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Risk Factors for Recurrence after Complete Cytoreductive Surgery and Perioperative Chemotherapy in Peritoneal Metastases from Gastric Cancer

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Abstract

Background and objective: The aim of this study is to analyze anatomical distribution, timing and outcomes of recurrence after complete cytoreduction and perioperative chemotherapy for peritoneal metastasis from gastric cancer (GCPM).

Method: Data of 193 GCPM patients who underwent a complete cytoreductive surgery (CRS) after treatment with neoadjuvant chemotherapy were entered into a prospective database and the recurrence was analyzed.

Result: The median time to progression was 16.2 months, median overall survival (OS) was 21.6 months and 5-year survival rate was 18.1%. Five years after CRS, 11 patients were disease free survivors. Recurrence rate was 68.5% (126/184). Mutivariate analysis confirmed small bowel peritoneal cancer index of ≥3 and pathologic non-responders after NAC as independent risk factors for recurrence. Patients were treated with systemic chemotherapy or second cytoreductive surgery for recurrence. However, survival after diagnosis of recurrence was poor with median survival of 2.9 months. The most common type of recurrence was diffuse peritoneal recurrence (71%, 90/126). Localized intra-abdominal recurrence was experienced in only 7 patients.

Conclusion: Pathologic non-responders and small bowel PCI of ≥3 are independent risk factors for recurrence. Exploratory laparoscopy after NAC might be a useful strategy for the selection of patients for CRS.

Keywords: Gastric cancer; Peritoneal metastasis; Hyperthermic intraperitoneal chemoperfusion; Neoadjuvant chemotherapy

Introduction

In the past, gastric cancer peritoneal metastasis (GCPM) had been considered as terminal disease, and treated with palliative chemotherapy or cytoreductive surgery (CRS). However, CRS or chemotherapy alone does not cure patients with GCPM [1].

In 1998, the Peritoneal Surface Oncology Group International (PSOGI) proposed a comprehensive treatment for GCPM. The basis of the treatment consists of complete resection of macroscopic metastasis in combination with perioperative chemotherapy (POC) for eradication of intraperitoneal micrometastasis [2,3]. After introduction of comprehensive treatment, long-term survival was significantly improved as compared with that after palliative treatment alone. Additionally, cure has been achieved in 10-20% of GCPM patients after the treatment [4,5]. However, 80-90% of patients have died of recurrence after complete cytotreduction and POC. Early detection of recurrence in GCPM is usually difficult as the accuracy of radiological methods for detecting peritoneal recurrence is low. By analyzing the timing and patterns of recurrence, patients at high risk for recurrence could be identified and recurrence could be prevented by additional treatments, resulting in improvement in the survival. However, risk factors for recurrence following CRS and POC have not been well investigated yet.

The present study was performed to clarify the timing, anatomical distribution, and outcome of recurrence after comprehensive treatment.

Methods

Patients and methods

Clinical and histopathological data regarding GCPM patients treated with CRS and POC between June 2006 and June 2015 at the hospitals belonging to NPO to support Peritoneal Surface Malignancy Treatment were analyzed. Patients with GCPM who underwent complete CRS (CC0: no residual visible tumor [2]) were included in the study.

The eligibility criteria for selection of patients included: (1) histologically or cytologically proven PM from GC, (2) absence of hematogenous metastasis and remote lymph node metastasis, (3) age 75 years or younger, (4) Eastern Clinical Oncology Group scale of performance status 3 or less, (5) good bone marrow, liver, cardiac, and renal function, (6) absence of other severe medical conditions or synchronous malignancy.

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Perioperative chemotherapy (POC) and Cytoreductive sugery (CRS)

Before CRS, patients had been treated with neoadjuvant intraperitoneal/systemic chemotherapy (NIPS) or systemic chemotherapy. Patients who refused IP port placement or had sever adhesion in peritoneal cavity were treated with DCS systemic chemotherapy. For NIPS, oral S-1 was administered for 14 days at a dose of 60 mg/m²/day, followed by 7 days of rest. Docetaxel (30 mg/m²) and CDDP (30 mg/m²) were administered by intraperitoneal infusion on days 1 and on day 8. For systemic DCS therapy docetaxel (30 mg/m²) and CDDP (30 mg/m²) were administered by systemic infusion on day 1 and on day 8 during consecutive 14 days oral administration of S-1 at a dose of 60 mg/m²/day. In DCS systemic chemotherapy, systemic administration of docetaxel and cisplatin (30 mg/m² each) on days 1 and on day 8 during oral administration of S1 (60 mg/m²/day) from day 1 to day 14. NIPS and systemic DCS therapy were performed in 3 courses with a 1-week drug holiday.

Four to six weeks after the last course of neoadjuvant chemotherapy, CRS was performed with the intent of achieving complete cytoreduction (CC0). The extent of abdominal tumor load was recorded in terms of the peritoneal cancer index (PCI) [6]. Following CRS, hyperthermic intraperitoneal chemoperfusion (HIPEC) was performed. Before June 2011, for HIPEC, 4 L of warmed saline with 20 mg/body of Mitomycin C (MMC) and 50 mg/body of CDDP was administered in peritoneal cavity, and 4 L of saline was circuited using a pump while heating with a heat exchanger in a HIPEC machine. During HIPEC, temperatures of 43℃ to 43.5℃ were maintained at all the peritoneal surface by hand stirring the heated saline. After June 2011, for HIPEC, 40 mg/body of docetaxel and 100 mg/body of CDDP were used.

The local ethics committee in each of our hospitals approved the study protocol, and written informed consent was obtained from all subjects. All patients were informed about the adverse effects of chemotherapy and CRS in accordance with the common terminology criteria for adverse events, version 4.0.

Follow-up

Follow-up consisted of physical examination and determination of tumor marker level performed every 6 weeks. Patients underwent a computed tomography (CT) scan of the abdomen every 3 months. Recurrence was diagnosed, when CT showed an abnormality typical of recurrence, and there was a progressive increase in serum carcino-embryonic antigen (CEA) or cancer antigen (CA) 19-9 tumor marker levels. Additionally, if there are any abnormal symptoms or findings by physical examination, endoscopy or retrograde colonography were performed to detect recurrent sites.

Histopathologic work up and response evaluation

Response to neoadjuvant chemotherapy for PM was evaluated based on histopathological evaluation using the general rules for gastric cancer treatment [7]. According to this rules, pathological response after chemotherapy is classified into 4 categories; Ef-0 through Ef-3, as follows: Ef-0 reflects no pathologic response or response less than one third of the tumor tissue; Ef-1 means that the cancer is detected in the tumor tissue ranging from one third to less than two thirds of the tumor tissue; Ef-2 reflects the degeneration of cancer tissue in more than two thirds of the tumor tissue; and Ef-3 responds to complete disappearance of the cancer cells. Patients with responses classified as Ef-2 or Ef-3 were grouped as pathologic responders, and other patients were classified as non-responders

Data analyses

The time from cytoreduction to first evidence of recurrence was defined as time to progression (TTP). The survival analysis was performed using the Kaplan-Meier method and compared by the log rank test. For multivariate analysis, a Cox regression was used. Categorical variables were compared by X^2 analysis or Fischer's exact test. Statistical analyses were performed SPSS version 11.5 (SPSS Inc., Chicago, IL) A p value <0.05 was considered statistically significant for a confidential interval of 95%.

Results

Patients

During the period from June 2006 to June 2015, 277 patients underwent CRS after neoadjuvant chemotherapy, and 193 patients received complete cytoreduction (CC0). In-hospital deaths after CRS were experienced in nine patients due to postoperative complications or progression of the disease. No significant correlation was observed between postoperative mortality and clinicopathologic parameters (Table 1).

Of the 193 patients, 86 and 107 patients were male and female, respectively, with a mean age of the patients was 52.7 years (range, 23 to 75) (Table 1). NIPS and systemic DCS therapy were performed in 154 and 29 patients, respectively. After CRS, HIPEC was performed in 132 patients. However, the other 61 patients did not undergo HIPEC, because the patients had co-morbidities or underwent complex operation.

Time to progression and survival

Nine patients who died of postoperative complication were eliminated from the analysis of recurrence. The mean and median follow-up was 57.5 months (range, 5-113 months), respectively. The median time to progression defined as the time from cytoreduction to time of first documentation of recurrent disease was 16.2 months. The median overall survival (OS) for this group of patients was 21.6 months and 5-year survival was 18.1%. There were 11 disease-free survivors, 5 years after CRS. The disease-free survival and overall survival are shown in (Figure 1).

Anatomic location of recurrence

Over all recurrence rate was 68.5% (126/184). Recurrence was mainly observed in the peritoneal cavity (77%, 97/126) (Table 2). Liver and lymph node metastasis were observed in 6 and 6 patients, respectively. Extraperitoneal tumor spread was experienced in 14 patients, and anatomical locations of recurrence were bone in 7, lung in 4, brain in 2, and skin in 1 patients respectively (Table 2).

Risk factors for recurrence

Correlation between recurrence and clinicopathological parameters is shown in Table 1. Small bowel PCI indicates the total size of lesions of peritoneal sectors 9, 10, 11, and 12 [6]. Chi-square test revealed that small bowel PCI level (≤2 vs. ≥3) and pathological response after neoadjuvant chemotherapy (Ef-2, 3 vs. Ef-0, 1, was significantly correlated with recurrence rates (Table 1). However, no significant difference was found between recurrence rates and lymph node metastasis (N0-1 vs. N2-3), histologic type (intestinal vs. diffuse), PCI cutoff level (PCI≥9 vs. ≤8), HIPEC (done vs. not done), cytology (positive vs. negative), synchronous/metachronous, primary/recurrence, macroscopic type, or clinical stage.

Characteristics	No. patients	recurrence (rates)	P (recurrence)	hospital death	P (hospital deaths)
Gender					
Male	86	55 (64%)	NS	4 (4.7%)	NS
Female	107	71 (66.4%)		5 (4.7%)	
Lymph node status					
pN0-1	48	29 (72.1%)	NS	1 (2.1%)	NS
pN2-3	145	97 (69.9%)		8 (5.5%)	
Histopathologic type					
Intestinal	25	15 (60.0%)	NS	0 (0%)	NS
Diffuse	168	111 (66.1%)		9 (8.1%)	
PCI cutoff					
≤8	168	110 (65.5%)	NS	6 (3.6%)	NS
≤9	25	16 (64%)		3 (18.8%)	
Small bowel PCI					
≤2	162	99 (68.8%)	P=0.039	6 (3.7%)	NS
≥3	31	27 (87.1%)	X2=4.26	3 (12.0)	
Chemotherapy prior to CRS					
NIPS	154	106 (69.0%)	NS	8 (5.2%)	NS
Systemic DCS Chemotherapy	29	20 (69.0%)		1 (3.4%)	
CRS					
CRS alone	61	38 (66.3%)	NS	4 (6.6%)	NS
CRS+HIPEC	132	88 (66.7%)		5 (3.8%)	
Cytology					
Class I	159	105 (70.4%)	NS	7 (3.1%)	NS
Class V	29	18 (69.0%)		2 7.7%)	
Unknown	5	3 (60%)			
Histologic effects					
EF-0, 1	91	67 (73.6%)	P=0.032	4 (4.4%)	NS
EF-II,III	102	59 (57.8%)	X2=4.61	5 (6.9%)	
Primary or recurrence					
Primary	128	87 (68.0%)	NS	4 (3.1%)	NS
Recurrence	65	39 (65.0%)		5 (7.7%)	
Macroscopic type					
Type 2	7	5 (76.4%)		1 (14.2%)	
Type 3	57	33 (58.9%)	NS	3 (5.2%)	NS
Type 4	129	88 (68.2%)		5 (3.9%)	
Stage					
Stage IV a	174	120 (69.0%)	NS	6 (3.4%)	NS
Stage IV b	19	10 (52.6%)		3 (15.8%)	
Total	193	126 (68.5%)		9 (4.7%)	

Table 1: Patients characteristics and recurrence rates.

Univariate analysis of disease-free survival showed cytology (negative vs. positive), small bowel PCI (≤2 vs. ≥3), PCI (≤8 vs. ≥9), and pathologic response after NAC (Ef-2, -3 vs. Ef-0, -1) as significant risk factors for recurrence (Table 3).

Mutivariate analysis confirmed small bowel PCI and pathologic response after NAC as independent risk factors for recurrent disease (Table 3).

Survival and treatment after diagnosis of recurrence

Second operations for CRS to remove recurrent disease were performed in 17 patients. CC0 resection underwent in 7 patients. However, complete cytoreduction could not be performed in 10 patients due to diffuse peritoneal involvement.

The median survival after the diagnosis of recurrence was 2.9 months (Figure 2), and 1 year and 2 year survival rates were 8.7% and 2.5%, respectively. Five patients with documented recurrences were

alive at the time of last follow-up. One of them had no evidence of disease 50 months after bilateral salpingo-oophorectomy for ovarian metastasis.
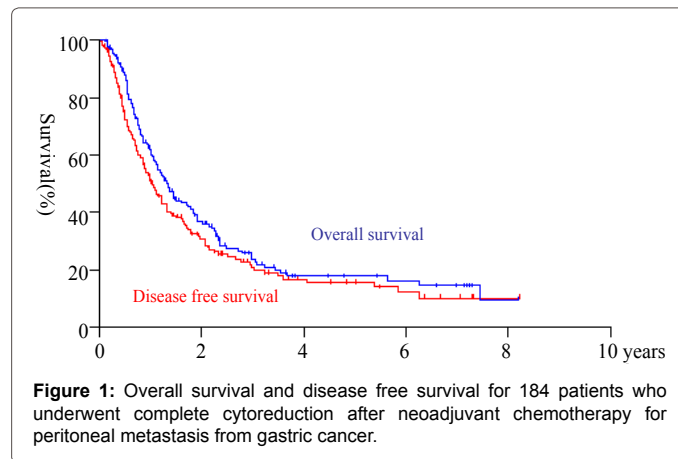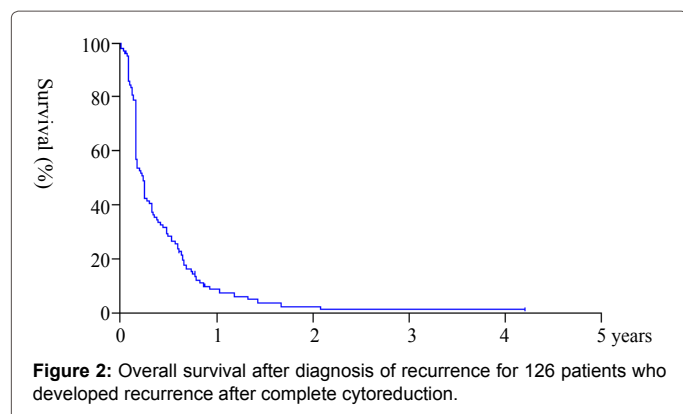

Figure 1: Overall survival and disease free survival for 184 patients who underwent complete cytoreduction after neoadjuvant chemotherapy for peritoneal metastasis from gastric cancer.

Peritoneum	97 (77.0%)
Bone	7 (5.6%)
Liver	6 (4.8%)
Lymph node	6 (4.8%)
Lung	4 (3.2%)
Liver hilum	2 (1.6%)
Brain	2 (1.6%)
Skin	1 (0.7%)
Esophago-jejunostomy	1 (0.7%)
Total	126

Table 2: Recurrence site.

Variables	Multivariate analysis (Cox hazard model) X²	P	Hazard ratio	95% CI	univariate analysis X²	P
Sex; male vs. female	0.012	0.911	1.022	0.698-1.496	1.561	0.211
Age; ≤65 vs. ≤66	1.019	0.312	1.274	0.796-2.038	0.475	0.475
Primary vs. recurrence	0.362	0.567	0.973	0.662-1.430	0.917	0.338
Lymph node status; N01 vs. N2,3	0.806	0.369	1.233	0.780-1.948	0.182	0.169
Cytology; negative positive	3.516	0.06	1.671	0.977-2.857	7.73	0.005*
HIPEC; not done vs. done	1.748	0.186	0.758	0.503-1.143	3.235	0.072
NIIP vs. neoadjuvant systemic chemo#	0.515	0.472	1.23	0.699-2.163	2.398	0.359
PCI ≤8 vs. ≥9	0.214	0.643	1.169	0.604-2.262	4.934	0.026*
Small bowel PCI≤2 vs. ≥3	4.303	0.038 *	1.716	1.030-2.858	3.848	0.049*
Pathologic response: Ef 0,1 vs. Ef 2,3	6.885	0.009 *	0.579	0.385-0.871	13.02	0.003*

Table 3: Risk factors after neoadjuvant chemotherapy and complete cytoreduction of peritoneal metastases from gastric cancer.

Figure 2: Overall survival after diagnosis of recurrence for 126 patients who developed recurrence after complete cytoreduction.

Discussion

Most patients with GCPM die within 6 months after palliative treatment, and the 5-year survival rate is 0% after systemic chemotherapy alone [8,9]. In late 1990s, an innovative treatment of combined with CRS plus HIPEC was established for treatment of PM from colorectal cancer and gastric cancer [10,11]. In this treatment, CRS using peritonectomy technique is performed for complete removal of macroscopic disease and HIPEC is performed to treat the microscopic residual disease in a single procedure [12].

However, the power to kill the entire cancer cell population by one cycle of HIPEC is limited. Yonemura et al. reported that one cycle of HIPEC reduced PCI level by only 3.5 [13]. Therefore, NIPS was developed to reduce intraperitoneal tumor load as much as possible before CRS [14,15]. Valle et al. reported that only 30% of GCPM patients with PM underwent complete CRS without neoadjuvant chemotherapy [16]. In contrast, incidence of complete CRS after NIPS was significantly increased, as compared with that without neoadjuvant chemotherapy [14].

The present study was based on the treatment results after combination of neoadjuvant chemotherapy plus CRS with or without HIPEC. The median OS of the present study (21.6 months) was higher than those reported by Glehen et al. (10.3 months) [4] and by Yang XJ et al. (12.0 months) [17]. In the present study, however, the 5-year survival rate is still low (18%) and is not satisfactory. To improve survival after CRS plus POC, analyses of recurrence are essential, and the additional therapy to prevent recurrence in patients with high risk for recurrence may improve survival after CRS plus POC.

So far, there has been no report describing precise analyses of timing and site of recurrence after CRS plus POC in patients with GCPM. Accordingly, we investigate the risk factors for recurrence. Glehen et al. reported positive peritoneal cytology and PCI ≥12 are the risk factors for recurrence [18]. Yang XJ et al. described that metachronous GCPM is an independent poor prognostic factor [17]. These results are obtained from the data of patients who received not only complete CRS but also incomplete CRS without NAC.

All patients in the present study were treated with NIPS or neoadjuvant systemic chemotherapy. Over all recurrence rate after NAC and CRS was 68.5%. HIPEC was not a factor for favorable prognosis. However, univariate analyses of our data revealed that positive cytology PCI ≥ 8, small bowel PCI ≥ 2, and pathologic non-responder are the risk factor for recurrence. Additionally, multivariate analyses showed that small bowel PCI≤2 and pathologic responder are independent prognostic factors for favorable prognosis.

Glehen et al. also reported positive cytology as a poor prognostic factor [4]. However, 67% of cases of positive cytology can be changed to be negative cytology by NIPS [14]. Accordingly, NIPS can reduce risk of recurrence after CRS.

So far, there has been no report about small bowel PCI as a risk factor for recurrence. Small bowel involvement is the most frequent limiting factor for complete CRS [19]. Yonemura et al. reported that small bowel PCI was significantly reduced after laparoscopic HIPEC [13]. If the small bowel PCI is ≥3 or PCI is ≥8 at the time of exploratory laparoscopy, laparoscopic HIPEC and NIPS can reduce small bowel PCI or PCI [13,14]. Patients whose small bowel PCI ≥3 or PCI ≥8 are recommended to undergo second look exploratory laparoscopy after NIPS. If small bowel is PCI ≥3 or PCI is PCI ≥8, CRS should be postponed and chemotherapy should be continued to reduce small bowel PCI and/or PCI.

In the present study, multivariate analyses showed that pathologic response was the most important risk factor for recurrence. Similarly, pathologic complete response has been recently been described to impact on survival in patients with esophagogastric adenocarcinoma receiving neoadjyuvant systemic chemotherapy [20]. These results indicate that patients with GCPM should be treated with neoadjuvant chemotherapy. Selection criteria for CRS are pathologic responders and/or patients, whose PCIs or small bowel PCIs are less than cutoff level. Second exploratory laparoscopy must be performed for selection of patients for CRS [21].

After CRS, present study shows that the most common recurrence was peritoneal recurrence (77%, 97/126). After complete resection of colorectal cancer peritoneal metastases, resection of recurrent disease improves survival [21]. In GCPM, however, complete resection of recurrent peritoneal metastases after CRS is usually very difficult, because recurrence is observed all around peritoneal cavity. In the present study, complete cytoreduction for recurrent lesions could be performed in only 7 patients among 125 patients with recurrence. After diagnosis of recurrence, all patients were treated with systemic chemotherapy. However, survival after diagnosis of recurrence was very poor with median survival of 2.9 months. These results indicate that removal of recurrent lesions or systemic chemotherapy does not improve survival of patients with recurrence.

Accordingly, new methods should be developed for the prevention of recurrence. Yu WS et al. performed RCT to verify the effects of early postoperative intraperitoneal chemotherapy (EPIC). They described that peritoneal recurrence was significantly reduced after EPIC. After CRS by peritonectomy, however, drugs administered intraperitoneally do not show even spread in perritoneal cavity, because of adhesion. Accordingly, EPIC may be an effective method for the prophylaxis of peritoneal recurrence, if it is started just after CRS and before the adhesion covers over residual micrometastasis in the peritoneal cavity.

The median time to progression was 16.2 months. Postoperative systemic chemotherapy should be continued until recurrence is detected. Selection of postoperative systemic chemotherapy should be discussed from this point onwards.

Conclusion

Pathologic non-responder, PCI and small bowel PCI higher than cutoff level are risk factors for recurrence after NAC and CRS for GCPM patients. Exploratory laparoscopy after NAC might be a useful strategy for the selection of patients for CRS.

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