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Prognostic effect of different etiologies in patients with gastric cardia cancer

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Abstract

There are still many controversies about the characteristics and prognosis of gastric cardia cancer. We aimed to evaluate the clinical characteristics and outcome between cardia and noncardia cancer. Also, we evaluated the clinical outcome according to etiologic factors.

We performed a retrospective cohort study of 92 patients with gastric cardia cancer from January 2003 to December 2013. The patients with noncardia cancer were selected as age- and sex-matched control.

The frequencies of gastroesophageal reflux disease (GERD) and negative *Helicobacter pylori* infection without atrophy were significantly higher in gastric cardia cancers, but there was no difference in the frequency of obesity. The frequency of early gastric cancers was 40.0%, which was significantly lower than that of noncardia cancer. The rate of recurrence, disease-free survival, and overall survival duration were significantly lower in gastric cardia cancers ($P < .01$), even though there was no significant difference in the rate of curative resection (R0). In terms of the etiologic factors, there were no differences of disease prognosis, regardless of the presence of GERD, obesity, and *H pylori* infection with associated gastritis.

Gastric cardia cancer showed distinct clinical characteristics and a negative prognostic impact compared with gastric noncardia cancer.

Abbreviations: BMI = body mass index, EGC = early gastric cancers, EGJ = esophago-gastric junction, ESD = endoscopic submucosal dissection, GERD = gastroesophageal reflux disease, *H pylori* = *Helicobacter pylori*.

Keywords: cardia, gastric cancer, prognosis

1. Introduction

The incidence of distal esophageal adenocarcinoma and esophago-gastric junction (EGJ) adenocarcinoma has increased in Western countries,[1,2] whereas the increasing tendency is not distinct in eastern countries.[3–5] Although squamous cell type remains the most common type of esophageal cancer in eastern countries, it is expected that the incidence of distal esophageal adenocarcinoma will increase due to a westernized dietary lifestyle and reduction of *Helicobacter pylori* (*H pylori*) infection.

In the distal esophageal adenocarcinoma, several risk factors have been identified including male sex, white ethnicity, high body mass index (BMI), obesity, gastroesophageal reflux disease (GERD), Barrett esophagus, lack of infection with *H pylori*, and low fruit and vegetable intake.[6–11] However, somewhat different risk factors for gastric cancer have been identified. *H pylori* infection is the main etiology, and the other risk factors include alcohol drinking, smoking, and dietary factors—high salt, high sodium intake, and low fruit intake.[12–17]*H pylori* infection in gastric carcinogenesis is believed to be a multistep process involving sequential changes of atrophy-metaplasia-dysplasia-cancer sequence, and *H Pylori*-associated chronic gastritis is thought as an initiation event.[18–22] Anatomically, it is expected that gastric cardia cancers have a distinct characteristics compared with noncardia cancers. In some areas, the 2 disease entities have something in common—etiologic factors and prognostic survival between gastric cardia cancer and esophageal adenocarcinoma.[1,2,3,24] Therefore, the researchers have made steady efforts on the classification of adenocarcinomas near EGJ. In the 7th edition of the American Joint Commission on Cancer, tumors within 5 cm of the EGJ are classified as esophageal cancer. However, conflicting factors between the 2 disease entities still exist.

In several diseases, etiological factors influence the course and outcomes. *H pylori* infection predicts a favorable outcome on the progression and clinical outcome of noncardia gastric cancer; *H pylori* infection predicted favorable outcome. Taken together, it can be inferred that the prognosis of a single disease entity with different etiologic factors may be different. The primary aim of this study was to compare the clinical characteristics and outcome between gastric cardia and noncardia cancer. Also, we aimed to evaluate the clinical characteristics and outcomes

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Ethical Standards: This study was approved by the Institutional Research Ethics Board of The Catholic University of Korea (VC19RESI0064) and adhered to the Declaration of Helsinki.

The authors report no conflicts of interest.

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according to the presence of obesity, GERD and *H pylori* infection (atrophic gastritis) state.

2. Materials and methods

2.1. Study population

We retrospectively reviewed the medical records of 90 consecutive patients with cardia gastric adenocarcinomas at the St. Vincent Hospital (Suwon, Korea), the Catholic University of Korea from January 2003 to December 2013. An age- and sex-matched control group consisted of 180 patients with noncardia gastric adenocarcinomas during the same period. The control group was randomly selected in a 2:1 ratio compared with the case group. The age and sex were matched between the case and the control groups using the match macro program of SAS software for Windows (release 9.2; SAS Institute, Cary, NC). We compared the clinical and pathologic characteristics including curative resection rate, recurrence rate, disease-free survival, and overall survival between the patients with cardia and noncardia gastric adenocarcinomas. Also, we evaluated the presence of obesity, GERD, and *H pylori* infection (atrophic gastritis) state.

2.2. Definition

The diagnosis of atrophy was based on its endoscopic morphometric classification.[25] The diagnosis of GERD was based on the reflux symptoms or upper endoscopy findings. *H. pylori* infection status was based on histopathology or rapid urease test. Obesity was defined as BMI $>25\,kg/m^2$. Cardia cancer defined as tumor was classified as cardiac if its center was within 1 cm proximal, or 5 cm distal, to the GEJ.

The histopathologic features recorded were tumor depth of invasion, histology, and lymph node status including number of metastatic lymph node and number of resected lymph node at operation. Tumor size, tumor location, depth of invasion, and nodal status were based on the 7th edition of the AJCC Staging System.[26] Early gastric cancers (EGCs) defined as tumor cells were confined to mucosa and submucosa regardless lymph node metastasis.

In gastric cardia cancer, we evaluated the clinical outcomes according to the presence of obesity, GERD, and *H pylori* infection (atrophic gastritis) state. As for *H pylori* infection and associated gastritis, we divided into 2 groups: group 1, the patients without *H pylori* infection and atrophic gastritis and group 2, the remaining patients with *H pylori* infection or atrophic gastritis. We compared the clinical outcome between these 2 groups.

2.3. Statistical analysis

All statistical analyses were carried out using SPSS software (version 22.0; IBM). Comparison of proportion of the patients was done by the χ^2 test. Survival curve was expressed by Kaplan-Meier method and log-rank test. P values of $<.05$ were considered significant for the analysis.

3. Results

3.1. Clinical characteristics and clinical outcomes of gastric cardia cancer compared with noncardia cancer

There was no difference in the frequency of obesity between patients with gastric cardia cancer and those with noncardia cancer. The presence of GERD was more frequent in gastric cardia cancer than noncardia cancer (35.9% vs 20.7%, $P<.01$). The frequency of negative *H pylori* infection and gastritis without atrophy was significantly higher in patients with gastric cardia cancer than those with noncardia cancer (20.7% vs 10.3%, $P<.01$) (Table 1). The frequency of EGC was up to 40.0% in gastric cardia cancer (34/92), which was significantly lower than that in noncardia cancer (71.7%, 102/184). The lesion size

Table 1

Clinical characteristics and outcomes of patients in cardia cancer and noncardia cancer.

	Cardia cancer (N = 92)	Noncardia cancer (N = 184)	*P*
BMI, kg/m^2 (%)	23.3 ± 3.6	23.0 ± 3.8	.34
>25	30 (32.6)	50 (27.2)	
Alcohol	29 (32.2)	50 (27.2)	.20
Smoking	25 (27.2)	49 (26.6)	.50
Atrophic gastritis	67 (71.3)	150 (81.5)	.13
Helicobacter pylori infection	41 (43.6)	63 (34.2)	.09
Atrophy(−) and *H pylori* (−)	19 (20.7)	19 (10.3)	<.01*
GERD	33 (35.9)	38 (20.7)	<.01*
Lesion size, cm (longest diameter)	5.14 ± 3.71	3.13 ± 3.19	<.01*
Early gastric cancer	34 (40.0)	102 (71.7)	<.01*
Stage Ia (7^{th} AJCC)	25	89	
Ib	9	13	
Advanced (stage III/ IV)	43(46.7)	53 (28.8)	<.01*
Surgical treatment	81 (88.0)	160 (86.9)	.11
R0 resection rate	75/81 (92.6)	156/160 (97.5)	.08
ESD	9/75 (12.0)	23 /156 (14.7)	.57
Recurrence rate	21/75 (28.0)	12/156 (7.7)	<.01*
Median disease-free survival period, mo	35.0 (23.8–46.2, 5.7)	66.0 (52.1–79.9, 7.1)	<.01*
Median overall survival period, mo	28.0 (20.1–35.9, 4.0)	76.0 (59.6–92.4, 8.3)	<.01*

AJCC = American Joint Cancer Committee, BMI = body mass index, ESD = endoscopic mucosal dissection, GERD = gastroesophageal reflux disease.
* Statistically significant.

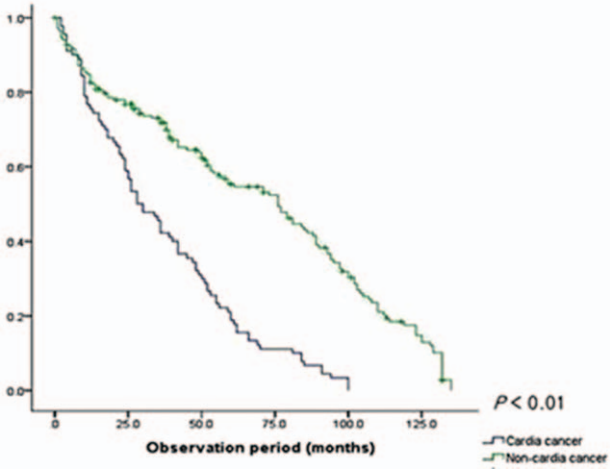

Figure 1. Disease-free and overall survival duration between cardia cancer and non-cardia cancer.

(longest diameter) was the longer in the patients with gastric cardia cancers (5.14 ± 3.71 cm vs 3.13 ± 3.19 cm, $P < .01$). For the frequency of stages III or IV advanced gastric cancers classified by 7th AJCC, were significantly higher in gastric cardia cancer than in noncardia cancer (54.3%, 50/92 vs 28.8%, 53/184, $P < .01$).

There was no significant difference in the rate of curative resection (R0) in patients with gastric cardia cancer compared with that in patients with noncardia cancer (92.6% vs 97.5%, $P = .08$). In 11 patients of gastric cardia cancer, endoscopic submucosal dissection (ESD) was performed, and 2 cases among them had surgical treatment due to incomplete resection by the extended criteria of ESD.[27] Finally, 9 patients had ESD procedure, and there was no difference compared with noncardia cancer (12.0%, 9/75 R0 resection, vs 14.7%, 23/156, $P = .57$). The rate of recurrence after curative resection (R0) was significantly higher in patients with gastric cardia cancer than in those with noncardia cancer (28.4% vs 8.0%, $P < .01$). The disease-free survival and overall survival duration were significantly longer in patients with noncardia cancer than in those with noncardia cancer (Fig. 1).

3.2. Prognosis based on etiologic factors (GERD, obesity, and H pylori infection)

There were no significant differences in disease-free and overall survival duration between obese and nonobese patients (Fig. 2). Also, the presence of GERD had no prognostic effect on disease-free and overall survival. As for *H pylori* infection and associated gastritis, there was no significant difference in disease-free and overall survival duration.

4. Discussion

There are 2 different main etiologies of gastric cardia cancer: Barrett esophagus and *H pylori*-associated atrophy/intestinal metaplasia. In the present study, we examined clinical characteristics and outcome between gastric cardia and noncardia cancer and in gastric cardiac cancer according to presence of obesity, GERD, and *H pylori* infection associated gastritis. When gastric cardia cancers were compared with noncardia cancers, the rate of recurrence, disease-free survival, and overall survival duration

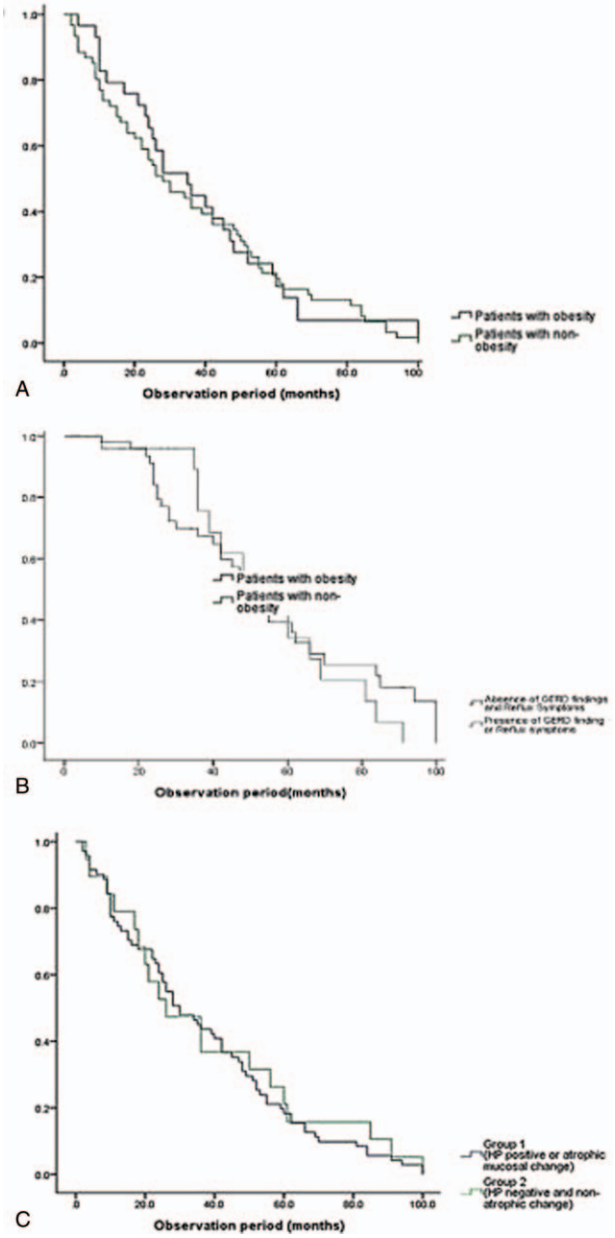

Figure 2. Disease-free and overall survival duration according to presence of (A) obesity, (B) gastroesophageal reflux disease, and (C) presence of *Helicobacter pylori*.

were significantly lower in gastric cardia cancer, even though there was no difference in the rate of curative resection (R0). The main causes were the higher frequency of advanced staged cancers and the lesser frequency of early gastric cancers in patients with gastric cardia cancers compared with noncardia cancers.

The poor prognosis of gastric cancer is due to an anatomical defect; the serosa in proximally one-third of the stomach is partially developed and local lymphatic drainage was prone to advanced lymph node group—splenic, celiac, or portal lymph nodes. Therefore, these are known to be diagnosed relatively as the more advanced stage, and it could be associated with unfavorable clinical outcomes.[28] In contrast, previous studies reported that there were no difference of outcomes

between proximal and distal gastric cancer, and it is still inconclusive.[29–31] This study suggested that the more advanced stage of gastric cardia cancer resulted in poor prognosis. If this result is consistently proven, we will have to approach gastric cardia cancer in a different way than the present therapeutic strategy. In locally advanced rectal cancer, the therapeutic strategy is somewhat different from colon cancer. It is likely that locally advanced gastric cardia cancer could be treated with concurrent chemoradiotherapy before curative resection similar to esophageal cancer and rectal cancer.

In this study, it was noteworthy that the rate of early gastric cancer was up to 40% in gastric cardia cancer. In Korean studies that were conducted from 1990 to 2006, the rate of early gastric cardia cancer was reported to be 15% to 22%.[32–34] In another previous study which was conducted from 1976 to 1995, it was reported to be only 5% to 6%.[34] The difference in our results, in comparison with previous studies, can be because of the latest advancements in diagnostic technology—endoscopic techniques and development of endoscopic equipment. Also, the endoscopic therapies, including ESD, were increased in gastric cardia cancer, and the rate of ESD was up to 12% in this study. There is a high possibility that such treatments will continue to increase in the future.

Previously, the association between gastric cardia cancer and serological evidence of both *H pylori* infection and atrophic gastritis was evaluated and it was performed in a nested case–control study. There was a negative association with *H pylori* infection, but a positive association between atrophic gastritis and cardia cancer in those with the infection. Our results were similar, and it meant that gastric cardia cancer shared something in common with adenocarcinoma of the distal stomach. The rest are likely to come from completely different etiologies. As for obesity, it was known that overweight and obese individuals were more likely to be at risk of gastric cardia cancer.[35,36] Obesity was implicated in a spectrum of reflux-related esophageal diseases ranging from esophageal inflammation (erosive esophagitis), metaplasia (Barrett esophagus) to neoplasia (gastroesophageal cancer).[37–40] Due to possible heterogeneity in the pathogenesis and biological behavior of gastric cardia cancer, we subanalyzed patients with cardia cancer according to obesity, presence of GERD, and *H pylori* infection with associated gastritis. There were no differences in recurrence rate, overall survival, and disease-free survival.

This study had several limitations and first the study design was a retrospective cohort. Selection or recalling biases might be present. Second, our study adopted BMI as an only indicator of obesity, and waist circumference was closely related to the increased risk of gastroesophageal junction cancer in previous studies.[41–44]

5. Conclusions

In conclusion, gastric cardia cancer had a negative prognostic impact compared with gastric noncardia cancer. Although a possible heterogenicity in the pathogenesis and biological behavior of gastric cancer could be present, there was no difference in prognosis. It was noteworthy that the frequency of early cancer of gastric cardia was higher compared with the previous studies, and we expected that the prognosis of gastric cardia cancers would be improved. However, it is difficult to make an early decision yet, and a broadened and larger scaled study is needed in the near future.

Author contributions

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