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ORIGINAL ARTICLE

Peritoneal cancer index is a prognostic indicator of survival in advanced gastric cancer with peritoneal carcinomatosis

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Abstract

Objective The peritoneal cancer index (PCI) has been used for the detailed evaluation of the peritoneal spread in tumors of a gynecologic origin and has been found to be a prognostic indicator of survival. The aim of this study was to identify the significance of the PCI in advanced gastric cancer (AGC) with peritoneal carcinomatosis (PC).

Methods From 2010 to 2018, a retrospective analysis was carried out of 60 AGC patients with PC, including 21 patients with a PCI ≤ 13 and 39 with a PCI > 13. All patients were treated with both surgery and intraoperative peritoneal hyperthermic chemotherapy (IPHC). The performance status (Karnofsky performance status), age, sex, Borromann's classification, differentiation, depth of invasion, lymph node metastasis, PCI, extent of gastrectomy, extent of lymph node dissection, and residual tumor volume were retrospectively evaluated and correlated to survival.

Results The overall 5-year survival rate was 43% and mean survival was (54.47 ± 4.53) months. The favorable clinical prognostic indicators of survival were Borromann's classification, differentiation, depth of invasion, PCI, and residual tumor volume on univariate analyses (P < 0.05). The Cox proportional regression hazard model showed that only the volume of residual tumor and PCI were associated with postoperative survival. The median survival time was 69.76 months for patients with a PCI ≤ 13 and 39.96 months for patients with a PCI > 13. There was a significant difference in survival rate between the two group (P = 0.004). Postoperative major morbidity and mortality rates were 23.81% and 4.76% in the PCI ≤ 13 group and 43.59% and 5.12% in the PCI > 13 group, respectively.

Conclusion The peritoneal spread in advanced gastric cancer with peritoneal carcinomatosis can be assessed in detail using the PCI. It is also a significant prognostic factor of survival and is useful in identifying subgroups.

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Key words: peritoneal cancer index (PCI); advanced gastric cancer (AGC); peritoneal carcinomatosis (PC); survival; complication

The incidence of gastric cancer is increasing year by year, ranking first in the incidence of gastrointestinal malignant tumors, and the mortality rate is the second highest of all cancers [1]. Peritoneal carcinomatosis (PC) is one of the most predominant means of metastasis in gastric cancer, diagnosed in 5%–20% of patients and is considered a fatal disease with limited treatment options [2–3]. It also has the most frequent pattern of postoperative recurrence, which is the major cause of death in advanced gastric cancer (AGC) with PC [4].

A meta-analysis demonstrated that intraoperative peritoneal hyperthermic chemotherapy (IPHC) combined with surgery had a positive effect on overall survival [5]. However, high morbidity and mortality after this treatment was also reported [6]. Surgeons must, therefore, select patients carefully to achieve a balance between the postoperative risks of the combined treatment and the potential benefits in survival and quality of life.

The peritoneal cancer index (PCI) is used to determine if surgical intervention should be attempted as a cure or if a palliation move is more suitable for cancer patients [6–7]. The aim of the present study is to identify the significance of the PCI for the detailed evaluation of peritoneal spread and for selecting AGC patients with PC who would

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benefit from surgery.

Patients and methods

From 2010 to 2018, 60 patients [mean age (49 ± 9.42) years, range 30–70 years], were treated for AGC with PC. The performance status (Karnofsky performance status), age, sex, Borromann's classification, differentiation, depth of invasion (T), lymph node metastasis (N), PCI, extent of gastrectomy, extent of lymph node dissection, and residual tumor volume were retrospectively evaluated and correlated to survival. The diagnosis and staging of AGC with PC was made by physical examination, hematological-biochemical examinations, tumor markers, and computed tomography (CT) scan. All patients received adjuvant chemotherapy based on platinum and fluorouracil after surgery. Patients who received palliative bypass operations, those aged over 70 years, those with extra-abdominal metastases and liver metastases, those who failed to follow-up, and those whom in severe condition (renal or myocardial failures etc.) were excluded from the study.

All patients received IPHC, which was performed immediately after surgical resection and intestinal reconstruction. Briefly, two inflow tubes were placed in the subphrenic cavity and one outflow tube was placed within the Douglas' pouch. Approximately 5–6 L of perfusate containing cisplatin (50 g/mL) and mitomycin (5 g/mL) with an invariable velocity (500–600 mL/min) was circulated for 60 min. The peritoneal temperature was maintained at 43 °C. After the intraoperative perfusion, the abdomen was suctioned dry of fluid.

The TNM staging system, according to the Union for International Cancer Control (UICC), was used to describe the operative findings and pathological diagnosis [8]. The determination of the absence or presence of peritoneal metastasis and the extent of lymph node dissection was based on the Japanese Classification of Gastric Carcinoma [9].

The PCI was calculated intraoperatively. This index is calculated according to the size of the lesions and the quadrants in which they are found. A score is allocated according to whether a lesion is seen in the central abdominal area, right upper quadrant, epigastrium, left upper quadrant, left flank, left lower quadrant, pelvis, right lower quadrant, right flank, upper jejunum, lower jejunum, upper ileum, or lower ileum. The score is dependent on the size of the preoperative tumor nodule. A score of 1 is given to lesion sizes up to 0.5 cm, a score of 2 is allocated to tumor sizes 0.5–5.0 cm, and a score of 3 is given to lesions > 5.0 cm or confluence. The sum of the scores equals the PCI. Residual disease that was unresectable was scored according to the completeness of cytoreduction (CC) score. This score is calculated using the size of the residual tumor nodules seen macroscopically after cytoreduction; CC-0 is no nodules seen, CC-1 is nodules < 2.5 mm, CC-2 is nodules between 2.5 mm and 25 mm; and CC-3 is nodules > 25 mm. Tissue samples taken intraoperatively were sent for histopathological analysis [10]. Patients were divided into two groups according to PCI.

Statistical analysis was carried out using SPSS 13.0 software (SPSS Inc, Chicago, USA). The χ^2 test was used for the comparison of the two groups. Postoperative survival curves were generated according to the Kaplan-Meier method and compared using the log-rank test. Independent prognostic factors were analyzed by the Cox proportional regression hazard method. $P < 0.05$ was considered to indicate statistical significance.

Results

The median overall survival was 54.47 months for the entire cohort, with 1-, 3-, and 5-year survival rates of 85%, 61%, and 43%, respectively. In order to assess the impact of different PCI for AGC patients with PC, we then performed a matched-paired analysis. Specifically, AGC patients with a PCI ≤ 13 were matched for performance status (Karnofsky performance status), age, sex, Borromann's classification, differentiation, depth of invasion, lymph node metastasis, PCI, extent of gastrectomy, extent of lymph node dissection, and residual tumor volume with patients with a PCI > 13 (Table 1). All patients underwent gastrectomy for the resection of the primary tumor, 38 of a subtotal manner and 22 of total. Small residual cancer volume was performed in 13 cases of the 21 patients in the PCI ≤ 13 group, 18 cases of the 39 patients in the PCI > 13 group.

The median survival time was 69.76 months in patients with a PCI ≤ 13 and 39.96 months in patients with a PCI > 13. There was a significant difference in survival rates between the two groups ($P = 0.004$; Fig. 1). The Borromann's classification, differentiation, depth of invasion, PCI, and volume of residual tumor were found to correlate with survival in the univariate analyses (Table 2). Age, sex, performance status, lymph node metastasis, extent of gastrectomy, and extent of lymph node dissection were not related to survival ($P > 0.05$). Moreover, while not significant, patients with an early lymph node metastasis stage tended to have increased survival compared to late stage ($P = 0.103$). The Cox proportional regression hazard model showed that a small volume of residual tumor and lower PCI were independent prognostic factors of survival (Table 2).

Table 3 shows the morbidity and mortality rates. Patients in both groups developed many complications after surgery; however, the morbidity and mortality rates with a PCI ≤ 13 were lower than those with PCI > 13, with

Table 1 Comparison of AGC patients with PC between PCI ≤ 13 and PCI > 13

	PCI ≤ 13	PCI > 13	*P*
Gender			0.316
Male	9	22	
Female	12	17	
Performance status			0.515
Score 90–100	11	17	
Score 70–80	10	22	
Borromann's classification			0.392
I + II	7	9	
III + IV	14	30	
Differentiation			0.635
Well	5	6	
Moderately	10	18	
Poorly	6	15	
Depth of invasion (T)			0.679
T3	7	11	
T4	14	28	
Lymph node metastasis (N)			0.628
N1	5	6	
N2	12	27	
N3	4	6	
Gastrectomy			0.064
Subtotal	10	28	
Total	11	11	
Extent of lymph node dissection			0.643
D1	6	3	
D2	13	26	
D3	2	10	
Residual tumor			0.244
CC-0 + CC-1	13	18	
CC-2 + CC-3	8	21	

a significant difference in the incidence of complications ($P = 0.016$). Postoperative major morbidity and mortality rates were 23.81% and 4.76% in the PCI ≤ 13 group and 43.59% and 5.12% in the PCI > 13 group, respectively. One death was directly related to respiratory failure,

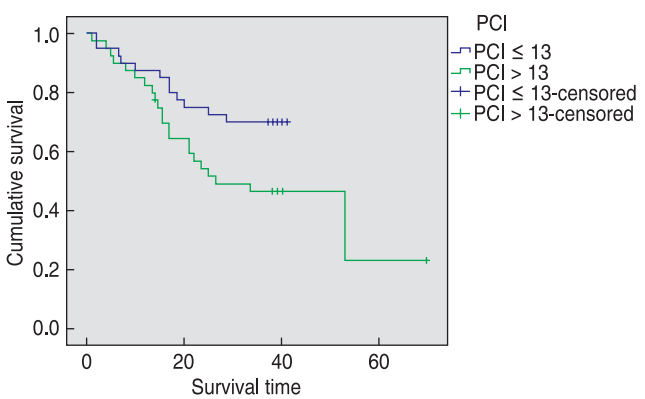

Fig. 1 The comparison of survival time between PCI ≤ 13 and PCI > 13

Table 2 Univariate analysis and Cox multivariate analysis to identify independent prognostic factors

	Median survival	Univariate *P*	Multivariate *P*
Gender		0.279	
Male	48.64		
Female	59.51		
Performance status		0.315	
Score 90–100	59.35		
Score 70–80	48.97		
Borromann's classification		0.048	0.596
I + II	63.83		
III + IV	42.95		
Differentiation		0.002	0.090
Well	72.50		
Moderately	47.29		
Poorly	24.38		
Depth of invasion (T)		0.006	0.118
T3	69.70		
T4	42.14		
Lymph node metastasis (N)		0.103	
N1	70.00		
N2	44.07		
N3	27.88		
Gastrectomy		0.309	
Subtotal	51.23		
Total	56.10		
Extent of lymph node dissection		0.099	
D1	74.50		
D2	48.54		
D3	33.13		
PCI		0.004	0.030
PCI ≤ 13	69.76		
PCI > 13	39.96		
Residual tumor		0.000	0.037
CC-0 + CC-1	74.49		
CC-2 + CC-3	37.41		

Table 3 The morbidity and mortality of AGC patients with PC between PCI ≤ 13 and PCI > 13

	PCI ≤ 13	PCI > 13	*P*
Morbidity	5 (23.81%)	17 (43.59%)	0.016
Wound abscess	0	1	
Ileus	1	4	
Anastomotic failure	1	4	
Bleeding	1	3	
Pancytopenia	0	1	
Cardiac & respiratory dysfunction	1	2	
Others	1	2	
Mortality	1 (4.76%)	2 (5.12%)	N.S.
Cardiac & respiratory failure	1	0	
Bleeding	0	1	
Others	0	1	

Note: N.S., no significance

resulting in multi-organ failure in the PCI ≤ 13 group. There were 2 deaths in the PCI > 13 group, 1 died of liver failure and the other abdominal bleeding.

All the patients which survived surgery were assessed every 3 months with physical examinations, hematological-biochemical examinations, tumor markers, and CT-scanning. Patient's follow-up period (from surgery to the date of death or the end of the study) was between 5 and 79 months (median: 29 months).

Discussion

The prevalence of PC has been estimated at 22% in gastric cancer patients and even after extensive resections, approximately 50% of patients die from recurrent disease within the first 2 years after surgery [11–13]. Several studies have demonstrated the efficacy of IPHC with improvements both in the survival rate and a decrease in the incidence of peritoneal recurrence of AGC patients with PC [14–16]. However, combining two aggressive procedures can lead to greater mortality and morbidity rates, with morbidity rates as high as 60% [17]. Therefore, surgeons must carefully select patients to achieve a balance between the postoperative risks of extensive surgery and the potential benefits in survival and quality of life.

The PCI gives valuable information about the exact distribution of seeding and tumor volume, representing in detail the extent of peritoneal spread. It has been used for the evaluation of spread at the peritoneal surfaces in peritoneal mesothelioma, colorectal cancer, and other cancers. In some studies, they have demonstrated a PCI around 10 is of prognostic significance for many malignant tumors with peritoneal spread [18–19]. Therefore, this value is used to determine if surgical intervention should continue as an attempt at curing the peritoneal metastases or whether the intervention should be for palliation only. The PCI is also a crucial prognostic indicator in the AGC with PC. In our study, we found that there was a significant difference in the survival rates between the PCI ≤ 13 and PCI > 13 groups. The median survival time was 69.76 months in patients with a PCI ≤ 13 and 39.96 months in patients with PCI > 13.

Survival was significantly influenced by the residual volume of tumors and PCI. Completeness of excision was found to be significant, improving 3-year survival from 13% to 52% [20]. For AGC patients without residual macroscopic metastases, the cytoreductive surgery plus IPHC procedure can improve postoperative survival rate and decrease the incidence of peritoneal recurrence, and is an independent prognostic factor for these patients. When the resection does result in sufficient reduction in tumor volume, IPHC does not seem to be beneficial as the gain in terms of survival is minimal [21]. Generally speaking, cytoreductive surgery is performed to treat the macroscopic disease and IPHC to treat the microscopic residual disease to eradicate the disease completely during a single procedure. It is verified in our article that a large volume residual tumor remaining results in reduced survival. This study, and also previously reported data, showed that only cytoreductive surgery achieves an R0 or R1 resection, with the intent to cure, the combination of IHPC can improve survival rate [22–24].

However, high morbidity and mortality rates after cytoreductive surgery combined with IPHC have been reported [23, 25]. Some reports suggest that postoperative complications, including anastomotic leakage, bowel perforation, renal dysfunction, respiratory failure, and other complications occur more frequently when IPHC is applied [26–28], while others claim the combination is safe [29–30]. In our study, the morbidity and mortality rates were significantly higher in the group with a PCI > 13 than those with a PCI ≤ 13 ($P = 0.016$). This was likely due to the extent of surgery being larger in the PCI > 13 group, causing more damage. Jacquet *et al* [31] reported the morbidity and mortality in patients with adenocarcinoma of the colon and appendix was 35% and 5% when IPHC was applied.

Several limitations in this study should be addressed. Firstly, all the patients included in this study were without extra-abdominal metastases and liver metastases. As such, results from this paper may not be extensively representative across the entire AGCs. Moreover, this study is a retrospective study with a small number of cases. Large sample multi-center randomized controlled studies are required to further verify the efficacy and safety of surgery and IPHC in AGCs.

The PCI is a significant predictor of survival in AGC patients with PC. Using PCI as a detailed evaluation of the peritoneal spread is possible. On the whole, surgery plus IPHC for AGC with PCI ≤ 13 is a relatively safe procedure.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

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