Clinical correlation between serum pepsinogen level and gastric atrophy in gastric neoplasms

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Received: July 31, 2018
Revised: September 12, 2018
Accepted: October 1, 2018

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Background/Aims: The relationship between the serum pepsinogen (sPG) level and changes in gastric mucosa has been well studied. Here, we evaluated the usefulness of sPG (I, II, I/II ratio) and intragastric pH as a biomarker of severe gastric atrophy in gastric neoplastic lesions.

Methods: A total of 186 consecutive Korean patients with gastric neoplastic lesions underwent endoscopic submucosal dissection (ESD) in this study. The serologic atrophy group had sPG I level $\leq 70$ ng/mL and an sPG I/II ratio $\leq 3.0$. Before ESD, overnight fasting venous blood and gastric juice samples were collected to measure the sPG level and intragastric pH. The degree of gastric atrophy was estimated by endoscopy, and the rapid urease test was performed to investigate Helicobacter pylori infection.

Results: Patients who met the criteria of serologic atrophy showed more severe endoscopic atrophic changes (61% vs. 18%, $p = 0.000$). Older patients and those with more atrophic changes at the gastric upper body demonstrated both a lower sPG I level and a lower PG I/II ratio and more severe endoscopic atrophy. The sPG I/II ratio was the lowest in low grade dysplasia than in high grade dysplasia and early gastric cancer (EGC) ($p = 0.015$). In addition, patients who tested negative for serologic atrophy and $H. pylori$ showed the lowest intragastric pH ($p = 0.000$).

Conclusions: A low sPG I level and a low I/II ratio were correlated with the severity of gastric atrophy in gastric neoplastic lesions, thus indicating it to be a sensitive biomarker of gastric precancerous lesions or EGC.

Keywords: Pepsinogens; Stomach neoplasms; Gastric mucosa; Atrophy

INTRODUCTION

Recently, serum pepsinogen I (sPG I) and PG II (sPG II), serum gastrin-17 (sG-17), and immunoglobulin G anti-Helicobacter pylori antibodies were proposed as non-invasive markers to assess the status of the gastric mucosa in patients with dyspeptic symptoms [1,2]. Both pepsinogen I (PG I) and PG II are precursors of pepsin. PG II is produced by all gastric glands (namely, oxyntic, cardiac, and pyloric) as well as duodenal (Brunner’s) glands, but PG I is secreted exclusively by oxyntic glands, which reflects its corpus secretion capacity [3]. Previous studies have shown that the sPG I level and/or I/II ratio reflect the morphological [4,5] and functional status of the gastric mucosa [6-8]. Several studies have reported the relationship between the sPG level and gastric mucosal changes [9,10]. Measuring the sPG I and sPG II levels offered a non-invasive and straightforward means of mass screening for gastric cancer in Japan when compared with endoscopy [11,12]. Moreover, recent studies have reported that advanced gastric atrophy is associated with high-fasting intragastric pH [13,14].
As in Japan, the prevalence of *H. pylori* (59.6% among adults aged ≥ 16 years in 2005) is high in Korea [15], but the efficacy of the sPG level and intragastric pH as a non-invasive marker for gastric atrophy in neoplastic lesions remains to be evaluated in Korea.

This study determined whether the sPG level and intragastric pH are related with the existence of gastric atrophy in gastric neoplastic lesions before endoscopic submucosal dissection (ESD). In addition, the relationships among the clinicopathological characteristics of gastric neoplasm, age, and sPG level in patients with gastric atrophy were investigated.

**METHODS**

**Patients**

A total of 186 consecutive patients who underwent ESD (120 men; mean age, 63.3 ± 9.0 years) for gastric neoplastic lesions (low grade dysplasia [LGD], high grade dysplasia [HGD], and early gastric cancer [EGC]) in our institution from April 2010 to September 2011 were enrolled in this study. Overnight fasting venous blood and gastric juice samples were collected from the subjects before ESD to measure the sPG level and intragastric pH. Immediately after the endoscope was inserted into the stomach, 5 to 10 mL of gastric juice was aspirated through the suction channel of the endoscope and collected in a trap placed in the suction line. The pH content of the gastric juice was measured immediately after collection. Gastric acid was measured using a set of pH test papers (Toyo Roshi Kaisha, Tokyo, Japan), which consisted of two-step indicators: one test paper indicated pH with a sensitivity of 1 (1 to 11) and the second with a sensitivity of 0.2 for the order of 0.1. The degree of gastric atrophy was estimated endoscopically, and the rapid urease test (Campylobacter-like organism [CLO]) was performed to investigate the status of *H. pylori* infection.

The exclusion criteria included (1) taking any drug inhibiting gastric acid secretion (within 4 weeks), (2) a history of gastrectomy, (3) major organ failure, and (4) a history of drug allergy.

**Serum PG levels**

The overnight fasting serum samples were centrifuged, and both sPG I and sPG II levels were determined. Serologic gastric atrophy was defined as sPG I ≤ 70 ng/mL and sPG I/II ratio ≤ 3.0, as described in a previous study [16]. In addition, based on their sPG I level and sPG I/II ratio, the patients were classified into three groups: (1) PG 3+: sPG I ≤ 30 ng/mL and sPG I/II ratio ≤ 2.0; (2) PG 2+: sPG I ≤ 50 ng/mL and sPG I/II ratio ≤ 3.0, but not meeting the criteria for PG index 3+; and (3) PG 1+: not meeting the criteria for PG index 2+ or 3+.

**Endoscopic examination**

ESD was performed on the same day of blood sampling by an experienced endoscopist at our center. A gastric neoplasm was defined as EGC or adenoma with either LGD or HGD, based on the World Health Organization classification. The extent of atrophic mucosa was expressed in accordance with the Kimura-Takemoto classification of the atrophic pattern. Then, according to the endoscopic findings and the matched Kimura-Takemoto classification of the atrophic pattern, all patients were classified into three groups: (1) normal group—without atrophic change in any area; (2) mild group—closed-type atrophic pattern; and (3) severe group—open-type atrophic pattern.

All patients underwent the CLO test with biopsy samples.

**Ethics approval**

All procedures in the study that involved human participants were performed in accordance with the ethical standards of the Institutional Review Board of the Dong-A University Hospital (DAUHIRB-10-129) and in agreement with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients before the study.

**RESULTS**

**Characteristics of the patients**

A total of 186 patients (120 men, 64.5%) of an average age of 63.3 ± 9.0 years were analyzed. The pathology of gastric neoplasm was found to be compatible with tubular adenoma with LGD in 82 (44.1%), HGD in 37 (19.9%), and EGC in 67 patients (36%). Using histology and the CLO test, *H. pylori* infection was detected in 58 of the 186
patients (31.2%). Based on the results of endoscopic examination and the Kimura-Takemoto classification of atrophic patterns, the patients were classified into three categories: 0 case of non-atrophic gastritis (0%), 49 cases of mild atrophy (26%), and 137 cases of severe atrophy (74%).

Table 1 summarizes the patient characteristics, including the pathology of their gastric neoplasm, *H. pylori* infection status, degree of gastric atrophy, and the mean value of sPG and intragastric pH. The sPG level and intragastric pH are also described.

### Clinical characteristics according to endoscopic atrophy
Considering that there was no non-atrophic gastritis patient, the 186 patients were divided into two groups according to their degree of endoscopic atrophy (mild or severe). The characteristics of each group are described in Table 2.

The mean age in the severe atrophy patient group (64.1 ± 9.0 years) was higher than that in the mild atrophy patient group (61.1 ± 8.4 years) (*p* = 0.04). In addition, patients who matched the criteria of serologic atrophy were more common in the severe atrophy group (61%) than in the mild atrophy group (18%) (*p* = 0.000). Patients with severe atrophy had a lower sPG I level (46.7 ± 37.4 vs. 78.6 ± 52.6) and a lower sPG I/II ratio (2.9 ± 1.6 vs. 4.2 ± 1.8) than those with mild atrophy (*p* = 0.000), although their sPG II level was comparable (*p* = 0.058).

### Clinical characteristics according to *H. pylori* and serologic atrophy
All enrolled patients were divided into the serologic atrophy group (n = 92) and serologic non-atrophy group (n = 94) by criteria; both groups were further divided into two subgroups based on the presence of *H. pylori* infection: serologic atrophy (+)/*H. pylori* (+); serologic atrophy (+)/*H. pylori* (−); serologic atrophy (−)/*H. pylori* (+); and serologic atrophy (−)/*H. pylori* (−).

Severe endoscopic atrophy type was more common in the serologic atrophy group than in the serologic non-atrophic group, irrespective of the *H. pylori* infection status, although the difference was not statistically significant.

The mean sPG I/II ratio was the highest in the serologic atrophy (−)/*H. pylori* (−) group (4.8 ± 1.8) and the lowest in the serologic atrophy (+)/*H. pylori* (−) group (2.0 ± 0.7).

Intragastric pH was the lowest in the serologic atrophy (−)/*H. pylori* (−) group (5.8 ± 1.4) and > 6 in the other groups.

Table 3 describes the clinical characteristics of the patients according to their serologic atrophy and *H. pylori* infection status.

### Characteristics according to gastric neoplasm pathology
No significant difference was noted in the degree of endoscopic atrophy in the three groups: LGD, HGD, and

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**Table 1. The clinical and pathological characteristics of the patients (n = 186)**

| Characteristic                  | Value          |
|--------------------------------|----------------|
| Age, yr                        | 63.3 ± 9.0     |
| Sex                            |                |
| Male                           | 120 (64.5)     |
| Female                         | 66 (35.5)      |
| Pathology of gastric neoplasm   |                |
| LGD                            | 82 (44.1)      |
| HGD                            | 37 (19.9)      |
| EGC                            | 67 (36)        |
| *Helicobacter pylori* infection status |               |
| Present                        | 58 (31.2)      |
| Absent                         | 128 (68.6)     |
| Degree of atrophy              |                |
| Normal                         | 0              |
| Mild                           | 49 (26)        |
| Severe                         | 137 (74)       |
| Serum level, ng/mL             |                |
| sPG I                          | 55.1 ± 44.1    |
| 1+                             | 58.6 ± 7.6     |
| 2+                             | 30.1 ± 10.6    |
| 3+                             | 15.9 ± 6.7     |
| sPG II                         | 18.1 ± 12.8    |
| sPG I/II ratio                 | 3.2 ± 1.8      |
| 1+                             | 2.6 ± 0.5      |
| 2+                             | 2.4 ± 0.4      |
| 3+                             | 1.3 ± 0.4      |
| Intragastric pH                | 6.2 ± 1.2      |

Values are presented as mean ± SD or number (%). LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen.
However, the sPG I/II ratio was significantly lower in the LGD and HGD groups than in the EGC group; it showed the lowest value in the LGD group (Table 4) \( (p = 0.015) \).

**Subgroup analysis of serological atrophy group**

We sub-analyzed several characteristics, including the mean age, *H. pylori* infection status, location of atrophic lesions, and sPG level, for the serologic atrophy group, which was again divided into three groups according to the PG index (Table 5). As the PG index increased from 1+ to 3+, the mean age of the patients and the percentage of the upper (proximal) gastric atrophy lesion were significantly increased in a stepwise manner \( (p = 0.000, p = 0.020, \text{each, respectively}) \).

**DISCUSSION**

Gastric cancer is one of the major cancers in the world, especially in East Asian countries such as Korea and Japan. The incidence and mortality of gastric cancer have decreased in several regions, including Korea, owing to advancements in diagnosis and treatment. However, with the rapid aging of the population, the absolute numbers of new cases and deaths from gastric cancer are expected to increase [17].

Correa’s hypothesis that “the intestinal type of gastric cancer develops from chronic inflammation leading to atrophic gastritis, intestinal metaplasia, dysplasia and cancer” has been widely accepted, and this pathogenesis may be caused by *H. pylori* infection [18]. A previous study revealed that chronic atrophic gastritis carries an 18-fold increased risk of gastric cancer in antral-predominant...
Atrophic gastritis and a 4.6-fold risk in corpus atrophic gastritis [19]. Currently, gastric cancer and atrophic gastritis are screened and diagnosed mainly by endoscopy and biopsy. However, due to the associated discomfort and cost-effectiveness, several non-invasive tests have recently been proposed as alternatives. As the severity of atrophic gastritis increases, normal gland function is lost and enzyme production is affected. Therefore, sPG produced by the gastric mucosa has been found to act as a marker of gastric mucosal status [4-8], and a low sPG I level and a low PG I/II ratio have been associated with severe gastric atrophy [4,5,20].

As the oxyntic gland’s atrophy progresses, the sPG I level decreases. In addition, when pyloric gland metaplasia of the proximal stomach occurs, the sPG II level increases. However, in severe atrophic gastritis, the sPG II level generally decreases to normal. Thus, the levels of sPG I and sPG II and the sPG I/II ratio reflect the morphological and functional status of the gastric mucosa. Based on several previous studies, a low sPG I level and a low sPG I/II ratio are reliable biomarkers for atrophic gastritis of the gastric fundus and are related with the severity of atrophy [4,21].

Although various cut-off values have been suggested for atrophic gastritis and gastric cancer, a sPG I level ≤ 70 ng/mL and a sPG I/II ratio ≤ 3 have frequently been used with a sensitivity of 73.2% to 84.6% and a specificity of 70% to 73.5%, respectively [11,22-24]. In the present study, we also defined serologic gastric atrophy as a sPG I level ≤ 70 ng/mL and a sPG I/II ratio ≤ 3. Patients who matched this criteria of serologic atrophy were more common in the severe atrophy group (61%) than in the mild atrophy group (18%) (p = 0.000). In addition, patients with severe atrophy showed a lower serum level of sPG I and a lower sPG I/II ratio than those with mild atrophy (p = 0.000). The mean sPG II level decreased slightly in the severe atrophy group than in the mild atrophy group, although the levels were comparable (17.1 ± 11.6 vs. 21.1 ± 15.3, respectively; p = 0.058). These results revealed the same tendency as reported by previous studies.

In addition, older patients and those with more atrophic changes at the upper gastric body (atrophic lesions located in the upper region) demonstrated a lower sPG

| Table 3. Clinical characteristics according to *Helicobacter pylori* and serologic atrophy status |
|---------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------|
| Characteristic                                               | Serologic atrophy group (n = 92)                                | Serologic non-atrophy group (n = 94)                           |
| H. pylori (+) (n = 27)                                       | H. pylori (-) (n = 65)                                          | H. pylori (+) (n = 31)                                         |
| Age, yr                                                       | 59.7 ± 10.0                                                    | 65.4 ± 8.3                                                    |
| Sex, male:female                                             | 15:12                                                          | 46:19                                                         |
| Pathology                                                    | H. pylori (+) (n = 27)                                        | H. pylori (-) (n = 65)                                       |
| LGD                                                         | 13                                                             | 31                                                            |
| HGD                                                         | 8                                                              | 12                                                            |
| EGC                                                         | 6                                                              | 22                                                            |
| Degree of atrophy                                            | 9 (9.8)                                                        | 40 (42.6)                                                     |
| Mild                                                        | 4 (14.8)                                                       | 5 (7.7)                                                       |
| Severe                                                       | 83 (90.2)                                                      | 54 (57.4)                                                     |
| Serum level, ng/mL                                           | 23 (85.2)                                                      | 60 (92.3)                                                     |
| sPG I                                                       | 38.6 ± 18.7                                                    | 30.0 ± 18.5                                                    |
| sPG II                                                      | 18.1 ± 5.8                                                     | 14.6 ± 8.0                                                    |
| sPG I/II ratio                                               | 2.1 ± 0.6                                                      | 2.0 ± 0.7                                                    |
| Intragastric pH                                              | 6.4 ± 0.6                                                      | 6.5 ± 0.9                                                    |
| Values are presented as mean ± SD or number (%).             |                                                                |                                                               |
| LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen. |
I level and a lower sPG I/II ratio, but more severe endoscopic atrophy. In these patients, serologic and endoscopic atrophy was more severe.

Using histology and the CLO test, *H. pylori* infection was detected in 58 of 186 patients (31.2%), with 18 patients (36.7%) showing mild atrophy and 40 (29.2%) showing severe atrophy. However, these results do not suggest a lesser association between *H. pylori* infection and gastric atrophy. Although the CLO test has a high sensitivity and specificity of 85% to 97% and 92%, respectively, it also has the possibility of a false negative result in atrophic gastritis or intestinal metaplasia due to uneven mucosal distribution of the bacteria [25,26]. Moreover, in the advanced stage of the disease, due to disease-related clearance of the infection, there is a possibility of underestimating *H. pylori* infection [27].

Kikuchi et al. [28] observed a lower level of sPG I and a lower sPG I/II ratio in the *H. pylori*-positive group. Ito et al. [29] reported improvements in gastric atrophy and intestinal metaplasia and increases in the sPG I level and in the sPG I/II ratio after *H. pylori* eradication in patients with atrophic gastritis, as explained by the pathophysiology of *H. pylori* infection. In a past study, a polypeptide secreted by *H. pylori* stimulated the chief cells directly and promoted the synthesis and secretion of pepsinogens, mainly PG II [30]. However, long-term persistent infection may cause PG gene mutation and glandular cell damage, which may result in corpus atrophy, decrease in the capability of PG I secretion, and increased gastric pH. PG II is secreted extensively, including in the metaplastic pyloric gland. Therefore, the sPG II level is almost constant and the sPG I/II ratio is correspondingly decreased [3-7]. In the present study, the mean sPG I/II ratio was the highest in the serologic atrophy (−)/*H. pylori* (−) group (4.8 ± 1.8) and the lowest in the serologic atrophy (+)/*H. pylori* (−) group (2.0 ± 0.7). Furthermore, severe endoscopic atrophy type was more common in the serologic atrophy group than in the serologic non-atrophy group, although the difference was not statistically significant.

In our study, gastric neoplastic lesions were classified into LGD, HGD, and EGC by our endoscopic pathology findings. The value of the sPG I/II ratio was the lowest in the LGD group than in the HGD and EGC groups (p = 0.015). Chang et al. [31] reported that the sPG I/II ratio was significantly lower in patients with LGD than in those with functional dyspepsia and that the ratio was not further decreased in patients with HGD, EGC, and

### Table 4. Characteristics according to gastric neoplasm pathology

| Characteristic | Total (n = 186) | LGD (n = 82) | HGD (n = 37) | EGC (n = 67) | p value |
|---------------|----------------|-------------|-------------|-------------|---------|
| Endoscopic atrophy |                 |             |             |             | 0.885   |
| Mild          | 49 (26.3)       | 21 (25.6)   | 11 (25.4)   | 17 (29.7)   |         |
| Severe        | 137 (73.7)      | 61 (74.4)   | 26 (74.6)   | 50 (70.3)   |         |
| Serological atrophy |             |             |             |             | 0.311   |
| Positive      | 92             | 44          | 20          | 28          |         |
| Negative      | 94             | 38          | 17          | 39          |         |
| PG index      |                |             |             |             | 0.087   |
| PG 1+         | 24             | 7           | 5           | 12          |         |
| PG 2+         | 34             | 17          | 6           | 11          |         |
| PG 3+         | 34             | 20          | 9           | 5           |         |
| Serum level, ng/mL |          |             |             |             |         |
| sPG I         | 55.1 ± 44.1    | 50.1 ± 43.4 | 50.4 ± 42.2 | 63.8 ± 45.3 | 0.132   |
| sPG II        | 18.1 ± 12.8    | 17.9 ± 13.6 | 17.0 ± 12.5 | 19.1 ± 12.0 | 0.715   |
| sPG I/II ratio| 3.2 ± 1.8      | 2.9 ± 1.7   | 3.2 ± 1.6   | 3.7 ± 1.8   | 0.015   |
| Intragastric pH| 6.1 ± 1.2     | 6.3 ± 1.2   | 6.4 ± 1.0   | 6.1 ± 1.3   | 0.302   |

Values are presented as number (%) or mean ± SD.

LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; PG, pepsinogen; sPG, serum pepsinogen.
AGC. These results of severe serologic atrophy in LGD comprehensively imply that LGD can be considered as a serious precancerous lesion that rationalizes the endoscopic resection of the lesion.

There are several limitations in our study. First, it was conducted at a single center and included a small sample size. Second, as we conducted the survey of patients with precancerous lesions and EGC before ESD, no normal control group or advanced gastric cancer group existed in our study. Third, we defined “serologic atrophy” using cut-off values of sPG I level $\leq 70$ ng/mL and the sPG I/II ratio $\leq 3.0$ with high sensitivity and specificity, respectively, based on previous studies. However, these cut-off values may not be suitable in Korea, because they may vary with regard to ethnicity, diet, environment, and disease epidemiology, thus necessitating further studies on the appropriate sPG cut-off value for gastric atrophy among Korean patients. Forth, the serum $H.\ pylori$ antibody status was not evaluated in this study.

In conclusion, a low sPG I level and a low sPG I/II ratio are closely related to the severity of gastric atrophy and dysplasia, but intragastric pH was not relevant. The age and location of atrophic lesions are related to the severity of gastric atrophy. We concluded that the sPG test is useful as a marker of gastric precancerous lesions and EGC; therefore, it is helpful not only in diagnosing a benign disease status with a high malignancy risk or early stage of gastric malignancy but also in improving the patient’s compliance and cost-effectiveness of screening. This test may also help in the primary selection of high-risk patients with premalignant gastric lesions who need endoscopic examination and biopsy.

### Table 5. Subgroup analysis of serological atrophy group

| Characteristic                  | Serologic atrophy group (n = 92) | p value |
|--------------------------------|----------------------------------|---------|
| Age, yr                        | PG 1+ (n = 24)                  | PG 2+ (n = 34) | PG 3+ (n = 34) |
|                                | 58.3 ± 8.5                      | 63.2 ± 8.6 | 68.0 ± 8.2     | 0.000 |
| Sex, male:female               | 15:9                            | 26:8     | 20:14          | 0.303 |
| Pathology of gastric neoplasm  |                                  |          |                | 0.059 |
| LGD                            | 7 (29.2)                        | 17 (50)  | 20 (58.8)      |       |
| HGD                            | 5 (20.8)                        | 6 (17.6) | 9 (26.5)       |       |
| EGC                            | 17 (34.7)                       | 50 (36.5)| 5 (14.7)       |       |
| Helicobacter pylori infection  |                                  |          |                | 0.035 |
| Present                        | 11 (45.8)                       | 5 (14.7) | 11 (32.4)      |       |
| Absent                         | 13 (54.2)                       | 29 (85.3)| 23 (67.6)      |       |
| Location                       |                                  |          |                | 0.020 |
| Upper                          | 1 (4.2)                         | 7 (20.6) | 10 (29.4)      |       |
| Lower                          | 23 (95.8)                       | 27 (79.4)| 24 (70.6)      |       |
| Endoscopic atrophy             |                                  |          |                | 0.688 |
| Mild                           | 5 (20.8)                        | 1 (2.9)  | 3 (8.8)        |       |
| Severe                         | 19 (79.2)                       | 33 (97.1)| 31 (91.2)      |       |
| Serum level, ng/mL             |                                  |          |                |       |
| sPG I                          | 58.6 ± 7.6                      | 30.1 ± 10.6| 15.9 ± 6.7     | 0.000 |
| sPG II                         | 24.2 ± 7.7                      | 13.0 ± 5.9| 12.1 ± 4.1     | 0.000 |
| sPG I/II ratio                 | 2.6 ± 0.5                       | 2.4 ± 0.4 | 1.3 ± 0.5      | 0.000 |
| Intragastric pH                | 6.3 ± 0.1                       | 6.7 ± 0.8 | 6.4 ± 1.0      | 0.137 |

Values are presented as mean ± SD or number (%).
PG, pepsinogen; LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen
KEY MESSAGE

1. A low serum pepsinogen I level and a low I/II ratio were correlated with the severity of gastric atrophy in gastric neoplastic lesions.
2. This study showed that serum pepsinogen test is useful as a marker of gastric precancerous lesion and early gastric cancer.
3. It is helpful to not only diagnose at benign disease status with high malignancy risk or early stage of gastric malignancy, but also improve patient’s compliance.

Conflict of interest
No potential conflict of interest relevant to this article was reported.

Acknowledgments
This study was supported by Dong- A university fund 2018.

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