What Is Appropriate Upper Endoscopic Interval Among Dyspeptic Patients With Previously Normal Endoscopy? A Multicenter Study With Bayesian Change Point Analysis

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Background/Aims

Appropriate interval for performing follow-up endoscopy among dyspeptic patients without abnormal findings on previous endoscopy is unclear. We analyzed the multicenter-collected data from the Korean Society of Neurogastroenterology and Motility.

Methods

We collected clinical data of the patients who visited the gastroenterology department and underwent 2 or more sessions of upper endoscopy during 2012-2017 at 6 university hospitals in Korea. Patients with endoscopic interval between 90 days and 760 days were included. For those with multiple endoscopic sessions, only the first 2 were analyzed. Positive outcome was defined as adenoma or cancer in the upper gastrointestinal tract. To identify the point of change and estimate the properties of the stochastic process before and after the change, we used Bayesian regression with Metropolis-Hastings algorithm.

Results

There were 1595 patients. Mean age was 58.8 years (standard deviation, 12.8). Median interval of endoscopy was 437 days (standard deviation, 153). On follow-up endoscopy, there were 12 patients (0.75%) who had neoplasia (4 with gastric cancer and 8 with gastric adnoma). As with the prior hypothesis, we presumed the change point (CP) of increase in frequency of organic lesion as 360 days. After random-walk Metropolis-Hastings sampling with Markov-Chain Monte Carlo iterations of 5000, the CP was 560 days (95% credible interval, 139-724). Estimated average of frequency of dysplastic lesions increased by a factor of 4.4 after the estimated CP.

Conclusion

To rule out dysplastic lesions among dyspeptic patients who had previously normal endoscopy, a 2-year interval could be offered as follow-up interval for repeat upper endoscopy.
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Key Words

Bayes theorem; Dyspepsia; Gastroscopy; Interval; Stomach neoplasms

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Introduction

Functional dyspepsia is one of the most common gastrointestinal problems causing both clinical and economic burden. Patients often seek for repeated medical evaluation in short periods. Although most of the dyspeptic patients who receive repeat upper gastrointestinal (GI) endoscopy before the recommended interval show normal or non-malignant findings, there are sporadic cases of malignant or premalignant lesions. The European consensus on "Management of precancerous conditions and lesions in the stomach" (MAPS guideline) has suggested an interval of 3 years for screening upper endoscopy.[1,2] This 3-year interval strategy has been shown more recently to be cost-effective as a surveillance strategy, in a European population between 50 and 75 years of age.[3] In countries where upper GI malignancies are more prevalent as in Asia, screening interval of 2 years has been advocated,[4,5] and is currently being carried out by national gastric cancer screening programs in Korea[6] and in Japan.[7] Repeated endoscopic evaluations among dyspeptic patients before the recommended screening intervals are not always necessarily directed against detection of malignancies, and inflammatory conditions such as peptic ulcer or reflux esophagitis that require medical therapy can be detected. However, detection of malignant or premalignant lesions at an earlier stage, rather than detection of non-malignant conditions such as benign peptic ulcer or reflux esophagitis, seems to be the main reason for the repeated endoscopy, in order to achieve a curative treatment. Currently, there have been recommendations for starting upper endoscopic evaluations for dyspeptic patients,[8,9] but studies to elucidate optimal endoscopic interval for dyspeptic patients after the initial evaluation are scarce.

The time point at which the frequency of neoplastic lesions starts to increase can be viewed as a change-point problem, which is one of the important problems of statistical inference in which one tries to detect abrupt change in a given sequence of random variables. Whereas classical frequentist methods are not quite satisfactory and put stringent restrictions in order to obtain asymptotic normality, the Bayesian approach on the other hand avoids asymptotics and provide more reliable inference conditional only upon the data actually observed.[10-12]

We analyzed the multicenter-collected data from the Korean Society of Neurogastroenterology and Motility.

Materials and Methods

Data Collection and Definitions

We retrospectively collected the clinical data of dyspeptic patients who visited the gastroenterology clinic and underwent 2 or more sessions of upper endoscopy during 2012-2017 at 6 university hospitals in Korea (Table 1). In each hospital, patients were randomly sorted before being selected for analysis. In cases where 3 or more sessions of endoscopy were performed, we only used the data from the first 2 sessions after 2012, referred to esophagogastroduodenoscopy 1 (EGD1) and esophagogastroduodenoscopy 2 (EGD2), respectively. Patients who had abnormal findings on the the first endoscopy since 2012 (EGD1) were excluded. An abnormal finding at the first endoscopy was defined as peptic ulcer, reflux esophagitis, subepithelial tumor, malignant-/premalignant-lesions, and polyps. Patients who had EGD1 to EGD2 interval < 90 days or > 760 days were also excluded. Positive outcome was defined as adenoma or cancer in the upper GI tract at the second endoscopy session (EGD2). We also collected other clinical data including gender, age, number of previous EGD sessions before 2012, EGD interval between the previous EGD before 2012 and the first EGD after 2012, presence of intestinal metaplasia, and hemoglobin lev-

Table 1. Baseline Characteristics of the Patients

Variable	Mean (range [min-max]) or n (%)
Hospitals	
Ilsan Paik Inje University	658 (41.25)
Daegu Catholic University	259 (16.24)
Asan Medical Center	191 (11.97)
Ewha University	187 (11.72)
Cheonan Dankook University	185 (11.60)
Gangneung Asan Medical Center	115 (7.21)
Gender (male)	845 (52.98)
Serum albumin (g/dL)[a]	4.3 (2.2-6.8)
Hemoglobin (g/dL)[b]	13.6 (6.5-19.1)
Age (yr)	58.8 (20.0-90.0)
Number of previous EGDs	1.72 (1-7)
EGD interval (day)	437.2 (90-757)
Previous EGD interval (day)[c]	520.1 (182-2281)
Previous EGD showed intestinal metaplasia	454 (28.46)

[a]Among 753 patients who were checked for serum albumin level.
[b]Among 954 patients who were checked for hemoglobin level.
[c]Among 771 patients who had underwent 2 or more previous esophagogastroduodenoscopy (EGD) sessions.

els. This study was approved by the institutional review boards in each participating hospital (IRB numbers are as follows; 2016-02-020-001 [Inje University Ilsan Paik Hospital], 2016-0043 [Asan Medical Center], 2017-04-036 [Ewha University Hospital], 2017-07-015 [Gangneung Asan Medical Center], CR-17-082 [Daegu Catholic University Hospital], and 2019-09-015 [Cheon-an Dankook University]).

Statistical Methods

We aim to identify the interval between EGD1 and EGD2 where the frequency of positive outcome started to rise. To identify the point of change and estimate the properties of the stochastic process before and after the change, we used the Bayesian regression with Metropolis-Hastings (MH) algorithm. The Bayesian module implemented in Stata 15.1 (StataCorp, College Station, Texas, USA) was used. Frequency of organic lesion on final endoscopy was assumed to show Poisson distribution. As the prior hypothesis, we assumed the point of change would be 360 days, and that the change point (CP) would be uniformly distributed between 90 and 760 days. We estimated the CP, as well as average of frequencies of dysplastic lesions before (mu1) and after (mu2) the CP. The size of Markov-Chain Monte Carlo (MCMC) iterations was set as 5000. For diagnostics of the Bayesian analysis, we analyzed the trace plot of the iterations, histogram of the estimated CP, autocorrelation plot of iterations to show a decrease of autocorrelation between the iterations, and the density plot comparing the first and the second half of the iterations.

To maximize the efficiency of the simulation and to decrease the autocorrelation between the iterations, we employed thinning of the chain by a factor of 3, ie, we discarded every 2 sample observations, thereby using only observations 1, 4, 7, and so on. We also used a long burn-in period of 10 000, and the maximum number of adaptive iterations of the MCMC procedure was set to be 50.

Results

Baseline Characteristics

There were 1595 patients including 845 (53.0 %) males who had no significantly abnormal findings on previous endoscopy (Table 1). Mean age was 58.8 years (standard deviation, 12.8). Mean interval of endoscopy was 437 days (standard deviation, 153). Mean total number of previous endoscopic sessions was 1.7 (range, 1-7).

Outcome

At EGD2, there were 12 patients (0.75%) who had upper gastrointestinal dysplastic lesions, including 4 patients with gastric cancer and 8 with gastric adenoma (Table 2). We calculated bimonthly frequency of organic lesion, as shown in Figure 1A. Frequency of EGD intervals is shown in Figure 1B.

Bayesian Change Point Analysis

As the prior hypothesis, we presumed that the CP in the interval of EGD showing an abrupt increase in the frequency of organic lesion would be 360 days. Our initial analysis showed a CP of 542.2 days (95% credible interval [CI] 143.9-728.6; Monte Carlo standard error [MCSE], 30.6), but high autocorrelation among the iterations (Supplementary Fig. 1) and wide 95% CIimplemented that the sampling algorithm was not efficient. We increased the burn-in period from 2500 to 10 000, and applied to thin of the chain from 1 to 3, discarding every 2 sample observations and only using observations 1, 4, 7, and so on. The scatterplots among the estimated parameters (Supplementary Fig. 2) revealed a high correlation between CP, mu1, and mu2. To increase the sampling efficiency, we treated the parameters in each separated blocks.

After refining the sampling and analytic methods, the analysis showed a CP of 559.9 days (95% CI, 139.1-724.6; MCSE, 13.7). Bayesian diagnostic plots are shown on Figure 2, which shows de-

Table 2. Patients With Abnormal Results on Follow-up Upper Endoscopy

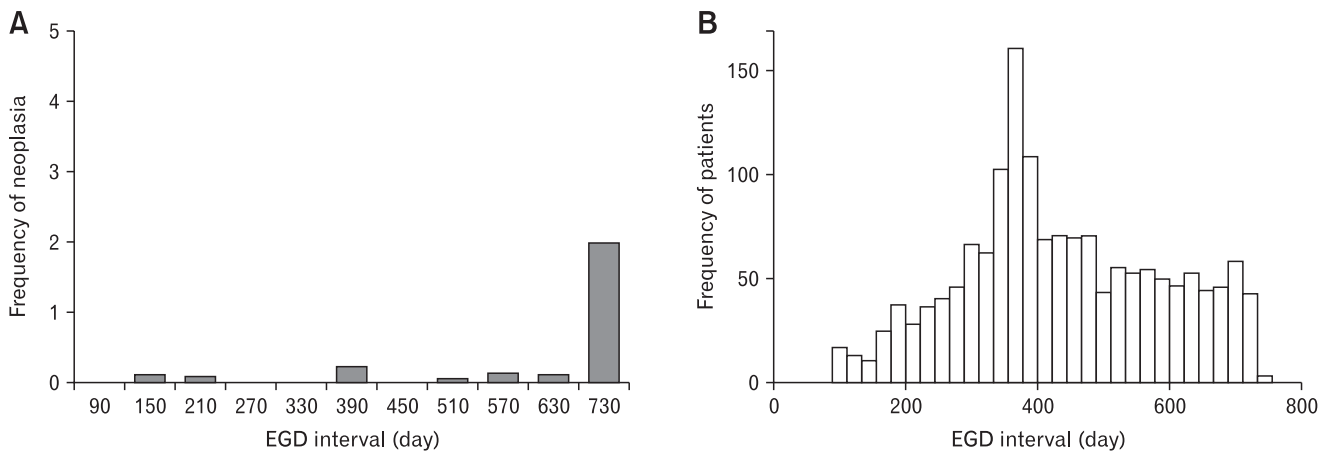| Results of follow-up endoscopy		No. of patients	Location and size	Endoscopic interval
Adenoma	Low grade dysplasia	8		Median 498 day (range, 266-750)
Gastric cancer	Early gastric cancer	3	Mid body posterior wall (12 mm)	432 day
			Low body anterior wall (9 mm)	611 day
			Low body greater curvature (10 mm)	710 day
	Advanced gastric cancer	1	Whole stomach (Borrmann type IV)	162 day

Figure 1. Frequency of upper gastrointestinal neoplasia and histogram of esophagogastroduodenoscopy (EGD) intervals. (A) Frequency of upper gastrointestinal neoplasia are shown in 2-month intervals. (B) Histogram of follow-up intervals.
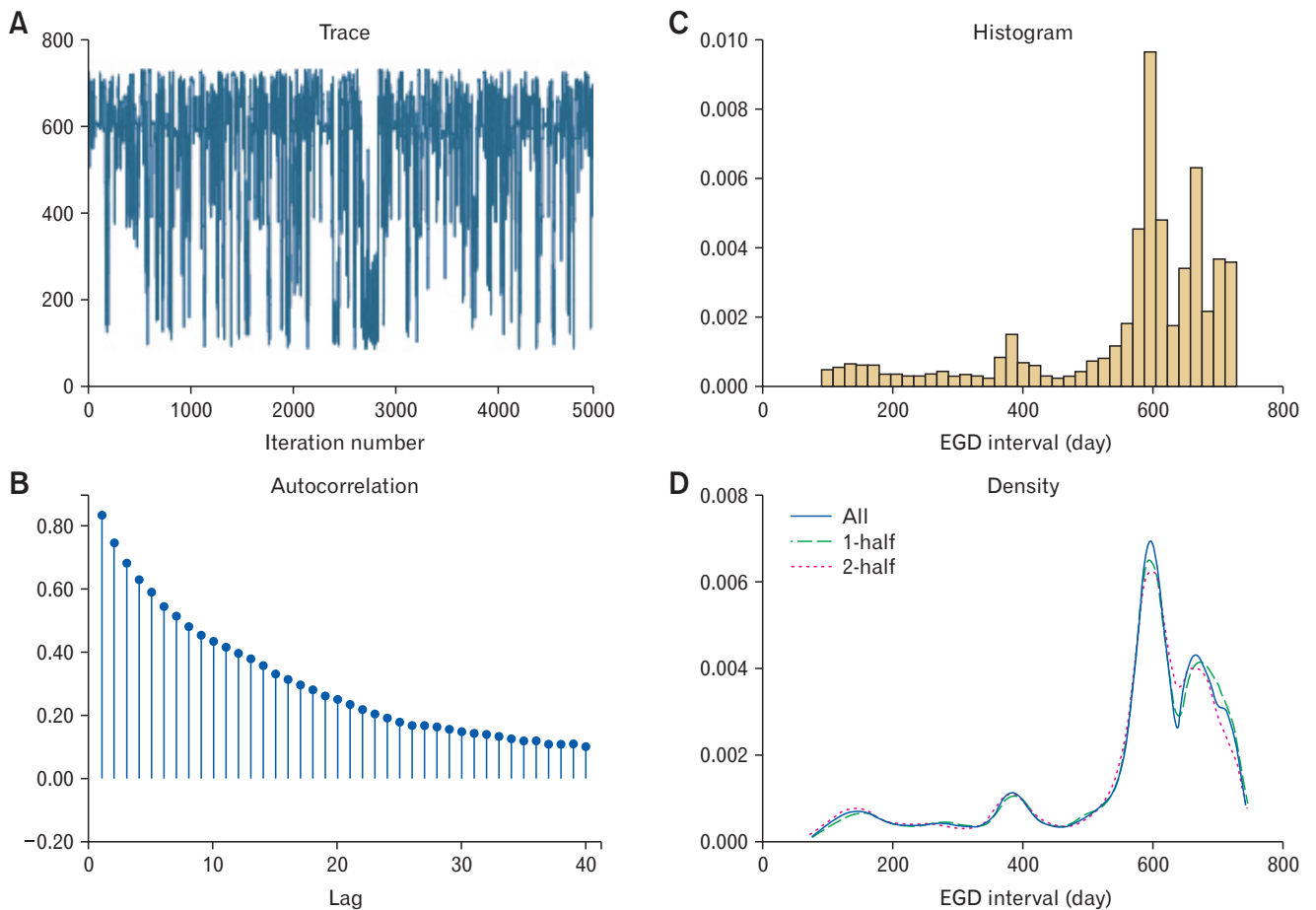

Figure 2. Diagnostic plots of change point (CP) analysis to estimate the time point with increase in dysplasia on follow-up endoscopy. CP analysis using random-walk Metropolis-Hastings sampling with Markov Chain Monte Carlo (MCMC) iterations of 5000, the CP was 560 days. The trace plot is shown at (A), with decreasing autocorrelation between the iterations shown at (B). Overall estimated histogram for frequency of upper gastrointestinal neoplasia is shown at (C). The density plots between the first and the second halves of the trace (D) show similar results. EGD, esophagogastroduodenoscopy.
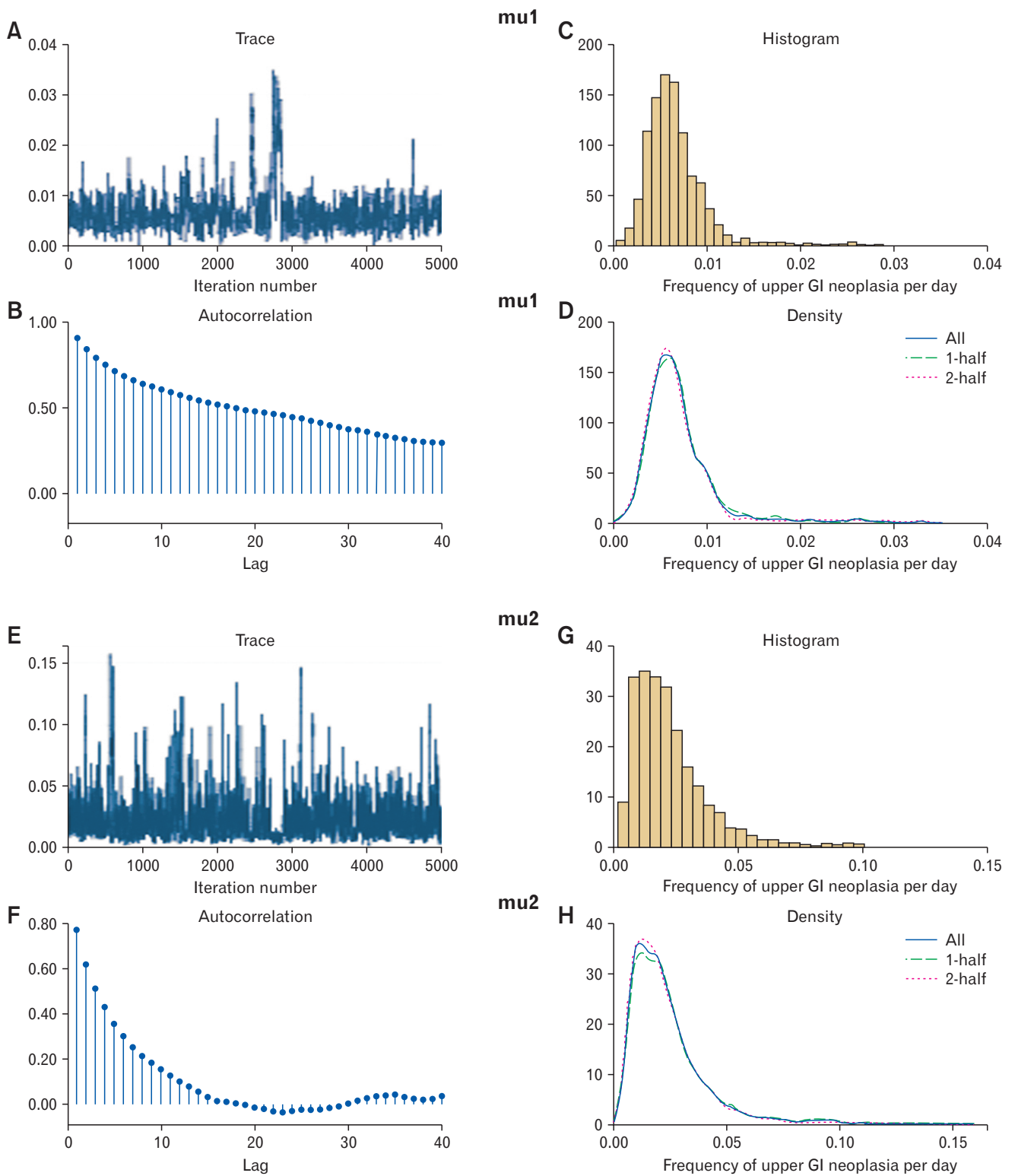
Figure 3. Diagnostic plots for estimated mean frequency of dysplastic lesions before (mu1) and after (mu2) the change point. For each estimated mu1 and mu2, the trace plot is shown at (A, E), with decreasing autocorrelation between the iterations shown at (B, F). Overall estimated histogram for frequency of upper gastrointestinal (GI) neoplasia is shown at (C, G). The density plots between the first and the second halves of the trace (D, H) show similar results.

creased autocorrelation among the iterations. There was an increase in the frequency of dysplastic lesions from an estimated average of 0.007 (95% CI, 0.002-0.021) cases per day before day 560, to 0.024 (95% CI, 0.006-0.073) cases per day after day 560. After day 560, the mean frequency increased by a factor of 4.4 (95% CI, 0.4-13.8). The Bayesian diagnostic plots for the estimated mean frequency of dysplastic lesions are shown in Figure 3.

Discussion

According to our Bayesian CP analysis, the time point, where upper GI neoplasia started to increase among dyspeptic patients who had no organic cause on previous endoscopy, was 560 days since the first endoscopy. Therefore, in order to screen for upper GI neoplasia among dyspeptic patients, a 2-year interval could be offered as a follow-up interval for repeat upper endoscopy. To the best of our knowledge, this is the first study to address this issue.

Efficiency describes the mixing properties of the Markov chain. High efficiency means good mixing (low autocorrelation) in the MCMC sample, and low efficiency means bad mixing (high autocorrelation) in the MCMC sample.[13] Our initial analysis showed high autocorrelation, and we refined our analysis by several methods. First, we improved the efficiency of the MH algorithm by blocking the model parameters. By default, all parameters are used as one block and their covariance matrix is used to adapt the proposal distribution. With many parameters, estimation of the covariance matrix becomes difficult and imprecise, and may lead to the loss of efficiency of the MH algorithm.[13] For optimal blocking, correlated parameters should be specified together. Supplementary Figure 2 shows the scatterplots between our model parameters, which reveal a high correlation between cp and mu1 and also between cp and mu2. On the other hand, there is no significant correlation between mu1 and mu2. We therefore blocked cp separately from mu1 and mu2 for increased sampling efficiency. Second, we applied thinning of the chain from 1 (including every observation) to 3 (discarding every 2 sample observations and only using observations 1, 4, 7, etc) for better mixing.[13] We also increased the burn-in period from 2500 to 10 000, which means the first 10 000 iterations of the MCMC sampler were discarded, in order for the Markov chain to reach its stationary distribution more efficiently.[13] Third, the maximum number of adaptive iterations of the MCMC procedure was adjusted from 25 to 50.

After we refined the sampling and analytic methods, the autocorrelation decreased markedly as shown on the diagnosis plots. The MCSE of estimated CP also decreased from 12.06 to 0.69 with much narrower 95% CI, which show that the estimated CP is much more accurate in the estimation of the posterior mean of cp.

The analytic methods for the Bayesian change-point analysis using MCMC sampling are well described for both statistical software packages R, SAS, and Stata.[14-18] With modern computational powers, the Bayesian analysis offers a practical way to accurately estimate the point of change.

There are limitations in this study. First, this study included data by retrospective chart review, and the patients who visited the university hospitals included in this study are likely to be biased. Since the EGD interval was not randomly allocated to patients, there may have been other factors involved that could have affected the EGD interval, such as the presence of an organic lesion before the previous EGD that we had investigated. Also, dyspepsia was not defined using standard criteria. We think we minimized this issue by including only patients who visited gastroenterology clinics for dyspeptic symptoms. Second, adenomas and early cancers are not likely to cause dyspeptic symptoms among our patients. Rather, it could reflect the missing rate of these lesions on EGD1. However, we aimed to analyze a real-world data that could reflect what could be expected on follow-up endoscopy for dyspeptic patients in daily practice. Third, the sample size was rather small. We used Bayesian analysis that is known to work with smaller sample sizes[12] to overcome this issue. Third, we only collected data between 90 and 760 days. Because of this, we were not able to show the frequency of upper GI neoplasia beyond 760 days. But, since the CP in our analysis was 560 days, the need for data with longer EGD intervals is less pronounced, while it is also true that a larger study with longer EGD intervals is required for future validation. Fourth, we did not investigate other diagnostic methods apart from EGD, such as abdominal computed tomography or ultrasonography to detect pancreaticobiliary lesions that could also have caused dyspepsia. However, patients with alarm features are primarily recommended to receive endoscopy, but not necessarily computed tomography, by Rome IV.[19] Fifth, although we applied various methods to achieve a robust result, the trace plot does wander within a broad range of CP estimates. We think there is a need for a larger study with more number of outcomes. Finally, the severity of intestinal metaplasia at EGD1 was not assessed in all patients, which could have influenced development of dysplasia.

In conclusion, we propose a 2-year interval for upper endoscopy to rule out upper GI neoplasia among dyspeptic patients who had previously normal endoscopy. Since non-neoplastic benign conditions, such as peptic ulcers or reflux esophagitis, which could be causing dyspeptic symptoms were not analyzed in our study, we are

not able to make a recommendation regarding appropriate EGD interval to diagnose these conditions. Further studies including data with such benign conditions as PUD, longer EGD interval, in addition to larger population-based studies are warranted.

Supplementary Materials

Note: To access the supplementary figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm19063.

Conflicts of interest: None.

Author contributions: Jong Wook Kim collected the data, analyzed the data, and wrote the manuscript; Kee Wook Jung and Joong Goo Kwon gave critical comments and collected the data; Jung Bok Lee analyzed the data; and Jong Kyu Park, Ki Bae Bang, Chung Hyun Tae, and Jung Hwan Oh collected the data.

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