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.
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.[22] 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/m². 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.[23] 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 χ² 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/m² (%)         | 23.3 ± 3.6             | 23.0 ± 3.8                  | .34     |
| Smoking                | 25 (27.2)              | 49 (26.6)                   | .50     |
| Atrophic gastritis     | 67 (71.3)              | 150 (81.5)                  | .13     |
| *H. pylori* infection  | 41 (43.6)              | 63 (34.2)                   | .09     |
| Atrophy (−) and *H. pylori* (−) | 19 (20.7)    | 19 (10.3)                   | <.01*   |
| Early gastric cancer   | 34 (40.0)              | 102 (71.7)                  | <.01*   |
| Stage IA (7th AJCC)    | 25                     | 89                          |         |
| 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                    | 3/75 (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.
(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%, 97/75 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 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.\textsuperscript{[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%.\textsuperscript{[32–34]} In another previous study which was conducted from 1976 to 1995, it was reported to be only 5% to 6%.\textsuperscript{[35]} 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.\textsuperscript{[35,36]} Obesity was implicated in a spectrum of reflux-related esophageal diseases ranging from esophagitis inflammation (erosive esophagitis), metaplasia (Barrett esophagus) to neoplasia (gastroesophageal cancer).\textsuperscript{[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.\textsuperscript{[41–44]}

5. Conclusions

In conclusion, gastric cardia cancer had a negative prognostic impact compared with gastric noncardia cancer. Although a possible heterogeneity 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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References

[1] Botterweck AA, Schouten LJ, Volovicis A, et al. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000; 29:645–54.
[2] Thrift AP, Whitteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Ann Oncol 2012; 23:3155–62.
[3] Okabayashi T, Gotoda T, Kondo H, et al. Early carcinoma of the gastric cardia in Japan: is it different from that in the West? Cancer 2000;89:2555–9.
[4] Hasegawa S, Yoshikawa T. Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies. Gastric Cancer 2010; 13:63–73.
[5] Chung JW, Lee GH, Choo KS, et al. Unchanging trend of esophaogastic junction adenocarcinoma in Korea: experience at a single institution based on Siewert’s classification. Dis Esophagus 2009;22:676–81.
[6] Poli H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal adenocarcinoma. Am J Gastroenterol 2013;108:200–7.
[7] de Jonge PJ, van Blankenstein M, Looman CW, et al. Risk of malignant progression in patients with Barrett’s oesophagus: a Dutch nationwide cohort study. Gut 2010; 59:1030–6.
[8] Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
[9] Cheng KK, Sharp L, McKinney PA, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. Br J Cancer 2000;83:127–32.
[10] Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett’s esophagus. N Engl J Med 2011;365:1373–83.
[11] Schneider JL, Corley DA. The troublesome epidemiology of Barrett’s esophagus and esophageal adenocarcinoma. Gastrointest Endosc Clin N Am 2017;27:553–64.
[12] Nagini S. Carcinoma of the stomach: a review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol 2012;4:156–69.
[13] Park B, Shin A, Park SK, et al. Ecological study for refrigerator use, salt, vegetable, and fruit intakes, and gastric cancer. Cancer Causes Control 2011;22:1497–502.
[14] Gonzalez CA, Perez G, Agudo A, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Int J Cancer 2003;107:629–34.
[15] Sokic-Milutinovic A, Alempijevic T, Milosavljevic T. Role of Helicobacter pylori infection in gastric carcinogenesis: current knowledge and future directions. World J Gastroenterol 2015;21:11654–72.
[16] Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001;345:784–9.
[17] Malfertheiner P, Megraud F, O’Morain CA, et al. Management of Helicobacter pylori infection—the Maastricht IV/Florence Consensus Report. Gut 2012;61:646–64.
[18] Correa P, Houghton J. Carcinogenesis of Helicobacter pylori. Gastroenterology 2007;133:659–72.
[19] Nardone G, Rosco A, Malfertheiner P. Review article: helicobacter pylori and molecular events in precancerous gastric lesions. Aliment Pharmacol Ther 2004;20:261–70.
Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992;52:6735–40.

Correa P, Piazuelo MB, Camargo MC. The future of gastric cancer prevention. Gastric Cancer 2004;7:9–16.

Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology 2001;121:1286–93.

Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst 2010;102:1344–53.

Bah A, Saraga E, Armstrong D, et al. Endoscopic features of Helicobacter pylori-related gastritis. Endoscopy 1995;27:593–6.

Hong D, Liu Y, Peng S, et al. Binding pancreaticogastrostomy in laparoscopic central pancreatectomy: a novel technique in laparoscopic pancreatic surgery. Surg Endosc 2016;30:715–20.

Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3:219–25.

Bruno L, Nesi G, Montinaro F, et al. Clinicopathologic findings and results of surgical treatment in cardiac adenocarcinoma. J Surg Oncol 2000;74:33–5.

Costa LB, Toneto MG, Moreira LF. Do proximal and distal gastric tumours behave differently? Arq Bras Cir Dig 2016;29:232–5.

Piso P, Wernert U, Lang H, et al. Proximal versus distal gastric carcinoma—what are the differences? Ann Surg Oncol 2000;7:520–5.

Kamagem CA, Linhares M, Lacerda CF, et al. Comparison of laparoscopic total gastrectomy and laparotomic total gastrectomy for gastric cancer. Arq Bras Cir Dig 2015;28:65–9.

Yoon HY, Kim HI, Kim CB. Clinicopathologic characteristics of adenocarcinoma in cardia according to Swierter classification. Korean J Gastroenterol 2008;52:293–7.

Yoon CM, Rew JS, Bom HS, et al. Early gastric cancer in Korea. Korean J Intern Med 1989;4:65–73.

Park JS, Lee YC, Kim WH, et al. Clinicopathologic characteristics of early gastric cancer in Korea. Yonsei Med J 2000;41:607–14.

Chen Y, Liu L, Wang X, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. Cancer Epidemiol Biomarkers Prev 2013;22:1395–408.

Turati F, Tramacere I, La Vecchia C, et al. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol 2013;24:609–17.

Du X, Hidayat K, Shi BM. Abdominal obesity and gastroesophageal cancer risk: systematic review and meta-analysis of prospective studies. Biosci Rep 2017;37.

Sethi S, Richter JE. Diet and gastroesophageal reflux disease: role in pathogenesis and management. Curr Opin Gastroenterol 2017;33:107–11.

Iijima K, Asanuma K, Koike T. Risk factors of Barrett’s esophagus. Nihon Rinsho 2016;74:1337–60.

Nimptsch K, Steffen A, Pischon T. Obesity and oesophageal cancer. Recent Results Cancer Res 2016;208:67–80.

MacInnis RJ, English DR, Hopper JL, et al. Body size and composition and the risk of gastric and oesophageal adenocarcinoma. Int J Cancer 2006;118:2628–31.

O’Doherty MG, Freedman ND, Hollenbeck AR, et al. A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. Gut 2012;61:1261–8.

Steffen A, Huerta JM, Weiderpass E, et al. General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2015;137:646–57.

Lin Y, Ness-Jensen E, Hveem K, et al. Metabolic syndrome and esophageal and gastric cancer. Cancer Causes Control 2013;26:1825–34.