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Does the interval of screening endoscopy affect survival in gastric cancer patients?

A cross-sectional study

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Abstract

Gastric cancer remains the second most common cancer in Korea; however, its mortality has decreased due to earlier diagnosis. In Korea, screening endoscopy has been performed nationwide since 1999. The aim of this study was to elucidate the benefit of screening endoscopy on actual survival in gastric cancer patients and to determine the optimal interval of screening endoscopy.

We analyzed 1651 patients diagnosed with gastric adenocarcinoma who underwent surgical treatment between June 2008 and December 2014. Patients were divided into 4 groups according to the interval of screening endoscopy prior to their gastric cancer diagnosis. (Group I = within 1 year, Group II = >1 but <2 years, Group III = more than 2 years, Group IV = no prior endoscopic examination). Patient demographics, clinicopathologic characteristics, and postoperative surgical outcomes including overall survival were compared.

The 5-year gastric cancer-specific survival rates of groups I and II were significantly higher than groups III and IV (90.9% vs 85.4%, $P = 0.002$, respectively). Multivariate analysis showed that screening interval was an independent factor for the diagnosis of advanced gastric cancer. The risk of advanced gastric cancer decreased in group I (odds ratio: 0.515, 95% confidence interval [CI] 0.369–0.719; $P < 0.001$) and group II (odds ratio: 0.678, 95% CI 0.517–0.889, $P = 0.005$).

Screening endoscopy was helpful in increasing the survival of gastric cancer patients. A 2-year endoscopic screening interval is suitable to detect early-stage gastric cancer.

Abbreviations: CI = confidence interval; UGIS = upper gastrointestinal series.

Keywords: endoscopy, esophagogastroduodenoscopy, gastric cancer, interval, screening, survival

1. Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide.[1] In Eastern Asia, including Korea and Japan, the prevalence of gastric cancer is high, and gastric cancer is the second most common cancer in Korea.[2,3] The mortality associated with gastric cancer has decreased as detection of early gastric cancer has increased. For resectable gastric cancer, the standard treatment has been radical gastrectomy with regional lymph node dissection.[4] Surgical resection of early gastric cancer results in an excellent prognosis with more than 90% 5-year survival rate.[3] In countries such as Korea and Japan where gastric cancer is a common malignancy, mass screening program have been established nationwide for early detection.[5]

In 1960, mass screening for gastric cancer via photofluorography (indirect upper gastrointestinal series [UGIS]) was introduced in Japan.[6] It has resulted in improvements of gastric cancer survival and cure rates.[7,8] In Korea, biennial UGIS or endoscopy has been recommended for people aged 40 years or older since the implementation of the National Cancer Screening Program in 1999.[9,10] Recently, endoscopy has become the preferred option over UGIS as the initial screening method for gastric cancer.[5,10,11] In previous reports, endoscopy showed higher detection rates of early gastric cancer compared with UGIS.[5,12–14]

In large populations with a high incidence of gastric cancer, endoscopic examination has been suggested as an appropriate and cost-effective screening method.[5,12,15–17] Despite the diagnostic advantages of endoscopy, it is unclear whether screening endoscopy will affect the survival of gastric cancer patients, as the evidence of actual survival benefit of screening endoscopy was limited.[11] We analyzed surgically treated gastric cancer patients at a tertiary hospital to assess the effect of screening endoscopy on surgical outcomes. The aim of this study was to elucidate the benefit of screening endoscopy on the survival of gastric cancer patients and to determine the optimal interval of screening endoscopy.

2. Methods

This study was conducted according to the principles of the Helsinki Declaration. All patients provided informed consent before surgery. As a retrospective analysis from our database, ethical approval was not necessary.

2.1. Patients and data collection

A total of 1724 patients were diagnosed with gastric adenocarcinoma and underwent surgical treatment by a single surgeon (JMB) between June 2008 and December 2014 at Samsung Medical Center. The surgeon prospectively collected data from patients on the interval of screening endoscopy using questionnaires. These data were analyzed retrospectively. Thirteen patients with remnant gastric cancer and 60 patients with incomplete medical records were excluded.

Patients were divided into 4 groups according to the interval of endoscopy prior to their gastric cancer diagnosis. Patients who had an endoscopy within a year prior to the diagnosis of gastric cancer were classified as group I. Patients with a screening interval of more than 1 year and <2 years prior to gastric cancer diagnosis were classified as group II. Patients who had a previous endoscopy more than 2 years prior to their diagnosis were classified as group III. Patients who were diagnosed with gastric cancer at the first endoscopy were classified into group IV.

Before operation, all patients were histologically confirmed to have gastric adenocarcinoma, and abdominal pelvic computed tomography with contrast was performed to evaluate distant metastasis. During the operation, the intra-abdominal cavity was explored under general anesthesia. Subtotal gastrectomy or total gastrectomy with D2 or more lymphadenectomy was performed based on Japanese gastric cancer treatment guidelines.[4]

Patient demographics, clinicopathologic characteristics, and postoperative surgical outcomes were compared and analyzed between groups. Pathologic tumor staging was based on the tumor node metastasis classification system of the American Joint Committee on Cancer/International Union Against Cancer, 7th Edition.[18]

All patients followed-up at 1, 3, and 6 months after the surgery and every 6 months thereafter. Overall survival was calculated as the interval from surgery to death, and loss to follow-up was censored. Surgical adverse events were classified by the Clavien-Dindo classification.[19]

2.2. Statistical methods and analysis

Continuous variables were reported as median with range. Continuous variables were compared using 1-way analysis of variance, and categorical variables were tested using the χ^2 test or Fisher exact test, as appropriate. Variables associated with P values <0.05 on univariate analysis were included in multivariate analysis. Multivariate analysis was performed using a logistic regression model with a stepwise backward elimination procedure. Risk factors included in the final model are presented as odds ratios with 95% confidence intervals (CIs).

Differences in patient survival between the groups were determined using the log-rank test and are presented as Kaplan–Meier curves. Cox regression analysis was performed to identify independent risk factors for patient overall survival.

All statistical analyses were executed using SAS 9.4 software (SAS Institute Inc, Cary, NC), and $P < 0.05$ was considered statistically significant.

3. Results

A total of 1651 patients were included in analysis. The median age was 56 years (range: 22–83 years), and 63.4% of the patients were male. Patient demographics and clinicopathological characteristics are shown in Table 1. More than half of the patients had no gastrointestinal symptoms upon diagnosis of gastric cancer. It was also found that younger patients (age ≤ 40 years) did not have regular screening endoscopies. In addition, it was shown that both tumor size and the proportion of patients with advanced gastric cancer increased in groups with longer endoscopic screening intervals. Additionally, there was no significant difference in lymph node metastasis or curative resection rates between groups. However, the distribution of stage differed among groups; the proportion of stage I patients in each group decreased as the screening interval increased. Surgical outcomes are shown in Table 2. Notably, the incidence rate of adverse events and the length of hospital stay were not significantly different among groups. There was no postoperative mortality in all groups.

3.1. Risk factors for advanced gastric cancer

According to univariate analysis, age, gender, and endoscopic screening interval were independent factors associated with the diagnosis of advanced gastric cancer. Multivariate analysis showed that age was an independent factor, which revealed that elder patients had more advanced disease. It was interesting that female patients had less advanced cases than male patients. It was evident that the risk of advanced gastric cancer was lower in group I (odds ratio: 0.515, CI: 0.369–0.719; $P < 0.001$) and group II (odds ratio: 0.678, CI: 0.517–0.889; $P = 0.005$) than in groups III and IV (Table 3, Fig. 1).

3.2. Recurrence and survival analysis

The median length of follow-up time was 52.8 months (range: 1–82.2 months). There was a significant difference in overall survival rates between groups I and II versus groups III and IV ($P = 0.012$) (Fig. 2A). The cumulative 5-year survival rate in the former groups was 87.3% compared with 83.0% in the latter. Gastric cancer-specific survival rates between groups I and II versus groups III and IV also showed statistically significant differences ($P = 0.002$) (Fig. 2B). The cumulative 5-year gastric cancer survival rate in the former groups was 90.9% compared with 85.4% in the latter.

Multivariate analysis using the Cox regression model showed a significant reduction in the hazard ratio in the groups screened within 2 years of gastric cancer diagnosis compared with the groups screened more than 2 years from the diagnosis (hazard ratio: 0.587, CI: 0.367–0.983; $P = 0.026$) (Table 4). However, there was no significant difference in survival rate between groups I and II (data not shown). Stage-adjusted overall survival rates were not significantly different among the 4 screening endoscopy interval groups (data not shown).

The gastric cancer recurrence rate of groups III and IV (8.4%) was higher than groups I and II (6.4%), although it was not statistically significant ($P = 0.076$, Table 5). Nevertheless, disease-free survival showed significant difference between groups I and II versus groups III and IV ($P = 0.045$, Fig. 2C).

4. Discussion

There have been many reports that have attempted to demonstrate the efficacy of screening endoscopy for gastric

Table 1

Clinicopathological characteristics of gastric cancer patient groups by screening endoscopy interval.

	Group I* (n = 239)	Group II† (n = 403)	Group III‡ (n = 458)	Group IV§ (n = 551)	P
Age, y	55 (23–79)	57 (30–82)	56.5 (26–83)	54 (22–82)	<0.001
<40	13 (5.4%)	21 (5.2%)	21 (4.6%)	75 (13.6%)	<0.001
Sex, M:F	166:73 (69.5%:30.5%)	230:173 (57.1%:42.9%)	299:159 (65.3%:34.7%)	353:198 (64.1%:35.9%)	0.009
Operation					0.515
B-I	65 (27.2%)	135 (33.3%)	128 (28.0%)	152 (27.6%)	
B-II	93 (38.9%)	144 (35.7%)	185 (40.4%)	213 (38.7%)	
TG	76 (31.8%)	116 (28.8%)	129 (28.2%)	168 (30.5%)	
O&C/bypass	5 (2.1%)	8 (2.0%)	16 (3.5%)	18 (3.3%)	
Symptoms‖					0.149
Yes	110 (46.0%)	175 (43.4%)	227 (49.6%)	236 (42.8%)	
No	129 (54.0%)	228 (56.6%)	231 (50.4%)	315 (57.2%)	
Tumor location					0.498
Lower	78 (32.6%)	161 (40.0%)	188 (41.0%)	226 (41.0%)	
Middle	105 (16.0%)	152 (37.7%)	177 (27.0%)	221 (40.1%)	
Upper	48 (17.0%)	75 (18.6%)	77 (27.2%)	83 (15.1%)	
Whole	8 (3.3%)	15 (3.7%)	16 (3.5%)	21 (3.8%)	
Differentiation					0.383
Differentiated	79 (33.1%)	157 (39.0%)	177 (38.6%)	198 (35.9%)	
Undifferentiated	160 (66.9%)	246 (61.0%)	281 (61.4%)	353 (64.1%)	
Tumor size, cm	2.7 (0.1–21)	3.0 (0.2–17)	3.25 (0.4–23)	3.7 (0.3–17)	<0.001
EGC vs AGC					<0.001
EGC	174 (72.8%)	273 (67.7%)	274 (59.8%)	322 (58.4%)	
AGC	65 (27.2%)	130 (32.3%)	184 (40.2%)	229 (41.6%)	
Lymph node metastasis					0.234
N0	22 (9.2%)	19 (4.7%)	35 (7.6%)	33 (6.0%)	
N+	217 (90.8%)	384 (95.3%)	423 (92.4%)	518 (94.0%)	
Stage					<0.001
I	177 (74.1%)	296 (73.4%)	304 (66.4%)	339 (61.5%)	
II	35 (14.6%)	54 (13.4%)	71 (15.5%)	87 (15.8%)	
III	19 (7.9%)	44 (10.9%)	63 (13.8%)	102 (18.5%)	
IV	7 (2.9%)	6 (1.5%)	17 (3.7%)	20 (3.6%)	
N/A	1 (0.4%)	3 (0.7%)	3 (0.7%)	3 (0.5%)	
Curative resection	231 (96.7%)	394 (97.8%)	438 (95.6%)	528 (95.8%)	0.118

AGC = advanced gastric cancer, B-I = Billroth I, B-II = Billroth II, EGC = early gastric cancer, N/A = not available due to unresectable cancer without seeding N+ = positive lymph node metastasis, N0 = no lymph node metastasis, O&C = open and close, TG = total gastrectomy.

* Previous screening endoscopy within 1 y.
† Previous screening endoscopy more than 1 y prior but within 2 y.
‡ Previous screening endoscopy more than 2 y.
§ No previous screening endoscopy.
‖ Gastrointestinal symptoms.

cancer in high prevalence countries such as Korea and Japan. Reports have suggested that endoscopic surveillance was associated with early detection of gastric cancer.[13,20,21] Since the stage of gastric cancer has been well correlated with survival,[18,22] it is assumed that screening endoscopy may improve gastric cancer prognosis. Randomized controlled trials are the most reliable method for evaluating the impact of screening on cancer survival; however, such trials are neither

Table 2

Surgical outcomes of gastric cancer patient groups by screening endoscopy interval.

	Group I* (n = 239)	Group II† (n = 403)	Group III‡ (n = 458)	Group IV§ (n = 551)	P
Adverse events					0.467
No	227 (95.0%)	387 (96.0%)	429 (93.7%)	524 (95.1%)	
Yes	12 (5.0%)	16 (4.0%)	29 (6.3%)	27 (4.9%)	
Clavien-Dindo classification					0.106
I	2 (0.8%)	2 (0.5%)	12 (3.0%)	7 (1.3%)	
II	7 (2.9%)	12 (3.0%)	9 (2.0%)	9 (1.6%)	
IIIa	2 (0.8%)	0	5 (1.1%)	7 (1.3%)	
IIIb	1 (0.4%)	2 (0.5%)	3 (0.7%)	4 (0.7%)	
Hospital stay, d	8 (6–90)	8 (6–46)	8 (3–46)	9 (5–46)	0.246

* Previous screening endoscopy within 1 y.
† Previous screening endoscopy more than 1 y prior but within 2 y.
‡ Previous screening endoscopy more than 2 y.
§ No previous screening endoscopy.

Table 3

Multivariate analysis of factors associated with the diagnosis of advanced gastric cancer.

	Odds ratio	95% CI	P
Age, y			
<65	1		
≥65	1.472	1.175–1.843	<0.001
Sex			
Male	1		
Female	0.805	0.650–0.997	0.046
Previous screening endoscopy			
None (Group IV)	1		
>2 y (Group III)	0.933	0.723–1.204	0.593
>1 and ≤2 y (Group II)	0.678	0.517–0.889	0.005
≤1 y (Group I)	0.515	0.369–0.719	<0.001

CI = confidence interval.

feasible nor ethical. In addition, the number of detected cancers in large screening cohorts was relatively small and typically insufficient for survival analysis.[16,20,21] Based on a survey of the existing literature, to the best of our knowledge, our study included the largest number of gastric cancer patients on survival analysis according to screening interval.

It is important to determine the optimal endoscopic interval for mass screening because it is related with both patient prognosis and financial cost. There have been several reports on the cost-effectiveness of screening endoscopy in Korea.[9,23] Chang et al[24] reported that from age 50 to 80 years, the most cost-effective strategy in men was annual endoscopy, and in women was biennial endoscopy. However, as the cost and feasibility of endoscopy varies according to country, the application of these suggestions to other countries will be very limited. In the present study, we analyzed the actual survival of surgically treated gastric cancer patients, which could influence on decisions for the optimal screening interval.

It was found that the proportion of gastric cancer patients under 40 years old was twice as high in group IV compared with the other groups, because these young gastric cancer patients were not included in the nationwide guidelines for screening endoscopy. These patients often have poor histologic differentiation, and the detection of cancer can be delayed, resulting in more advanced stage at presentation.[25,26] In particular, the linitis plastica type of gastric cancer is known to be very difficult to be diagnosed in its early stage by endoscopic examination.[27] Since the incidence of gastric cancer is low in young patients, expanding a nationwide mass screening program to include this younger population would be not cost-effective.[28] Further study is needed to propose tailored screening guidelines for this population. It was interesting that female patients showed less advanced cases, but the overall survival rates of female patients was not different from that of male patients, which suggested that female patients had poorer prognoses than male patients. It is possible that hormonal effects and/or accompanying diseases may induce this difference; however, further evidence is needed.

It was also an interesting finding that there was no significant difference in lymph node metastasis or curative resection rates among the screening interval groups, although both tumor size and the proportion of patients with advanced gastric cancer increased in groups with longer endoscopic screening interval. It was deduced that there should be a difference in depth of tumor invasion because staging was decided by combination of the depth of tumor invasion and the status of lymph node metastasis. It implies that endoscopic findings could effectively detect

differences in the depth of tumor invasion and size of tumor, suggesting that endoscopy was an efficient method for screening.

Age was an independent factor for the diagnosis of advanced disease and overall survival rates by multivariate analysis. Patients over 65 years old showed more advanced cases and lower overall survival rates, which suggested that people over 65 years of age may face difficulties in completing a screening endoscopy, possibly due to disability, accompanying diseases, or unwillingness. It may be inevitable to modify the screening guideline recommendations according to age.

In the present study, it was found that the risk of diagnosing advanced gastric cancer was reduced when screening endoscopy was performed at 1- to 2-year intervals, which was consistent with previous reports suggesting that 1- to 3-year endoscopic screening intervals might help detect early-stage gastric cancer.[15,16,20,29–31] According to our results, stage-adjusted overall survival rates were not significantly different among the screening interval groups. Thus, these results may suggest that the survival benefit of screening endoscopy was achieved by the early detection of gastric cancer.
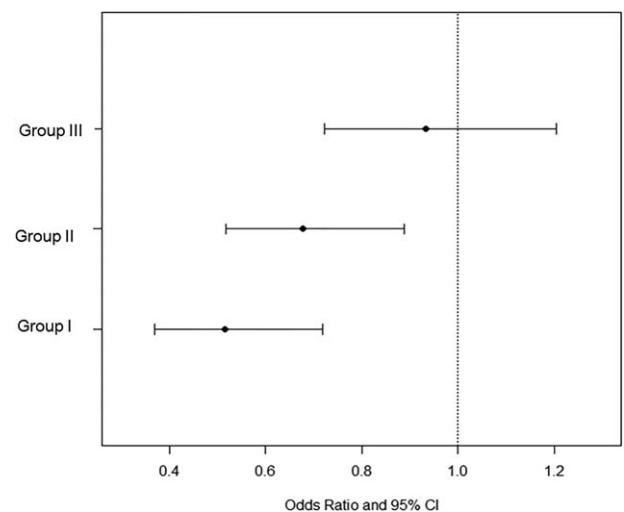

Figure 1. Risk of advanced gastric cancer between groups compared with group IV. Group I: Previous screening endoscopy within 1 year. Group II: Previous screening endoscopy more than 1 year prior but within 2 years. Group III: Previous screening endoscopy more than 2 years. Group IV: No previous screening endoscopy (Reference).
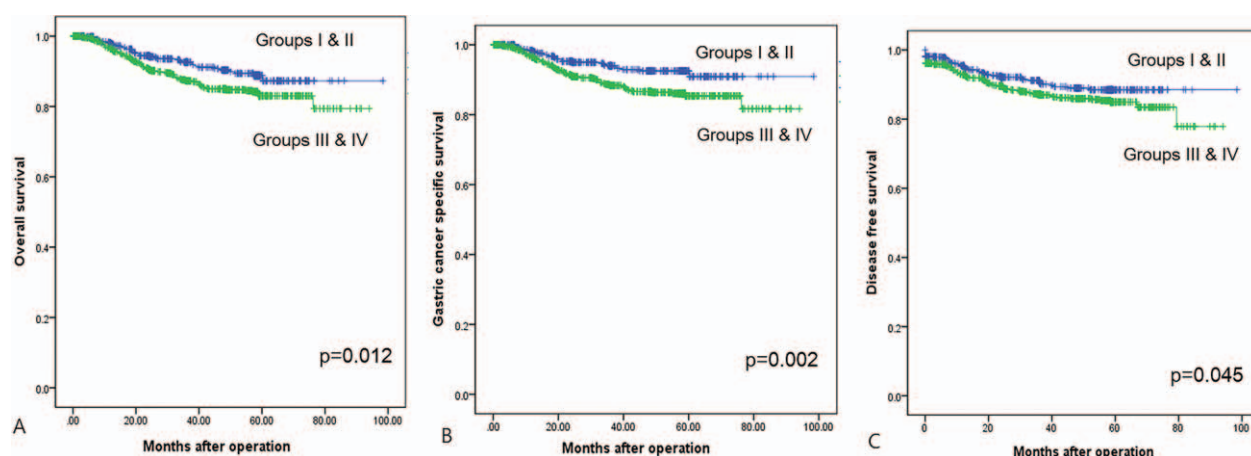
Figure 2. (A) Overall survival rates according to screening interval. (B) Gastric cancer-specific survival rates according to screening interval. (C) Disease-free survival rates according to screening interval. Group I: Previous screening endoscopy within 1 year. Group II: Previous screening endoscopy more than 1 year prior but within 2 years. Group III: Previous screening endoscopy more than 2 years. Group IV: No previous screening endoscopy.

Table 4

Multivariate analysis for the overall survival of gastric cancer patient groups.

	Hazard ratio	95% CI	P
Age	1.034	1.015–1.053	<0.001
Sex			
Male	1		
Female	0.949	0.624–1.443	0.806
Screening interval			
>2 y (Groups III and IV)	1		
≤2 y (Groups I and II)	0.587	0.367–0.983	0.026

CI = confidence interval.

Table 5

Pattern of recurrence according to of gastric cancer patient groups by screening endoscopy interval.

	Groups I and II (n=642)	Groups III and IV (n=1009)	P
Recurrence rate	41 (6.4%)	85 (8.4%)	0.076
Pattern of recurrence			
Locoregional recurrence[*]	10 (1.5%)	14 (1.3%)	0.940
Distant metastasis[†]	32 (5.1%)	77 (7.6%)	0.030

Because proportion of patients had both locoregional and distant recurrences, the total number of recurrence is greater than the number of patients who had gastric cancer recurrence.
[*] Anastomosis site, perigastric lymph nodes.
[†] Peritoneal seeding, extra-abdominal metastasis, paraaortic lymph nodes.

The recurrence rate in this study did not show significant difference according to screening interval group. However, the disease-free survival showed significant difference between groups I and II versus groups III and IV. It was found that there were more stage IV patients or noncurative cases in groups III and IV, which might affect gastric cancer-specific survival rates but not the recurrence rates.

In Korea, the screening guideline for gastric cancer recommends to get screening endoscopy or UGIS biennially for adults age 40 or older even if there is no symptom or sign. In addition, it would be very important to try to find out who, how, and where it was performed endoscopy screening or diagnostic endoscopy. Since the quality of endoscopy screening is a very important in the early diagnosis of these lesions. Briefly, about 80% of our

patients had previous screening endoscopy at primary clinics and about 20% of patients had screening endoscopy at secondary or tertiary hospitals. The qualification of endoscopists is one of the essential parameters to improve endoscopy quality. Endoscopy specialists are, however, relatively small to meet the nationwide volume of screening endoscopy.[32] Further study regarding the quality of endoscopy which effects on the sensitivity of screening endoscopy may be needed.

There are some limitations to the present study. First, our assessment of the screening interval prior to the diagnosis of gastric cancer was based on questionnaires completed by patients at the outpatient clinic. However, a single surgeon interviewed all the patients, which minimized variation between interviewers. Another limitation is that gastric cancer patients treated with

endoscopic resection were not included in this study. Considering that most mucosal cancers treated with endoscopic resection are likely to be stage IA with an excellent prognosis,[33] the effect on overall survival would not be so significant. Chung et al[20] also suggested that the annual endoscopic screening would aid in the detection of small, endoscopically treatable gastric cancers. Besides tumor size, differentiation is another factor that determines the appropriateness of endoscopic resection.[4,34] Further studies are needed to evaluate whether frequent screening endoscopy will reduce the need for gastrectomy.

In conclusion, it was found that screening endoscopy improved survival in gastric cancer patients. In addition, the risk for an advanced gastric cancer diagnosis decreased with shorter screening intervals. Screening endoscopic examinations within 2-year intervals is highly recommended to detect gastric cancer in the early stages.

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