Review

Gastric cancer screening by combined assay for serum anti-*Helicobacter pylori* IgG antibody and serum pepsinogen levels—"ABC method"

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Abstract: The current status of screening for gastric cancer-risk (gastritis A, B, C, D) method using combined assay for serum anti-*Helicobacter pylori* (*Hp*) IgG antibody and serum pepsinogen (PG) levels, "ABC method", was reviewed and the latest results of our ongoing trial are reported. It was performed using the following strategy: Subjects were classified into 1 of 4 risk groups based on the results of the two serologic tests, anti-*Hp* IgG antibody titers and the PG I and II levels: Group A [*Hp*(−)PG(−)], infection-free subjects; Group B [*Hp*(+)PG(−)], chronic atrophic gastritis (CAG) free or mild; Group C [*Hp*(+)PG(+)], CAG; Group D [*Hp*(−)PG(+)]), severe CAG with extensive intestinal metaplasia. Continuous endoscopic follow-up examinations are required to detect early stages of gastric cancer. Asymptomatic Group A, which accounts for 50–80% of all the subjects may be excluded from the secondary endoscopic examination, from the viewpoint of efficiency. *Hp*-infected subjects should be administered eradication treatment aimed at the prevention of gastric cancer.

Keywords: gastric cancer, cancer screening, pepsinogen (PG) I, II, anti-*Helicobacter pylori* (*Hp*) IgG antibody, serum pepsinogen test method (PG method), screening for gastric cancer-risk (gastritis A, B, C, D) method (ABC method)

Introduction

In 2010, gastric cancer remains one of the most important gastrointestinal cancers. It is the fourth most common cancer and second leading cause of cancer deaths (700,000 deaths annually) worldwide.[1)] In 2002, an estimated one million new cases of gastric cancer were diagnosed, with almost two-thirds occurring in developing countries. High-risk areas include East Asia (Japan, China), Eastern Europe and parts of Central and South America.[2)]

It is important to introduce an efficient and cost-effective practical mass screening method for early detection of gastric cancer. It may be possible to reconstitute the screening system of gastric cancer according to the risk level, so that unnecessary annual invasive screening examinations are avoided.

It is well established that gastric carcinogenesis is a continuous process starting from superficial gastritis to the development of glandular atrophy, metaplasia and dysplasia, and finally, adenocarcinoma.[3)] This process usually takes decades and seems to be initiated by infection with the gastric bacterium, *Helicobacter pylori* (*Hp*)[4)] in many, if not most cases. The long history of the disease process potentially provides opportunities for early detection of precancerous lesions and consequent appropriate intervention. The application of strategies directed towards the elimination of risk factors is of paramount importance in the control of gastric cancer.[5)]

The high prevalence of intestinal metaplasia among *Hp*-infected patients suggests that the risk of development of gastric cancer will continue to remain high. Since gastric cancer is potentially curable if diagnosed early, it is insufficient to check for *Hp* antibody titers alone for the diagnosis of subjects with severe atrophic gastritis. The serum pepsinogen test method, or the "PG method"[6)–19)] is also needed

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Abbreviations: PG method: serum pepsinogen test method; ABC method: screening for gastric cancer-risk (gastritis A, B, C, D) method.

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in *Hp*-positive subjects. Conversely, low-risk subjects who do not have atrophic gastritis or *Hp* infection can be screened by the combination of the PG method and *Hp* serology, or the screening for gastric cancer-risk (gastritis A, B, C, D) method or the "ABC method".

Here, the author reviews the present status of gastric cancer screening using the ABC method, including the latest results of our ongoing trial.

Gastric cancer and *Hp* infection

The discovery of *Hp* in 1982 has not only changed the concept of upper gastrointestinal tract diseases, but also of clinical gastroenterological practice.[4] Results of clinical and basic research accumulated over the last decade clearly demonstrate the existence of a close relationship between *Hp* infection and the risk of gastric cancer.[20)–34)] *Hp* infection is now recognized as the main acquired factor involved in the pathogenesis of peptic ulcer disease and chronic gastritis, as also gastric cancer.[20)]

Gastric cancer almost never occurs in the absence of *Hp* infection. Observation of 1,526 individuals over a period of 10 years revealed that gastric cancer was found in 5% of all individuals infected with *Hp* and in none of the uninfected individuals.[28)]

Uemura N. *et al.*[25)] followed up patients who underwent endoscopic therapy for gastric cancer that resulted in complete cure, and compared the incidence rate of gastric cancer at another site in the stomach (metachronous gastric cancer) between patients who were and were not treated with an *Hp* eradication regimen. During the 54-month follow-up period, metachronous gastric cancer was not found in any of the patients administered *Hp* eradication treatment, but in 10% of those who did not receive the eradication therapy. Over longer periods, however, occurrence of gastric cancer was also detected among the patients who had received *Hp* eradication therapy, however, the incidence was clearly lower than that in the patients who had not received *Hp* eradication therapy. Other reports[30)] lend support to these findings.

Eradication of *Hp* decreases the severity of gastritis, producing significant changes in the serum PG levels; both serum PG I and PG II levels decrease, with elevation of the PG I to PG II ratio.[35)–38)] Furuta T. *et al.*[35)] determined the optimal cutoff values for the percent change of the serum PG I/II ratio. The cutoff was tentatively set as +40%, +25%, and +10% when the serum PG I/II ratios before treatment were less than 3, equal to or greater than 3, but less than 5, and equal to or greater than 5, respectively. Since the method involving determination of the percent change of the serum pepsinogen levels has the advantage that no endoscopy is required, repeated examinations will be more acceptable to the patients. Thus, the serological method may be a useful non-invasive method for determining eradication of *Hp*.

Hp antibody titers[39)] vary greatly depending on the test kit used in Japan. Use of an *Hp* antibody test kit with Japanese strains without an indeterminate range is recommended.

The PG method

Serum pepsinogen (PG)[40)–42)] is classified into two biochemically and immunologically distinct types, namely, PG I and PG II.[43)–47)] PG I is produced by the chief and mucous neck cells in the fundic glands, while PG II is produced by these cells and also by the cells in the pyloric glands and Brunner's glands. It is widely accepted that the serum PG levels reflect the functional and morphologic status of the stomach mucosa. As the fundic gland mucosal area reduces, the PG I levels gradually decrease, while the PG II levels remain fairly constant. As the result, a stepwise reduction of the PG I/II ratio is closely correlated with the progression from normal gastric mucosa to extensive atrophic gastritis.[6)–19)]

Serum PG was used as a biomarker of the gastric mucosal status, including to detect atrophic changes and inflammation, before the discovery of *Hp*.

PG is a serum marker of atrophic gastritis, which is a precancerous change in the stomach, rather than being a tumor marker.[13),14)] The PG method[6)–19),48)–74)] allows the diagnosis of advanced atrophic gastritis, a high risk factor for gastric cancer, and can be applied to gastric cancer screening using the serum PG I level and PG I/II ratio as indices, based on the association between CAG and gastric cancer, and the correlation between the serum PG levels and the presence of CAG. Thus, for the detection of gastric cancer, patients at high risk for gastric cancer have been screened clinically by the PG method.[11)–15)]

In 10-year follow-up studies, from 1992 to 2001, of 882 individuals from a Tokyo Teishin Hospital Health Care Center in Japan, where screening for gastric cancer by the PG method and endoscopy is practiced, Kaplan–Meier survival estimates stratified by age revealed no reduction of the cumulative survival estimate during 4 years in individuals in their 40's, 50's and 60's[63),64)] (Fig. 1).

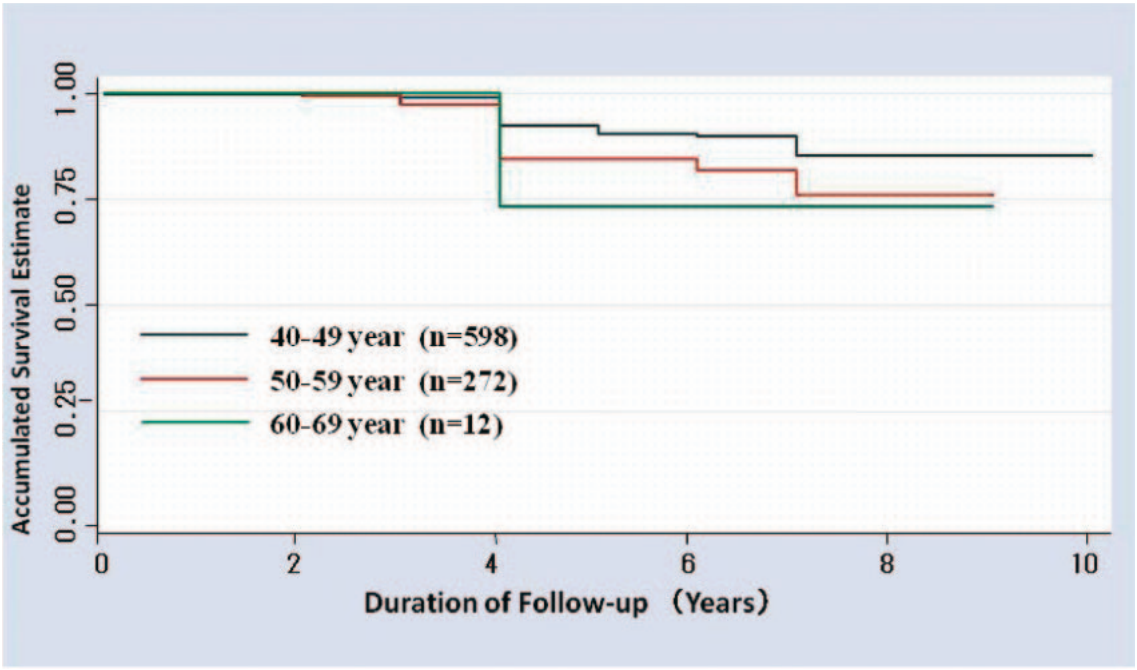

Fig. 1. Accumulated survival rate for each age-group by the PG method using Kaplan–Meier analysis at Tokyo Teishin Hospital Care Center in Tokyo for the ten-year period (1992–2001); n = 882[63),64)]

Table 1. Evidence of a decrease in gastric cancer mortality by the PG method at a municipality of Hiroshima Prefecture using Mantel–Hentzel estimate of the odds ratio[63)]

	Odds ratio	95% of confidence intervals	Number of individuals
Visit within 1 year	0.238	(0.061–0.929)	41
Visit within 2 years	0.375	(0.155–0.905)	41
Visit within 3 years	0.290	(0.111–0.759)	36
Visit within 4 years	0.423	(0.164–1.091)	32
Visit within 5 years	0.440	(0.171–1.135)	31

In cancer screening by the PG method in a municipality of Hiroshima prefecture in Japan, the number of reported deaths from gastric cancer was 41. In a case-control study based on the 41 deaths and 3 controls, the odds ratio (95% CI) for death within 3 years after screening by the PG method was 0.290 (0.0111–0.759), indicating the potential contribution of the PG method to a significant reduction of gastric cancer mortality within 3 years[63)] (Table 1).

The PG method identifies atrophic gastritis, a high-risk factor for gastric cancer, and therefore, may be called a mass screening test method for gastric-cancer-risk, rather than as one for gastric cancer itself.

It is of great significance to detect early gastric cancer by screening of high-risk patients detected using the PG method and following the patients up by endoscopy on a regular basis. As reported elsewhere,[15)] we have obtained good results of the mass screening system using the PG method alone.

However, a controversial and the most important weak point in the mass screening system by the PG method alone is the presence of the PG method-negative gastric cancer, especially, diffuse-type gastric cancer.

Although it is possible to detect such cancers by an endoscopic examination once in 5 years,[15)] patients will benefit from screening by the less invasive combination of the PG method and serum anti-*Hp* antibody assay, the "ABC method",[39),75),76)] which can also detect PG method-negative gastric cancer.

We have confirmed that the ABC method is useful for the detection of both the intestinal and diffuse types of gastric cancer from the residual serum samples of 51 gastric cancer cases found among 43,438 subjects who had undergone screening as part of a health checkup at a certain workplace from the year 2000 to 2005;[63)] of the total, 7 cases were PG method-negative and *Hp* serology-positive. Thereafter, we decided to introduce the ABC method at this work place in Tokyo for the first time.

Stratification of the risk of gastric cancer by the ABC method[39)]

Results of much basic research suggest that *Hp* infection is closely associated with the development of gastric cancer.[4),5)] Domestic[74),77)–80)] and foreign epidemiological studies also lend support to the notion that *Hp* infection is a risk factor for gastric cancer, except that the odds ratio varied from study to study. It has also become evident that atrophy of the gastric mucosa is a high-risk factor for the development of gastric cancer, and that the serum PG levels are correlate with atrophy of the gastric mucosa. The ABC method allows stratification of risk for the development of gastric cancer.[24),26),29),34),57),72)] Other reports[69)–71),81)] from Japanese researchers also support these findings.

Cohort studies[57)] in 4,655 normal male individuals who could be followed up for at least 10 years show that gastric cancer developed only in individuals infected with *Hp* and did not develop in normal individuals testing negative for *Hp*. As chronic gastritis progressed, a gradual and significant increase in the incidence of gastric cancer and hazard ratio was noted (Table 2). The most advanced and severe cases of gastric atrophy judged by the pepsinogens assessment, when combined with a negative *Hp* serology, probably due to a *Hp* antibody spontaneous disappearance,[54),57)] was associated when an even greater progression to dysplasia and cancer.

Of 8,286 individuals of Matsue city in Japan who underwent endoscopic screening for gastric cancer during health checkup in which *Hp* antibodies were measured in addition to the PG method, 2,802 were classified as group A [*Hp*(−)PG(−)], 3,395 as group B [*Hp*(+)PG(−)], and 2,089 as group C [*Hp*(+)PG(+) and *Hp*(−)PG(+)].[81)] According to a follow-up over the subsequent 14 years, gastric cancer occurred in 46 individuals in Group C (1.87%) and 7 individuals in Group B (0.21%), while there were no cases from Group A. Therefore, we can discriminate between low-risk and high-risk groups for the development of gastric cancer using the ABC method.

The above results show that (1) the risk of gastric diseases is very low in individuals with a healthy gastric mucosa (Group A), (2) there is an elevated risk of peptic ulcer, *etc.*, in Group B, (3) individuals in Group C are at a higher risk of developing diseases resulting from atrophy of the gastric mucosa, such as gastric cancer, gastric adenoma and hyperplastic polyps, and (4) individuals in Group D [*Hp*(−)PG(+)], with advanced atrophy, are at a higher risk of developing gastric cancer. The risk of gastric cancer is highest in Group D, followed by that in Groups C, B, and A, in descending order.[34),57),63),64)]

Table 2. Incidence of gastric cancer and hazard ratio associated with atrophic gastritis at a workplace in Wakayama Prefecture for the eight-year periods (1994–2002); n = 5,209[39)]

Group*	A	B′	B	C	C′	D
Number of individuals	966	501	2,327	1,329	53	33
Person-year	9,487	5,007	22,436	12,665.5	524.5	306
Mean age (years)	48.3	46.8	49.5	50.4	47.9	49.3
Follow-up period (years)	9.8	10.0	9.6	9.5	9.9	9.3
Incidence of gastric cancer	0	1	25	30	3	4
Hazard ratio	1	2.1	9.8	19.6	54.8	120.4

*Group: A: *Hp*(−)PG(−), B′: *Hp*(±)PG(−), B: *Hp*(+)PG(−), C: *Hp*(+)PG(+), C′: *Hp*(±)PG(+), D: *Hp*(−)PG(+).

The ABC method allows stratification of the risk for the development of gastric cancer into four (A, B, C, and D) groups. The advantages of this examination are as follows: (1) Serum PG levels do not vary greatly within 10 years or so in more than 90% of adults, (2) *Hp* infection is originally acquired in childhood in most cases, (3) the antibody titer is relatively stable in people aged 40 years or older, and (4) this examination can be performed simultaneously with a regular health checkup.

If individuals are classified into a high-risk group or low-risk group through primary screening using the ABC method, it may be possible to reconstitute the screening system for gastric cancer according to the risk level of the patients, instead of implementing annual screening for all individuals.

Ongoing trial of the ABC method in Tokyo

Since 1991, we have been performing mass screening for gastric cancer risk.[11),15)] The mass screening system consists of primary screening of high-risk-employees for gastric cancer using serum samples and secondary examination by endoscopy among those presenting for a health-checkup.

We initiated the ABC method in 2007, in which people in group A are advised to have endoscopic examination every five years, those in group B every three years, those in group C every two years, and those in group D annually. During the three years from 2007 to 2009, we examined a total of 48,073 individuals after excluding those who met the

Table 3. Subjects of "the ABC method" at a work place in Tokyo for three-year periods (2007–2009)[76]

Screened case	Total number of 3 years 48,073 (100%)	2007 year 15,043 (100%)	2008 year 16,080 (100%)	2009 year 16,950 (100%)
Group A*	35,177 (73%)	10,628 (71%)	11,696 (73%)	12,853 (76%)
B*	7,883 (17%)	2,911 (19%)	2,681 (17%)	2,291 (14%)
C*	4,489 (9%)	1,374 (9%)	1,527 (9%)	1,588 (9%)
D*	524 (1%)	130 (1%)	176 (1%)	218 (1%)
Requiring endoscopy	6,965 (15%)	3,346 (22%)	2,154 (13%)	1,465 (9%)
Underwent endoscopy	3,921 (8%)	1,627 (11%)	1,535 (10%)	759 (4%)

*Group: A: *Hp*(−)PG(−), B: *Hp*(+)PG(−), C: *Hp*(+)PG(+), D: *Hp*(−)PG(+).
Group A is excluded from the secondary endoscopic examination from the view point of efficiency.

exclusion criteria based on the information obtained from them by interview.[76]

Serum samples collected at the time of the general health checkup were used to measure the serum PG I and II levels (LZ test, 'Eiken' Pepsinogen I and II: LA; latex agglutination method) and serum anti-*Hp* antibody (E-plate 'Eiken' *H. pylori* antibody: EIA; enzyme immunoassay method). Individuals with PG I levels of $\leq$70 μg/l and PG I/II ratio of $\leq$3 were classified as PG-positive, and those with a serum *Hp* antibody titer of $\geq$10 U/ml were classified as *Hp*-positive.

Based on the results of the above tests, the subjects were classified into the following four groups: group A [*Hp*(−)PG(−)], group B [*Hp*(+)PG(−)], group C [*Hp*(+)PG(+)], and group D [*Hp*(−)PG(+)], respectively. There were 35,177 individuals in group A, 7,883 individuals in group B, 4,489 individuals in group C, and 524 individuals in group D. Based on the time of the most recent endoscopic examination, 6,965 of all the individuals were advised to undergo endoscopic examination, and 3,921 (56%) actually underwent endoscopy[76] (Table 3).

Of the 3,921 individuals, 23 were found to have gastric cancer (detection rate of gastric cancer: 0.05%, positive predictive value: 0.59%). Five of them were found to have advanced cancer, and it was the first time for all of them to have undergone screening for gastric cancer risk by the ABC method, for reasons such as mid-career hiring. The remaining 18 (78%) had early gastric cancer and 12 (52%) had intestinal-type gastric cancer. Endoscopic resection was performed in 12 of the patients (52%), and radical surgical resection was possible in the remaining 11 individuals, including those with advanced cancer. Histopathologically, 48% of the detected cancers were of the diffuse type, with the ratio of the diffuse type increasing gradually over the years (25% in 2007, 63% in 2008, and 100% in 2009).

From 2007 to 2009, individuals in group A (low-risk group), accounting for 73% of all the individuals, were excluded from the secondary endoscopic examination, to resolve the shortage of manpower, which resulted in successful examination of the risk of gastric cancer.

The percentages of people in group A in 2007, 2008, and 2009 were 71%, 73%, and 76%, and those in group B were 19%, 17% and 14%, respectively. Consequently, the annual rate of increase of group A subjects was estimated to be about 3% and the rate of decrease of group B was estimated to be about 3% per year. The number of individuals in group A will continue to increase at the rate of about 3% per year, which is expected to contribute to a further reduction in the number of individuals who are advised to undergo mass screening examination for gastric cancer in the future.[76]

It remains to be seen whether the ABC method,[39),75),76),82] which was introduced in 2007 and has been studied for only 3 years, is effective. Because 70% of the patients with gastric cancer have been found in group B, for which endoscopic examination would have been performed only once in 5 years by the conventional PG method, the ABC method is likely to detect PG-negative gastric cancer at an early stage.

It is also suggested that the ABC method, which also allows detection of diffuse-type gastric cancers and successful endoscopic resection, can reliably detect gastric cancer earlier. However, as I will mention the weak points and points of caution of the ABC method later in the appendix of this manuscript, there are several problems for adopting the ABC method in clinical practice for primary gastric cancer screening, especially to exclude *Hp*-infected individuals from group A.

At present, it is still too early for us to draw any definitive conclusions, but the ABC method should

be positioned as an effective method for stratifying gastric cancer risk suitable for the circumstances in Japan, where the number of people infected with *Hp* or testing positive for PG is decreasing. It is hoped that more experience will be accumulated at many institutions besides this clinic in Japan, as well as in other countries across the world.

Conclusion

Although there is still room for improvement of the ABC method, I think it is useful to select high-risk and low-risk populations for development of gastric cancer, and to detect not only the intestinal type, but also the diffuse type of gastric cancers in the early stage. I believe it can be a step towards reaching the ultimate goal of mass screening, that is, eradication of gastric cancer.

Appendix

Technical recommendations for adopting the ABC method[39]

1. According to the ABC method, it is recommended that the risk for gastric cancer be stratified into four groups according to the anti-*Hp* IgG antibody titer before eradication of *Hp* and the serum PG levels, as follows: group A [*Hp*(−)PG(−)], group B [*Hp*(+)PG(−)], group C [*Hp*(+)PG(+)], and group D [*Hp*(−)PG(+)]. For the PG method, the cutoff points for identifying the risk of gastric cancer should be ≤70 µg/l for pepsinogen I and ≤3 for the PG I/II ratio, and inquiries about a history of *Hp* eradication, previous treatment of peptic ulcer (especially, treatment with PPIs), previous gastric resection, and impairment of renal function are essential.
2. PG levels do not vary from one test kit to another, whereas *Hp* antibody titers vary greatly depending on the test kit used in Japan. Use of an *Hp* antibody test kit with Japanese strains without an indeterminate range is recommended.
3. To exclude *Hp*-infected individuals from group A:
   (1) Measures for individuals who have received *Hp* eradication: What is most important is an inquiry about a history of *Hp* eradication. If serum PG levels change significantly or both serum PG I and PG II levels are low, it may be assumed that the person has received *Hp* eradication therapy. (2) Measures for individuals who are false-negative for *Hp* antibody: It is highly likely that elevated PG levels, especially a PG II level of ≥15 µg/l, reflect the presence of histological gastritis associated with *Hp* infection. In this case, the presence of *Hp* should be checked using other antibodies or test methods. (3) Measures for individuals in whom *Hp* infection resolved spontaneously: low PG levels, especially a PG I level of ≤35 µg/l and PG I/II ratio of 4.0 to 3.1, may indicate the possibility of previous infection with *Hp* or spontaneous resolution of *Hp* infection.
4. The interval for screening by the ABC method need not be yearly, and an interval of 5 years or so is recommended. It is recommended that endoscopic examination be performed at least once every 3 years for group B, at least once every 2 years for group C, and annually for group D, and that group A be excluded from the examination.

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Profile

Professor Kazumasa Miki was born in 1942. He graduated and obtained his PhD from the School of Medicine at the University of Tokyo, Japan. He performed pioneering work on the basic and clinical application of pepsinogen for long time, over 30 years. He became Assistant Professor in 1981, and subsequently Senior Lecturer and Associate Professor at the First Department of Internal Medicine, Faculty of Medicine, University of Tokyo. He is currently Emeritus Professor at the Division of Gastroenterology and Hepatology of the Department of Internal Medicine (Omori), Toho University, Tokyo, as well as Consultant of the Cancer Institute, Ariake Hospital, of the Japanese Foundation for Cancer Research. He had also been Chairman of the Research Committee of Studies of the Ministry of Health, Labor and Welfare in Japan from 1996 to 2006.

Miki has won awards which includes Asahi Cancer Award in 2005, Award of Princess Takamatsu Cancer Research Fund in 2008, and 2009 ACG Governors Awards for Excellence in Clinical Research, and holds the post of Councilor/Director in many gastroenterological societies in Japan. These include the Japan Gastroenterological Endoscopy Society (JGES) and the Japanese Society of Cancer Screening and Diagnosis. He also sits on the editorial board of Digestive Endoscopy and President of Japan Research Foundation of Prediction Diagnosis Therapy for Gastric Cancer (JRF PDT GC), and Japanese Representative Councilor of China and Korea as well as President of Kanto District of JGES.