Diseases of the Esophagus (2009) **22**, 676–681
DOI: 10.1111/j.1442-2050.2009.00946.x

DISEASES OF THE ESOPHAGUS

Original article

Unchanging trend of esophagogastric junction adenocarcinoma in Korea: experience at a single institution based on Siewert's classification

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SUMMARY. **The incidence of adenocarcinoma of the esophagogastric junction (AEG) has been increasing in Western countries. It is unclear, however, whether similar changes are occurring in Asia. We therefore investigated the incidence of AEG in Korea, and assessed the clinical characteristics of three types of AEG based on Siewert's classification. We retrospectively reviewed the medical records of 16 811 patients diagnosed with esophageal squamous cell carcinoma (ESC, *n* = 1450) or gastric noncardiac adenocarcinoma (GNCA, *n* = 14 751) between 1992 and 2006. The patients were divided into three 5-year cohorts (cohort A [1992–1996], *n* = 2734, cohort B [1997–2001], *n* = 5727, and cohort C [2002–2006], *n* = 8350), and the ratios of AEG (*n* = 610) to non-AEG (ESC and GNCA) in each cohort were compared. Using Siewert's classification, the tumors were categorized into one of three types, and patient demographic features and 5-year survival rates were compared. The ratio of AEG to non-AEG cases did not change over time (0.037, 0.034, and 0.039 for cohorts A, B, and C, respectively; *P* = 0.40). Of the 610 patients with AEG, 23 (3.7%) had type 1 tumors, 47 (7.7%) had type 2, and 540 (88.5%) had type 3. The 5-year survival rate of patients with type 1 AEG was much lower (4.8 ± 4.7%) than that of those with type 2 (47.9 ± 7.8%) and type 3 (47.4 ± 2.5%) tumors. Unlike in Western countries, the ratio of AEG to non-AEG cases has not increased over time in Korea. Type 1 AEG was rarer and associated with a more unfavorable prognosis in Korea than in Western countries.**

KEY WORDS: **Barrett's esophagus, esophageal adenocarcinoma, esophagogastric junction, gastric cardiac adenocarcinoma, Siewert's classification.**

INTRODUCTION

Population-based studies have shown that the incidence rates of adenocarcinoma of the esophagus and esophagogastric junction have increased in Western countries.[1–3] Although squamous cell carcinoma of the esophagus (ESC) is still predominant, more than half of newly diagnosed tumors are adenocarcinoma of the distal esophagus and esophagogastric junction.[4]

The prevalence of gastroesophageal reflux disease (GERD), which has historically been less common in Asian than in Western populations, has increased markedly over time in Korea, from 3.5% in 2001 to 12.0% in 2006.[5,6] Given that symptomatic GERD and Barrett's mucosa (BE) are risk factors for esophageal cancer, the incidence of adenocarcinoma of the esophagogastric junction (AEG) may also be increasing.

Owing to the lack of a clear definition, there is limited consensus regarding the classification of esophagogastric tumors. More recently, AEG tumors have been categorized using Siewert's classification, which was approved at the Second International Gastric Cancer Congress.[7,8] Little is known, however, regarding the patterns of AEG according to Siewert's classification in Korea.[9] We therefore investigated recent trends in the incidence of AEG in Korea, and assessed the clinical characteristics and prognosis of the three types of tumor as defined by Siewert's classification.

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SUBJECTS AND METHODS

Definition of ESC, gastric noncardiac adenocarcinoma (GNCA), and AEG

We retrospectively reviewed the medical records of 16 811 patients who had been diagnosed with esophageal cancer or gastric adenocarcinoma between January 1992 and December 2006 at the Asan Medical Center, a 2200-bed university hospital in Seoul, Korea. Patients were classified based on the International Classification of Diseases for Oncology (ICD-O, second edition, WHO, 1990). All patients with primary malignant neoplasms of the esophagus (C15.0–15.9) and stomach cancers (C16.0–16.9) were included, except for those with malignant lymphomas. ESC was defined as a primary malignant neoplasm of squamous cell origin (ICD-O M 8050–8082). Gastric noncardiac adenocarcinomas (GNCA) were defined as primary gastric malignant neoplasms, including adenocarcinomas of the stomach other than AEG.

We reviewed available endoscopic, radiologic, and pathologic results of patients with adenocarcinomas (ICD-O, M codes 8050-8082) associated with the lower third of the esophagus (C15.5) and with cardiac cancer (C16.0). AEGs were defined as tumors centered within 5 cm proximal or distal to the anatomic cardia.

The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

Definition of cohorts

Patients were divided into three consecutive 5-year cohorts (cohort A, 1992–1996, cohort B, 1997–2001, and cohort C, 2002–2006). The ratio of AEG to non-AEG (ESC and GNCA) was assessed in all studied patients and within each cohort.

Classification and analysis of AEG tumors

AEG tumors were categorized using Siewert's classification, based on results from a combination of contrast radiography, endoscopy with orthographic and retroflexed views of the esophagogastric junction, computer tomography, and intraoperative findings.[7] Type 1 tumors were adenocarcinomas of the distal esophagus that generally arose from an area of specialized intestinal metaplasia in the esophagus. Type 2 tumors were true carcinomas of the cardia, arising from the cardiac epithelium or a short segment of intestinal metaplasia. Type 3 tumors were subcardial gastric carcinomas that infiltrated the esophagogastric junction and distal esophagus from below.

Data reviewed included demographic parameters, degree of tumor differentiation (well differentiated, moderate, undifferentiated: poor, and signet-ring cell type), depth of tumor invasion (pT category), status of lymph node metastasis (pN category), and stage according to the International Union Against Cancer guidelines.[10] Among the therapeutic modalities analyzed were endoscopic resection and surgical procedures, including total gastrectomy, proximal gastrectomy, Ivor–Lewis operation, palliative chemotherapy, and neoadjuvant chemotherapy. A primary endoscopic resection was performed if the lesion was less than 20 mm in diameter, and was a well-differentiated, elevated cancer without ulceration.[11] Patients were offered primary surgery if staging examinations were indicative of or showed evidence of a more advanced tumor stage (>T1), lymph node involvement, or metastasis.[12]

Statistical analysis

SPSS 12.0 was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). The three cohorts were compared using the χ^2 test (linear-by-linear association), and the three types of tumors were compared using the Pearson χ^2 test. Numerical variables are expressed as means ± standard deviations. Five-year survival rates were analyzed by the Kaplan–Meier method, and differences among the three cohorts were examined using the log–rank test. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

AEG was histopathologically confirmed in 610 patients, ESC in 1450 patients, and gastric GNCA in 14 751 patients. The demographic data for the AEG, ESC, and GNCA groups are summarized in Table 1. All types of tumors showed male predominance, with the highest male-to-female ratio observed for the ESC groups, followed by the AEG and GNCA

Table 1 Demographics of patients with esophageal cancer and gastric adenocarcinoma

	ESC	AEG	GNCA	*P*-value
Patients (*n*)	1450	610	14751	
Male : female (%)	94 : 6	76 : 24	67 : 33	<0.01
Age (year, mean ± SD)	62.9 ± 8.5	58.4 ± 11.9	56.9 ± 12.5	<0.01

AEG, adenocarcinoma of the esophagogastric junction; ESC, esophageal squamous cell carcinoma; GNCA, gastric noncardiac adenocarcinoma; SD, standard deviation.

Table 2 Ratio of AEG, ESC, and GNCA, and the proportion of stage I and II cancers over a 15-year period

	Cohort A (1992–1996)	Cohort B (1997–2001)	Cohort C (2002–2006)	Total patients
AEG	100	193	317	610
ESC + GNCA	2634	5534	8033	16 201
ESC	258	561	631	1450
GNCA	2376	4973	7402	14751
AEG/ESC + GNCA	0.037*	0.034*	0.039*	
No. of patients with stage I/II AEG (%)	29 (29.0%)**	60 (31.1%) **	185 (58.4%)**	

*$P = 0.40$; **$P < 0.01$. AEG, adenocarcinoma of the esophagogastric junction; ESC, esophageal squamous cell carcinoma; GNCA, gastric noncardiac adenocarcinoma.

groups ($P < 0.01$). Age at the time of diagnosis showed a similar pattern, with ESC patients being the oldest, followed by AEG and GNCA patients ($P < 0.01$). The ratio of AEG to non-AEG cases (ESC and GNCA) was similar for the three cohorts (0.037 for cohort A, 0.034 for cohort B, and 0.039 for cohort C, $P = 0.40$) with no significant changes over time (Table 2).

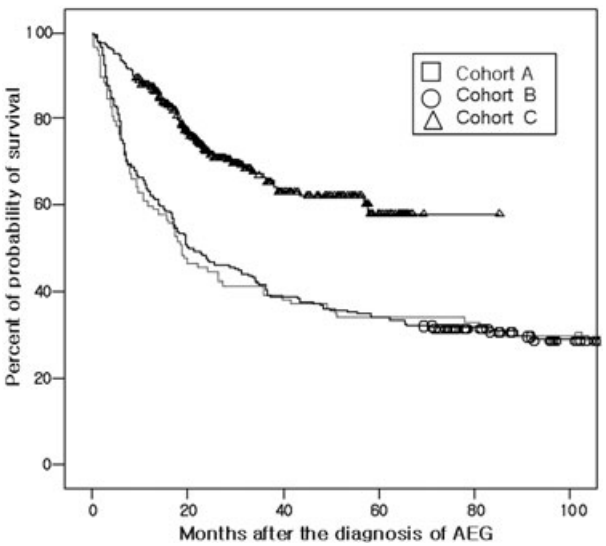

Fig. 1 Five-year Kaplan–Meier survival rates for three consecutive cohorts. The rate for cohort C was greater than those for cohorts A and B ($P < 0.01$). AEG, adenocarcinoma of the esophagogastric junction.

In each cohort, the proportion of AEGs classified as early-stage disease (stages I and II) increased gradually over time, from 29.0% in cohort A, to 31.1% in cohort B, and 58.4% in cohort C ($P < 0.01$ for each). The 5-year survival rate also increased over time, from 34.0 ± 4.8% in cohort A, to 34.2 ± 3.4% in cohort B, and 57.9 ± 4.3% in cohort C ($P < 0.01$) (Fig. 1).

Of the 610 patients with AEG (all cohorts), 23 (3.7%) had type 1 tumors, 47 (7.7%) had type 2 tumors, and 540 (88.5%) had type 3 tumors. The proportions of the three types of AEG tumor did not change over time (Table 3).

Age at the time of diagnosis was lower in patients with AEG type 3 tumors than in those with type 1 or 2 tumors; the proportion of patients with undifferentiated cancers was significantly greater in the type 3 group than in the type 1 group ($P < 0.01$). The proportions of early-stage (stage I, II) cancer were 13% for type 1, 42.6% for type 2, and 46.1% for type 3; the differences were not statistically significant (Table 4).

Table 5 summarizes the treatment modalities. Primary resection (surgical resection plus endoscopic resection) was performed in 402 patients (65.8%) with AEG, and the need for primary resection was greater

Table 3 Trends of AEG over time

	Cohort A (1992–1996)	Cohort B (1997–2001)	Cohort C (2002–2006)	*P*-value
AEG type 1, *n* (%)	4 (4%)	11 (5.7%)	8 (2.5%)	0.18
AEG type 2, *n* (%)	6 (6.0%)	13 (6.7%)	28 (8.8%)	0.54
AEG type 3, *n* (%)	90 (90%)	169 (87.6%)	281 (88.6%)	0.82
Total patients	100	193	317	

AEG, adenocarcinoma of the esophagogastric junction.

Table 4 Demographic and morphologic tumor characteristics and proportions of stage I and II AEG

	AEG type 1($n = 23$)	AEG type 2($n = 47$)	AEG type 3($n = 540$)	*P*-value
Age, years	64.7 ± 10.5	62.8 ± 12.7	57.7 ± 11.8	0.01
Male : female (%)	87 : 13	91 : 9	74 : 26	0.01
Undifferentiated tumors (%)	6 (26.1%)	18 (38.3%)	291 (53.9%)	<0.01
Stage I/II tumors (%)	3 (13.0%)	20 (42.6%)	249 (46.1%)	0.07

AEG, adenocarcinoma of the esophagogastric junction.

Table 5 Relationship between treatment and Siewert's classification in AEG patients

	AEG type 1 ($n = 23$)	AEG type 2 ($n = 47$)	AEG type 3 ($n = 540$)
Primary resection (%)	3 (13%)*	28 (59.6%)*	371 (68.7%)*
Endoscopic resection	0 (0%)	3 (6.4%)	9 (1.7%)
Total gastrectomy	1 (4.3%)	20 (42.5%)	348 (64.4%)
Proximal gastrectomy	0 (0%)	3 (6.4%)	13 (2.4%)
Ivor–Lewis operation	2 (8.6%)	2 (4.3%)	1 (0.2%)
Palliative chemotherapy	10 (43.4%)	8 (17.0%)	69 (12.8%)
Neoadjuvant chemotherapy	0 (0%)	1 (2.1%)	4 (0.7%)
No treatment	10 (43.4%)	10 (21.3%)	96 (17.8%)

*$P < 0.01$ among all groups. AEG, adenocarcinoma of the esophagogastric junction.

in the type 3 group than in the type 1 group ($P < 0.01$). Three patients in cohort B and nine in cohort C underwent primary endoscopic resection; two patients underwent additional gastrectomy owing to noncurative resection. Remarkably, the 5-year survival rate in patients with type 1 AEG was much lower (4.8 ± 4.7%) than in those with type 2 (47.9 ± 7.8%) or type 3 (47.4 ± 2.5%) tumors (Fig. 2).

DISCUSSION

We show here that the ratio of AEG to non-AEG tumors in the Korean population has remained unchanged over the 15-year period from 1992 to 2006, a trend that stands in contrast to the increasing incidence of AEG observed in Western countries over the same period. Our findings are consistent, however, with the results of a previous study in Asia, which showed that the relative ratio of esophageal adenocarcinoma and ESC in a single institution was unchanged.[9,13]

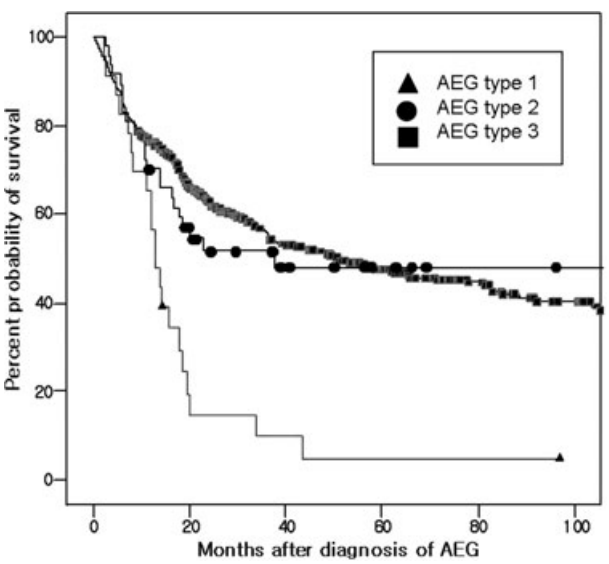

Fig. 2 Five-year Kaplan–Meier survival rates for AEG tumor types. The rate for type 1 was significantly lower than those for types 2 and 3 ($P < 0.01$). AEG, adenocarcinoma of the esophagogastric junction.

Despite the increased prevalence in Korea of GERD and BE, both of which are considered premalignant conditions for esophageal adenocarcinoma,[14] the frequency of AEG in Korea has not increased. Recent investigations regarding the rate of annual progression have indicated that, out of every 1,000 patients with BE, 5 develop AEG, indicating that progression from GERD to AEG takes many years.[15–17] In addition, it has been suggested that GERD is most common in patients aged 30–40 years in Korea.[6] In the present study, AEG was most common in patients aged around 55–60 years. These findings suggest that 20 to 30 years may be required for GERD to develop into AEG. Thus, the time span we assessed, 15 years, may not have been sufficient to show a change in the prevalence of AEG.

Although the prevalence of AEG has remained unchanged, the proportion of patients with early-stage tumors (stages I and II) has increased over time. Moreover, the survival rate of patients with AEG has increased over time, from 34.0 ± 4.8% in 1992–1996 to 57.9 ± 4.3% in 2002–2006. This improved prognosis may be due to recent advances in cancer therapy and the promotion of a nationwide screening and surveillance program in Korea in 2002, which has increased early detection rates and led to more favorable clinical outcomes.

Among the classification systems for esophagogastric tumors are ICD-O, Siewert's, Liverpool, and the recently proposed Chandrasoma classification.[18,19] Previous population-based studies have been based on the ICD-O classification, which lacked accurate definitions of tumors of the esophagogastric junction and the cardia. Thus, for many tumors, it was unclear if they were esophageal or stomach adenocarcinomas.[20,21] Siewert's classification is the most commonly used method, in which the esophagogastric junction is defined as the upper end of the typical longitudinal fold.[7,8] The definition of the esophagogastric junction determines the surgical procedures used; hence, this classification method is increasingly accepted worldwide.[23–25]

In contrast to findings in Western populations, we found that AEG type 3 tumors were much more

common than AEG type 1 and 2 tumors in Korea.[8] Although the reason for this difference is unclear, the prominence of type 3 tumors may reflect the characteristics of *Helicobacter pylori* infection. A persistently high level of *H. pylori* infection in the general adult population contributes to an increased prevalence of gastric cancer in Koreans. Although the prevalence of *H. pylori* infection has decreased from 66.9% in 1998 to 59.6% in 2005, it remains high.[25] The *cagA*$^{+}$ *H. pylori* strain has been isolated from more than 90% of Korean patients with *H. pylori* infections,[26] and this strain has been reported to protect against the development of AEG type 1 and 2 tumors.[27,28] The observed distribution of AEG types in Korean individuals was similar to findings in other Asian countries, in which the prevalence of *H. pylori* is also relatively high.[22,23]

Our study demonstrated differences in clinical characteristics relative to tumor stage at diagnosis, as well as showing the 5-year survival rates in patients with the three types of AEG. Patients with type 1 AEG tumors were less likely to have early-stage tumors and had a markedly poorer prognosis. In Western populations, however, patients with type 1 AEG tumors showed an increased frequency of early-stage cancers and a better survival rate compared with patients with type 2 or 3 AEG tumors.[8] The well-organized screening and surveillance programs for premalignant lesions, such as BE and dysplasia, in Western countries may account for these differences in clinical outcomes.[29,30]

This study had several limitations. Because it was not a population-based study, we could not determine the overall incidence of AEG. However, we can speculate on the trends of AEG because patients in our center comprised 7.3–8.0% of all cancer patients in Korea in 1998–2002.[31] Second, we could not identify the premalignant lesions (such as GERD, BE, and BE around tumors) responsible for all tumors, particularly in cohort A, owing to the long study period. Third, although we tried to classify AEGs based on agreement between the radiologist, endoscopist, and pathologist, there were some difficulties in classifying AEGs, particularly in cases of the early period or those with advanced tumors. In conclusion, the ratio of AEG has not increased over time in Korea. The distribution and prognosis of the three types of AEG tumors, as defined by Siewert's classification, differed from those in Western populations. Additional long-term investigations are required to confirm that the patterns of AEG are not changing in Asian populations.

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