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Three-year interval for endoscopic screening may reduce the mortality in patients with gastric cancer

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Abstract

Background Endoscopic screening has been adopted in South Korea for the national screening of gastric cancer (GC). This study aimed to assess the effect on overall survival of GC patients and determine the optimal endoscopic screening interval.

Methods The baseline characteristics and overall survival of GC patients treated at the National Cancer Center, Korea, between 2010 and 2016 were compared between those without a history of endoscopic evaluation (group N) and those in whom the interval between the last endoscopic evaluations and diagnosis of GC was ≤ 1, 1–2, 2–3, 3–4, or > 4 years (groups 1–5, respectively).

Results A total of 2362 patients met the criteria for the study (1060 in group N and 1302 in groups 1–5). More patients in groups 1–5 were diagnosed with stage I GC (83.7, 83.7, 71.8, 78.2, and 71.6%, respectively) than in group N (62.4%, $P < 0.001$) and were treated endoscopically (38.8, 33.8, 24.7, 21.8, and 15.5%, respectively, vs. 13.5%; $P < 0.001$). Group 2 had less-advanced tumor stages ($P = 0.001$) and was more likely to have received endoscopic treatments ($P = 0.026$) than group 3. Hazard ratios for death were significantly lower in groups 2 (0.45; 95% confidence interval [CI], 0.32–0.64) and 3 (0.57; 95% CI, 0.33–0.98) than in group N; the decrease was not significant in group 4 (0.49, 95% CI, 0.20–1.20).

Conclusions Endoscopic screening every 3 years may reduce the mortality of GC patients, though screenings at least every 2 years may benefit patients with less-advanced stages.

Keywords Endoscopic screening program · Overall survival · Gastric cancer · Screening

Despite a reported decline in incidence worldwide, 921,000 new cases of gastric cancer (GC) are reported each year, and it remains the third most common cause of cancer-related death [1]. The prevalence of GC is particularly high in East Asian countries, including Japan, China, and Korea [2–4]. In the latter, the age-standardized rate per 100,000 person-year is the highest at 41.8. Although the clinical outcome may be improved with early detection and timely treatment, patients are often not diagnosed until late stages when signs and symptoms become more apparent. To improve detection, Japan implemented a national screening program in 1983 with upper gastrointestinal series using barium meals [5], and Korea launched a National Cancer Screening Program (NCSP) in 1999 using upper gastrointestinal series or endoscopy every 2 years for individuals of at least 40 years of age in the general population [6].

Large-scale randomized controlled studies assessing the effect of endoscopic screening on GC mortality and the optimal interval for surveillance are difficult to conduct, although small case-controlled, cohort, and cross-sectional studies have provided some important data [7–9]. Several studies have examined the relationship between screening endoscopies and the stage of GC as a surrogate for clinical outcome [10–12], and others have suggested that endoscopic

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screenings performed every 2 years are beneficial and cost-effective [13–16]. However, more data are needed to clarify the reduction in mortality and determine the optimal interval for endoscopic surveillance. Thus, we utilized a patient registry that prospectively includes GC patients receiving endoscopic or surgical resection with curative intent to define the reduction in morality as a result of endoscopic screening and the optimal time interval for surveillance.

Materials and methods

Study design and participants

This study was approved by the institutional review board of the National Cancer Center, Goyang, South Korea (no. NCC2017-0151), and the requirement for patient consent was waived as the rights and welfare of the patients were not violated.

Between April 2010 and June 2016, a total of 3873 patients were diagnosed with GC and treated by endoscopic submucosal dissection (ESD) or surgical resection with curative intent. When the patients presented to the outpatient clinic, they were asked to complete a questionnaire from which information such as presenting symptoms, previous medical history, comorbidity, family history, smoking, and drinking history, whether they had received periodic endoscopic evaluations, and the timing of the last screening endoscopy was collected with their consent. Other data including baseline characteristics, treatment modality, and survival were collected retrospectively by reviewing electronic medical records. Patients were followed until June 2017.

Cases with sufficient information, including the final pathology with correct stage, were included in the study. Patients who had a history of previous endoscopic evaluation but did not specify the timing of the last evaluation and patients who reported that the last evaluation was more than 20 years ago were excluded from the final statistical analyses. Additionally, patients who reported that the last endoscopic evaluation was within 3 months prior to the diagnosis of GC were also excluded because of the possibility of repeated endoscopy for a lesion suspicious for GC or for symptoms associated with gastric cancer. Patients with a history of metachronous GC or another type of malignancy within 1 year of the GC diagnosis were also excluded from the study.

Diagnosis and treatment

Esophagogastroduodenoscopy (EGD) with biopsy was performed in all patients who visited an outpatient clinic for a possible diagnosis of GC. Upon confirmation of primary malignancy in the stomach through pathologic evaluation of the biopsy sample, further evaluations to assess staging and operability were performed via computed tomography (CT) of the abdomen and laboratory tests, including those for blood counts, chemistry, creatinine levels, and liver function. Endoscopic ultrasounds were performed in select cases to further delineate the depth of invasion in the stomach wall before deciding on the treatment strategy. In cases where metastases were suspected, CT of the chest and whole-body positron emission tomography were performed.

Endoscopic treatment was considered the first-line treatment for lesions that satisfied the expanded criteria proposed in a previous study [17], including differentiated-type mucosal cancers without ulceration or with ulcerations ≤ 3 cm in diameter. Surgical resection was primarily recommended for lesions with possible submucosal invasion or with confirmed undifferentiated histology; however, ESD was tried and further treatment was discussed with the patients in select cases, such as when the patient requested endoscopic treatment or there was a comorbidity that might increase the risk involved with the surgical procedure. Every specimen that was endoscopically resected was evaluated and mapped pathologically. For the lesions that did not meet the expanded criteria for ESD, additional surgical treatment was carried out [18] and the patients with these lesions were eventually considered to have been managed with surgery. Surgical resections were performed in all patients who presented with lesions that were unsuitable for endoscopic management.

Staging

Staging of GC was in accordance with the 7th edition of the tumor, node, and metastasis (TNM) staging system proposed by the American Joint Committee on Cancer [19]. The final pathologic staging was used in statistical analysis instead of the clinical or surgical staging. Early GC was defined as tumor confined in mucosa and submucosa layer regardless of lymph node involvement status.

Follow-up and outcome

Upon confirming the curative resection by pathologic evaluation after endoscopic treatment, patients were followed with EGD and biopsy of the scar lesion 3 and 6 months after ESD and annually thereafter. CT was performed annually for 5 years to identify possible recurrences at abdominal lymph nodes.

After surgical resection, patients were followed 6 and 12 months after surgery and annually for 5 years thereafter with EGD as well as with CT of the abdomen if the patients were not candidates for adjuvant chemotherapy. Adjuvant chemotherapy was administered if the final pathology

showed tumor invasion beyond the muscle (T3 or higher) or lymph node metastasis (N1 or higher), after which patients were followed every 6–12 months with EGD and CT for at least 5 years if possible.

The primary outcome of the study was overall survival, defined as the time from the diagnosis of GC until death from any cause. Surviving patients were censored at the date of their last follow-up.

Statistical analysis

The baseline characteristics of patients were compared according to their EGD history. Continuous variables are expressed as means ± standard deviations, and categorical variables are summarized as frequencies and percentages. The differences in the distributions of groups according to EGD history were tested using Student's *t* tests and Pearson's chi-squared method for each variable where appropriate. A logistic regression model was used to test whether stages and treatments (ordinal logistic regression and binary logistic regression, respectively) differed according to EGD history. An analysis of overall survival was performed using the Cox proportional hazard model, and the curves were plotted using the Kaplan–Meier method. Four baseline variables, including age, body mass index (BMI), sex, and family history, were considered in a multivariable analysis. The final multivariable model was determined using a backward variable selection method with an elimination criterion of $P > 0.05$. We utilized smoothing splines based on a penalized spline (p-spline) function and confirmed a U-shaped relationship between the hazard ratio (HR) of mortality and EGD history duration [20]. *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.0 statistical software.

Results

Baseline characteristics

Among the 3873 patients who were initially screened, 302 patients were excluded for various reasons: 115 patients with a prior history of GC, 119 patients did not have sufficient pathology data (including final stage), and 68 patients had invasive malignancy within 1 year of GC diagnosis. An additional 1049 patients were excluded that did not specify the timing of the last endoscopic evaluation before diagnosis or reported the last evaluation was more than 20 years ago. A further 160 patients in which the last endoscopy was within 3 months of the diagnosis were excluded, as it is likely that the last endoscopy was not conducted as a routine screening procedure. As a result, 2362 patients were included in final analyses (Fig. 1), including 1060 in the no EGD group (group N) and 1302 in the EGD groups, which were classified according to the length of time from the last endoscopy before the diagnosis of initial GC: group 1, ≤ 1 year; group 2, 1–2 years; group 3, 2–3 years; group 4, 3–4 years; group 5, 4–20 years.

The detailed baseline characteristics of all patients are shown in Table 1. Overall, the mean age of patients was 59.74 years, and the patients were predominately male (67.40%). Most patients did not have family history of GC, whereas 559 (23.66%) had family members who were diagnosed with GC. There were no significant differences in sex and family history between those who did not previously have endoscopic evaluations and those who underwent

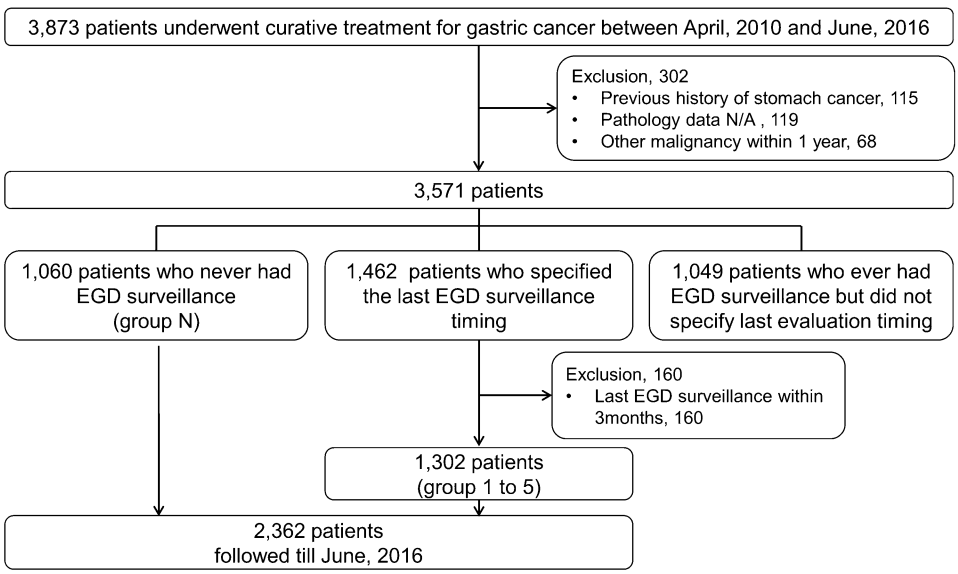

Fig. 1 Study design and patient selection

Table 1 Baseline characteristics

Variables	Total ($N=2362$)	EGD history		
		No ($n=1060$)	Yes ($n=1302$)	P
Age (years), mean ± SD	59.74 ± 12.00	58.91 ± 12.63	60.42 ± 11.43	0.0026*
BMI (kg/m^2), mean ± SD	23.81 ± 3.20	23.57 ± 3.19	24.01 ± 3.19	0.0009*
Sex, *n* (%)				
Male	1592 (67.40)	721 (68.02)	871 (66.90)	0.5629†
Female	770 (32.60)	339 (31.98)	431 (33.10)	
Family history, *n* (%)				
None	1449 (61.35)	657 (61.98)	792 (60.83)	0.0912†
Stomach cancer in 1st degree relative	485 (20.53)	196 (18.49)	289 (22.20)	
Stomach cancer beyond 1st degree relative	74 (3.13)	38 (3.58)	36 (2.76)	
History of other malignancy	354 (14.99)	169 (15.94)	185 (14.21)	
Curative treatment modality, *n* (%)				
Surgery	1825 (77.27)	917 (86.51)	908 (69.74)	< 0.0001†
ESD	537 (22.73)	143 (13.49)	394 (30.26)	
Adjuvant chemotherapy, *n* (%)				
No	1838 (77.82)	753 (71.04)	1085 (83.33)	< 0.0001†
Yes	524 (22.18)	307 (28.96)	217 (16.67)	
T stage, *n* (%)				
T1	1632 (70.80)	620 (60.61)	1012 (78.94)	< 0.0001†
T2	189 (8.20)	104 (10.17)	85 (6.63)	
T3	264 (11.45)	155 (15.15)	109 (8.50)	
T4	220 (9.54)	144 (14.08)	76 (5.93)	
N stage, *n* (%)				
N0	1745 (75.61)	686 (66.99)	1059 (82.48)	< 0.0001†
N1	203 (8.80)	109 (10.64)	94 (7.32)	
N2	166 (7.19)	99 (9.67)	67 (5.22)	
N3	194 (8.41)	130 (12.70)	64 (4.98)	
M stage, *n* (%)				
M0	2254 (95.43)	983 (92.74)	1271 (97.62)	< 0.0001†
M1	108 (4.57)	77 (7.26)	31 (2.38)	
Final stage, *n* (%)				
Stage I	1703 (72.10)	661 (62.36)	1042 (80.03)	< 0.0001†
Stage II	277 (11.73)	153 (14.43)	124 (9.52)	
Stage III	274 (11.60)	169 (15.94)	105 (8.06)	
Stage IV	108 (4.57)	77 (7.26)	31 (2.38)	

SD standard deviation, *BMI* body mass index, *ESD* endoscopic submucosal dissection

*Student's *t* test

†Pearson χ^2 test

endoscopic surveillance. Patients were followed for a median of 36.6 months (range 0.1–71.5 months).

Stage and treatment

The groups with histories of endoscopy (i.e., groups 1–5) had significantly higher proportions of patients with early GC than the group without a history (group N) (all P values < 0.05; Fig. 2A). Moreover, the distributions of patients with early and advanced GC differed between groups 2 and 3; no significant differences were observed between groups 1 and 2, 3, and 4 ($P=0.293$), and 4 and 5 ($P=0.121$). These findings were reflected in the final cancer stages, as significantly fewer patients in group N were diagnosed with stage I than in groups 1–5 ($P<0.001$; Fig. 2B). In addition, group 2 had significantly fewer patients with advanced tumor stages than group 3 ($P=0.001$), whereas no differences were observed between groups 1 and 2, 3, and 4 ($P=0.244$), and 4 and 5 ($P=0.281$).

Patients who had undergone EGD screening (groups 1–5) were more likely to have been treated with ESD than patients who never had an EGD evaluation (group N) (30.26

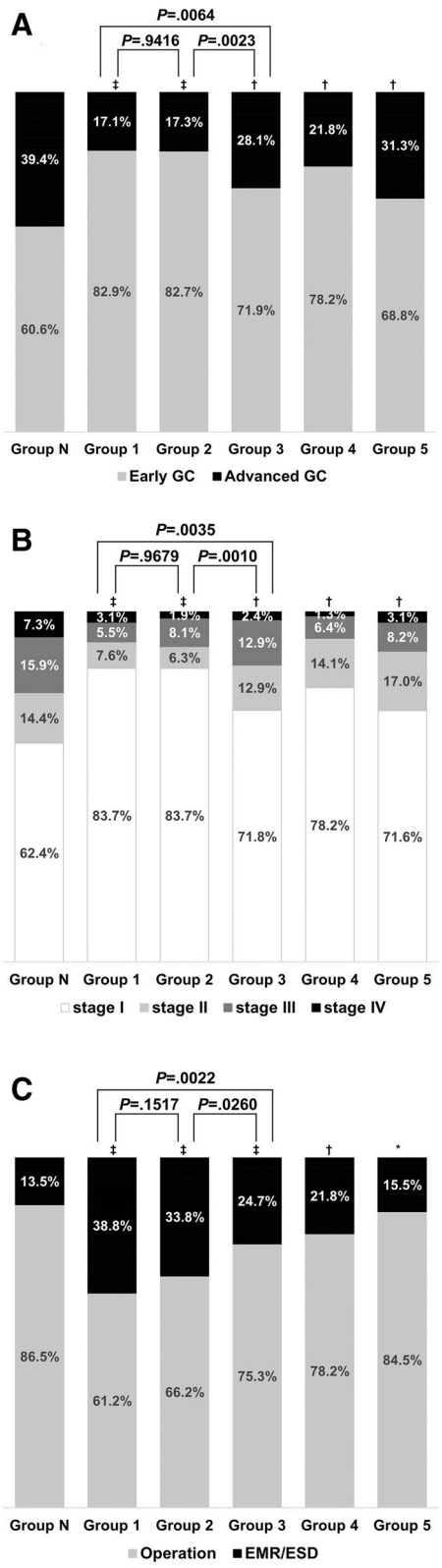

Fig. 2 Distributions of early and advanced gastric cancer (Early GC and Advanced GC, respectively) (**A**), tumor stages (**B**), and treatment modalities (**C**) according to surveillance history. *$P \geq 0.05$, †$P < 0.05$, ‡$P < 0.001$ for the difference between Group N and each group

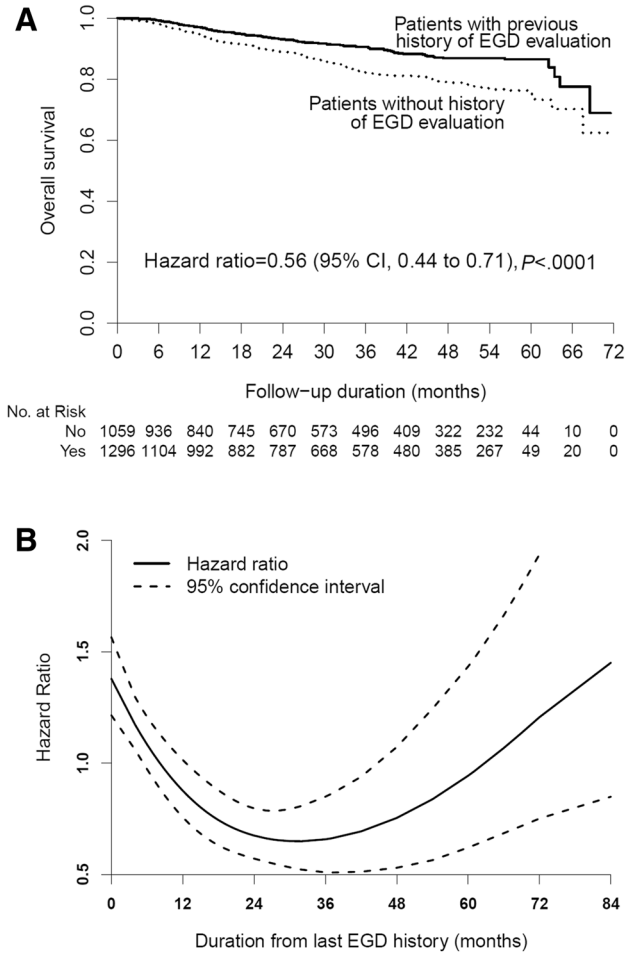

Fig. 3 Kaplan–Meier curves for overall survival according to EGD history (**A**) and U-shaped relationship of hazard rations and surveillance history obtained from spline analysis (**B**)

vs. 13.49%; $P < 0.001$). Moreover, the longer the interval between the endoscopy and GC diagnosis, the less likely the patients were to have been treated endoscopically, such that patients with interval of > 4 years between EGD and diagnosis underwent treatments similar to those with no screening (Fig. 2C). A significant difference was noted between groups 2 and 3 ($P = 0.026$) but not between groups 1 and 2, 3, and 4 ($P = 0.617$), and 4 and 5 ($P = 0.214$). In addition, more patients in group N underwent adjuvant chemotherapy after curative resection of GC (28.96 vs. 16.67%; $P < 0.001$) (Table 1).

Overall survival

The overall survival of patients who had a history of EGD evaluation (groups 1–5) was significantly higher than those who did not (group N) ($P < 0.001$; Fig. 3A). A univariable analysis revealed that a history of EGD evaluation, its interval, and patient age and BMI were significantly associated

with overall survival. After adjusting for age and BMI, the HR for death was recalculated using a multivariable Cox proportional hazard model. The risk for mortality was significantly decreased in patients who had received an EGD evaluation 1–3 years before their diagnosis (groups 2 and 3) with HR of 0.45 (95% confidence interval [CI] 0.32–0.64) and 0.57 (95% CI 0.33–0.98) compared with that in patients without a previous EGD evaluation. And it increased as the interval between the last EGD and the diagnosis of GC increased. However, there was no difference between those who were evaluated within 1 year of diagnosis and those who had not undergone surveillance (group 1 vs. group N: HR 0.75; 95% CI 0.51–1.11) (Table 2).

Using a spline analysis, the calculated HRs and CIs were plotted on the basis of the multivariable analysis to better illustrate the successive change in HR as the interval between the last EGD and the diagnosis increases. The spline analysis confirmed a U-shaped relationship between the interval and the risk for mortality, with the lowest mortality among the study participants at and interval of 32 months (HR 0.65; 95% CI 0.52–0.81) (Fig. 3B).

When the 1049 patients who were initially excluded from the analysis because of a lack of data regarding the timing of the last EGD evaluation were included in the survival analysis, the reduction in mortality was significant ($P = 0.009$) and the overall difference between those with and without surveillance remained significant ($P < 0.001$) (See Supplementary Table 1).

Discussion

In the current study, we evaluated the mortality, tumor staging, and treatment modality according to the interval of endoscopic screening in a single population from a registry of prospectively enrolled patients undergoing curative treatment for GC at the National Cancer Center, Korea. Our analyses revealed that the mortality was ~ 43–55% lower in patients that had endoscopic evaluations 1–3 years before their diagnosis of GC. Furthermore, we found that patients who had EGD evaluations within 2 years of their diagnosis had significantly lower pathologic stages of GC and were more likely to be managed endoscopically. This finding is of note, particularly because tumor stage is the most important factor affecting patient survival, and may be partly explained by the high 5-year overall survival rate in patients with early GC after surgical resection in Korea, which is over 95% [21]. The fact that the mortality was similar in patients in groups 2 and 3 despite the increased proportion of advanced cancer stages may be partly explained by the more frequent use

Table 2 Univariable and multivariable model using Cox proportional hazard model

Variables	Total ($N = 2362$)	Survivor ($n = 2079$)	Death ($n = 283$)	Univariable analysis		Multivariable analysis[a]	
				HR (95% CI)	*P*	HR (95% CI)	*P*
EGD history, *n* (%)							
No history (group N)	1,060	889 (83.87)	171 (16.13)	1 (Ref)		1 (Ref)	
≤1 year (group 1)	289	259 (89.62)	30 (10.38)	0.71 (0.48–1.05)	0.0853	0.75 (0.51–1.11)	0.1551
1–2 years (group 2)	571	531 (92.99)	40 (7.01)	0.45 (0.32–0.64)	< 0.0001	0.45 (0.32–0.64)	< 0.0001
2–3 years (group 3)	170	156 (91.76)	14 (8.24)	0.52 (0.30–0.90)	0.0191	0.57 (0.33–0.98)	0.0421
3–4 years (group 4)	78	73 (93.59)	5 (6.41)	0.41 (0.17–0.99)	0.0485	0.49 (0.20–1.20)	0.1189
4–20 years (group 5)	194	171 (88.14)	23 (11.86)	0.74 (0.48–1.15)	0.1767	0.73 (0.47–1.13)	0.1541
Age	2362	2079 (88.02)	283 (11.98)	1.04 (1.03–1.05)	< 0.0001	1.04 (1.03–1.05)	< 0.0001
BMI	2355	2073 (88.03)	282 (11.97)	0.87 (0.84–0.90)	< 0.0001	0.88 (0.85–0.91)	< 0.0001
Sex, *n* (%)							
Male	1592	1403 (88.13)	189 (11.87)	1 (Ref)			
Female	770	676 (87.79)	94 (12.21)	1.03 (0.81–1.32)	0.8042		
Family history, *n* (%)							
None	1449	1264 (87.23)	185 (12.77)	1 (Ref)			
Stomach cancer in 1st degree relative	485	434 (89.48)	51 (10.52)	0.77 (0.56–1.05)	0.0959		
Stomach cancer beyond 1st degree relative	74	66 (89.19)	8 (10.81)	0.82 (0.40–1.66)	0.5764		
History of other malignancy	354	315 (88.98)	39 (11.02)	0.83 (0.59–1.17)	0.2821		

HR hazard ratio, *CI* confidence interval, *Ref* reference

[a]Adjusted for age and BMI in 2355 patients with death observed in 282 patients

of curative surgical resection in these patients who are not candidates for endoscopic resection. However, further investigation is needed to explain this discrepancy.

To decide what time interval is optimal for GC screening, two aspects should be taken into account, namely, the reduction in mortality and the stage of disease, which may determine the curative treatment modality and thus influence the quality of life after treatment. A recent study of a Korean population that participated in the NCSP found a reduction in mortality even in patients with GC whose last surveillance was more than 4 years ago, with the lowest odds ratio at an interval of 12–23 months [22]. In addition, the authors reported a dose-dependent relationship between the number of screenings performed and the mortality reduction [22]. The results from another Korean study found a significantly lower mortality in patients whose last surveillance evaluations were within 2 years compared to those who never had an evaluation or had them more than 2 years ago [8]. Caution should be applied when basing an optimal screening interval on the results of these studies, as the Korean NCSP program had already incorporated a 2-year interval for GC screening. However, a case-controlled study from Japan reported a 30% mortality reduction with a surveillance period of 3 years or less [7]. The data from the present study suggest that a screening interval of 1–3 years can reduce mortality; a continuous spline analysis indicated that the lowest mortality was associated with an interval of 32 months.

Other studies have examined GC screening and cancer stage at the time of diagnosis. For example, a study including participants who had undergone endoscopy during a health checkup found that annual screening was associated with a higher proportion of patients diagnosed with early GC than biennial surveillance; however, this study only included several hundreds of GC patients [10]. In a cross-sectional study of patients who had surgical resection for GC, early GC was more frequently detected in those who had surveillance within 2 years than in those whose last endoscopies were more than 2 years ago, with no difference in the proportions of patients diagnosed with advanced GC [8]. Another study that analyzed consecutive patients at a single center found a benefit of detecting early GC when screening was performed at a 3-year interval [12]. A study based on Korean NCSP data showed that GC surveillance was significantly associated with an increased proportion of patients with localized disease according to categories suggested by Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review of the National Cancer Institute, even in those whose last screenings were more than 3 years ago [11]. The results from our study demonstrate that a higher proportion of patients receiving endoscopy within 4 years of diagnosis had early GC that was managed with endoscopic treatment after curative resection compared with those who did not undergo surveillance. On the basis of these results and those from previous studies, we can conclude that a surveillance interval of 3 years in the general population may reduce the mortality rate, with additional benefit provided in regard to the choice of treatment modality with a screening interval of 2 years or less.

There have been concerns regarding the quality of endoscopic screening in the NCSP when applied by physicians with various levels of experience to the general population. The evidence regarding quality indicators for endoscopic screening is lacking despite the clinical importance of false negativity and successive interval cancer [23, 24]. A recent study found that longer observation times are needed to improve the detection rate of neoplasms in the stomach [25]; however, specific directions as to how endoscopic screening should be performed are not provided by the NCSP. Additional studies evaluating quality indicators for EGD are needed to accurately determine the optimal interval for endoscopic screening.

There are several limitations of this study that should be noted. First, this study is not a randomized controlled study, and thus may include uncontrolled biases. The information regarding the histories of previous endoscopic evaluations and the intervals between the last endoscopies and the diagnoses was collected from patient questionnaires completed at the time of initial presentation. As a result, these data may be subject to recall and selection biases, as patients with long intervals are more likely to incorrectly report the timing of their last evaluation or not provide an answer. Indeed, of the 2511 patients who reported having a previous endoscopic evaluation, obscure data were obtained from 1049. Combined with the 160 patients who were excluded because of evaluations that occurred within 3 months of diagnosis, the high rate of exclusion (48.1%) may further increase the concern regarding the biases. However, when this patient population was included in the survival analysis, the reduction in mortality remained significant. Another potential source of bias was the small but significant differences in ages and BMIs between the groups. These differences may partly have been due to the fact that older individuals are likely to undergo endoscopic screening more frequently than younger patients [26]. Second, this study did not include patients who were treated with palliative chemotherapy after their initial diagnosis, which may explain the subtle reduction of mortality in patients with a screening interval of >4 years compared to those screened within 3–4 years. A previous study showed that patients who had not been screened or had longer screening intervals tended to have a distant stage of GC according to SEER staging [11]. Further investigation is needed to assess the influence these patients would have on the current findings. Lastly, we did not investigate the influence of other individual risk factors for developing GC, including *Helicobacter pylori* infection [27], smoking [28], and the presence of premalignant lesions such as atrophic

gastritis or intestinal metaplasia [29]. Surveillance endoscopy may be more beneficial in patients with these known risk factors. As for the family history, further analysis of current patient groups showed no significant difference in this distribution of family history according to EGD history (See Supplementary Table S2). However, further studies that stratify patients according to such risk factors would provide more detail regarding the suitable surveillance interval for each situation. Furthermore, the timing when to start endoscopic screening would be another important issue.

In conclusion, the results from this study show that endoscopic surveillance at an interval of 3 years may reduce the overall mortality in patients with GC. More frequent surveillance of every 2 years would provide greater benefit to patients with less-advanced stages of GC that can be managed with endoscopic treatment rather than surgical resection. These findings will be of value in building strategies for population and individual screening programs, particularly in regions with high GC incidence and mortality.

Author contributions SIC contributed to data acquisition, analysis and interpretation of data, and drafting of the manuscript; BP contributed to statistical analysis, interpretation of data, and drafting of the manuscript; JJ contributed to statistical analysis, interpretation of data, administrative support; Y-IK contributed to material support and critical revision of the manuscript for important intellectual content; JYL contributed to material support and critical revision of the manuscript for important intellectual content; CGK contributed to material support and critical revision of the manuscript for important intellectual content; IJC contributed to material support and critical revision of the manuscript for important intellectual content; M-CK contributed to material support and critical revision of the manuscript for important intellectual content; S-JC contributed to study concept and design, critical revision of the manuscript for important intellectual content, obtained funding, and study supervision.

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Compliance with ethical standards

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