), and p TNM stage (HR=4.823, p=0.028, 95% CI=1.091-4.636) were the prognostic indicators of survival Table 3).

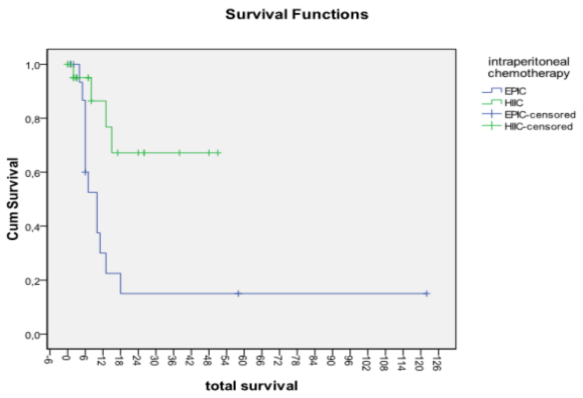

Figure 1. Survival of patients that underwent D_2 gastrectomy and HIPEC (green line), or D_2 gastrectomy and EPIC (blue line), p=0.0054. The numbers of patients at risk in 6, 12 and 48 months respectively for both groups are shown.

3.3 Recurrence

Table 4. Analysis of recurrence

	Factor	*p* value
Univariate		
	HIPEC	0.001
	Nodal involvement	0.025
	pTNM stage	0.006
	Degree of differentiation	0.002
Multivariate		
	HIPEC	0.008
	pTNM	0.012

During follow-up 11 (57.9%) patients in the EPIC group and 4 (17.4%) patients in the HIPEC group were recorded with recurrence. In the EPIC group, 8 patients were recorded with distant metastases and 3 patients with locoregional ones. In the HIPEC group all 4 patients were recorded with distant metastases. The factors related to recurrence are listed In Table 4. By multivariate analysis it was shown that HIPEC (p=0.008) and pTNM stage (p=0.012) were favorable prognostic indicators of recurrence (Table 4).

4 Discussion

In 1989, Cunliffe and Sugarbaker, based on the patterns of recurrence for both gastrointestinal and ovarian carcinomas developed a novel therapeutic approach with perioperative intraperitoneal chemotherapy integrated in surgery [17]. The pharmacologic rationale for intraperitoneal chemotherapy was further developed by additional pharmacologic studies [18].

Non-randomized studies have shown that perioperative intraperitoneal chemotherapy has been effectively used in locally advanced gastric cancer with or without peritoneal carcinomatosis [7-14, 19, 20]. One experimental study has provided sufficient evidence that HIPEC improves survival in gastric cancer with peritoneal carcinomatosis [21]. EPIC seems to offer significant survival benefit in patients with gastric cancer and peritoneal carcinomatosis as shown by a prospective randomized trial [22]. Another prospective randomized trial has shown that HIPEC offers significant survival benefit in patients with advanced gastric cancer. The same study has also shown that patients treated with HIPEC have improved survival over those treated with EPIC or even those treated with surgery alone [23]. From another prospective randomized trial it has been conducted that EPIC as an adjuvant to resectable gastric cancer is an efficient treatment in stage III patients but does not offer any survival benefit in other stages [13].

According to data of gastric cancer 40-60% of patients with locally advanced tumors (T_3, T_4) develop locoregional recurrence even after potentially curative gastrectomy because cancer emboli are present outside the operative field in approximately half of the patients during surgery [5, 24]. Intraoperative washing cytology has been found to be positive in 5-20% of the cases [24, 25]. The prognosis of patients with positive peritoneal cytology is similar to that of patients with established peritoneal carcinomatosis. Systemic chemotherapy does not offer any survival benefit in patients with gastric cancer [26]. In gastric cancer without peritoneal carcinomatosis neo-adjuvant chemotherapy is theoretically effective to down-stage the tumor and make easier its resection but the conclusions from randomized studies have been contradictory [27, 28].

So far, it is likely that intraperitoneal chemotherapy administered during the immediate perioperative period is the most efficient method to eradicate the microscopic residual emboli before they are entrapped in fibrin and connective tissue that will not allow the cytostatic drug to penetrate into them [29]. The synergistic effect of cytostatic drugs and heat appear to be more efficient than the administration of cytostatic drugs under normothermia [23]. It seems that EPIC does not permit the uniform distriburion of cytostatic drugs. The anterior surface of the stomach covered by the left lobe of the liver after abdominal closure is not adequately perfused. The anterior surface of the right lobe of the liver covered by the undersurface of the right hemidiaphragm is not adequately perfused as well as the small bowel loops or the male pelvis. As a consequence, the microscopic emboli retained in these areas are not sufficiently eradicated. During wound healing they are stimulated by growth factors and give rise to recurrent tumors in 2-3 years after initial surgery. This explains why in the present study the rate of recurrence in the EPIC group was increased as compared to that of HIPEC group, and survival in the HIPEC group was significantly improved as compared to that of EPIC group. These findings are in agreement with others [23], although the total number of the included patients was small, the study was not a randomized one, and a minority of the patients had peritoneal carcinomatosis. It is of importance that no locoregional recurrence has been recorded in those patients treated with HIPEC.

The morbidity and the hospital mortality were acceptable and did not differ between the two groups. In addition, no chemotherapy side effects were recorded which means that either EPIC or HIPEC are well tolerated by patients with advanced gastric cancer.

5 Conclusion

HIPEC is a well-tolerated therapeutic approach and may have a role in the treatment of advanced gastric cancer as a method that may contribute to a significant decrease of locoregional recurrences.

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