The effect of *H. pylori* eradication for gastric cancer prevention

After it became clear that *H. pylori* infection is an important risk factor for gastric cancer, the issue of whether *H. pylori* eradication therapy can decrease the incidence of gastric cancer has attracted increasing attention. Intervention studies to assess the preventative effect of *H. pylori* eradication on gastric cancer have been conducted in healthy individuals worldwide. However, the incidence of gastric cancer is very low in Western countries and the study populations enrolled in those countries were not large enough to detect a significant effect of eradication therapy, resulting in the discontinuation of most studies.[21]

You *et al.* reported a study of 3,365 Chinese patients who were randomized to an *H. pylori* eradication group, a garlic group, or a vitamin group and then were followed for 7.3 years in 2006. They found no difference of gastric cancer among the three groups.[22] However, longer follow-up for 15 years subsequently revealed a significant reduction of gastric cancer in the *H. pylori* eradication group (odds ratio, 0.61; $p = 0.032$).[23] Because the incidence of progression from *H. pylori*-positive atrophic gastritis to gastric cancer is very low, it has been suggested that it would be difficult to demonstrate a significant difference unless the sample size is increased or the observation period is longer. In recent years, You *et al.* have reported a significant difference due to *H. pylori* eradication after long-term (10 years or more) observation. In order to define the preventive effect on gastric cancer of *H. pylori* eradication therapy, they are now conducting a large-scale randomized placebo-controlled study involving approximately 200,000 people in Linqu County, which has a high incidence of gastric cancer (Unpublished data, presented in IARC Meeting, 2013). This is a massive project in which subjects are allocated to either an *H. pylori* eradication group or a non-eradication group and then are followed endoscopically for almost 10 years to assess the development of gastric cancer. If this study is completed successfully, it is likely to determine how effective *H. pylori* eradication therapy is for reducing the incidence of gastric cancer.

In contrast, we conducted a clinical trial with a small sample size and short follow-up period that involved patients who had undergone endoscopic mucosal resection for early gastric cancer, a population in which gastric cancer is very likely to develop. The annual incidence of gastric cancer has been reported to be only 0.1% to 0.4% in *H. pylori*-positive patients,[2),3)] while the incidence of metachronous recurrence after endoscopic surgery for early gastric cancer is far higher (3% to 5%).[24),25)] To investigate the ectopic recurrence of gastric cancer, 544 patients who had received endoscopic treatment for early gastric cancer were randomly allocated to *H. pylori* eradication or non-eradication groups and were followed up for 3 years by annual endoscopic examination. Metachronous recurrence was detected in 9 and 24 subjects from the eradication group and the non-eradication group, respectively, and there was a significantly lower relapse rate in the eradication group ($p < 0.01$ according to intention-to-treat analysis).[26)] *H. pylori* eradication therapy reduced the incidence of differentiated gastric cancer by at least two-thirds irrespective of whether the patients had atrophic gastritis, intestinal metaplasia, or early gastric cancer. Data obtained up to 8–10 years after completion of this study were also analyzed, revealing a persistent difference in the incidence of metachronous gastric cancer between the *H. pylori* eradication and non-eradication groups. Thus, our findings indicate that the preventive effect of *H. pylori* eradication therapy on gastric cancer persists for a long time.[27)]

A large-scale cohort study involving about 80,000 Taiwanese patients with peptic ulcer was reported, in which patients were followed up for 10 years after *H. pylori* eradication therapy.[28)] The subjects were assigned to an early eradication group that received *H. pylori* eradication therapy at the time of diagnosis or a late eradication group that received eradication therapy at 1 year or more after diagnosis. It was found that the incidence of gastric cancer was markedly lower in the early eradication group than in the late eradication group. This study is important because it not only demonstrated that *H. pylori* eradication therapy reduces the incidence of gastric cancer, but also showed that earlier eradication is more effective.

It has been shown that 95% of gastric cancer in Korea is associated with *H. pylori*.[14)] The National Cancer Screening Program in Korea was initiated to provide gastric cancer screening for people aged 40 or older by double contrast radiography or endoscopy in 1999. The screening rate of 46% achieved in Korea is significantly higher than that in Japan,[29)] and such widespread screening may decrease gastric cancer deaths. Indeed, 5-year survival rate of gastric cancer patients was 47% in 2002, when X-ray studies were mainly used for screening, while it increased to 67%

in 2010 when endoscopic screening was predominant. The detection rate of gastric cancer endoscopy has been reported to be 4 times greater than with double contrast radiography (0.26% vs. 0.07%).[10] In Korea, there have been demands for the government to approve national health insurance coverage for *H. pylori* eradication therapy in patients with chronic gastritis but there is no public knowledge-based application system like that in Japan; hence, a new clinical study involving about 100,000 subjects is required and this will be completed after 7 years at the earliest.

Health insurance cover for *H. pylori* eradication therapy in Japan

Cancers can be broadly classified into lifestyle-related tumors and infection-related tumors. In Western countries, infections only cause a low percentage (10% or less) of all cancers. In Japan, however, it has become clear that approximately 25% of cancers are infection-related, including liver cancer caused by hepatitis viruses, cervical cancer due to papillomaviruses, and gastric cancer related to *H. pylori*. Although cervical cancer is uncommon and only accounts for 1.3% of all cancers, gastric cancer and liver cancer account for about 17% and 6.5%, respectively, and the total for these three cancers is nearly 25% (Fig. 2).[30] Since it has become clear that most gastric cancer cases are due to *H. pylori* infection rather than lifestyle factors, it is time for a major revision of the strategies for fighting this cancer. When cancer is suspected to be related to infection, proactive preventative measures are likely to lead to a dramatic reduction in the incidence and a significant decrease of cancer mortality. In Japan, preventative measures for liver cancer have been focused on hepatitis virus infection since 2002,

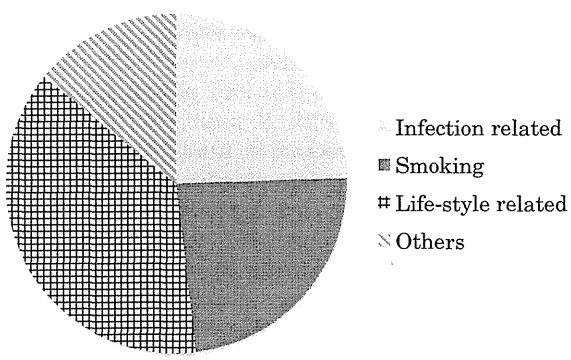

Fig. 2. Cause of cancer in Japan.

leading to a reduction of mortality.[31),32)] However, the annual number of gastric cancer deaths has remained at around 50,000 for the last few decades, suggesting that current preventative measures are inadequate. Even though there is a difference in the causative agent between liver cancer (hepatitis viruses) and gastric cancer (bacteria), the preventive measures for gastric cancer should not be markedly different from those for liver cancer because both are related to infection. Thus, the fundamental preventive approach to gastric cancer should be shifted from conventional secondary prevention based on double contrast radiography screening to primary prevention by *H. pylori* eradication therapy.

The Japanese Society for Helicobacter Research published a guideline which recommended that all *H. pylori*-infected persons should receive eradication therapy in 2009.[3)] In response to this, the Ministry of Health, Labour and Welfare (MHLW) approved the expansion of national health insurance cover for *H. pylori* eradication therapy to include three new indications (gastric MALT lymphoma, post endoscopic resection of early gastric cancer, and ITP), in addition to gastric and duodenal ulcer. This was the first time in the world that a national health scheme had included *H. pylori* eradication therapy for indications other than gastric and duodenal ulcer, and it represented an innovative approach. To achieve expansion of health insurance cover for *H. pylori* eradication therapy to include chronic gastritis, the presidents of the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society, and the Japanese Society for Helicobacter Research submitted a joint petition to the Minister of the MHLW. Following this public knowledge-based application, *H. pylori* eradication therapy became available to patients with chronic gastritis on February 21, 2013. The MHLW notification states that eradication therapy is covered by national health insurance when a patient with endoscopically diagnosed chronic gastritis is positive for *H. pylori*.[5)]

One year after this expansion of insurance coverage, the prescription of *H. pylori* eradication therapy was 5-fold higher than before, with an estimated 1.5 million prescriptions per year.[33)]

Strategy and expected effect of eliminating gastric cancer in Japan

In order to eliminate gastric cancer in Japan, the strategy for adolescents should differ from that for elderly persons. This is because eradication of

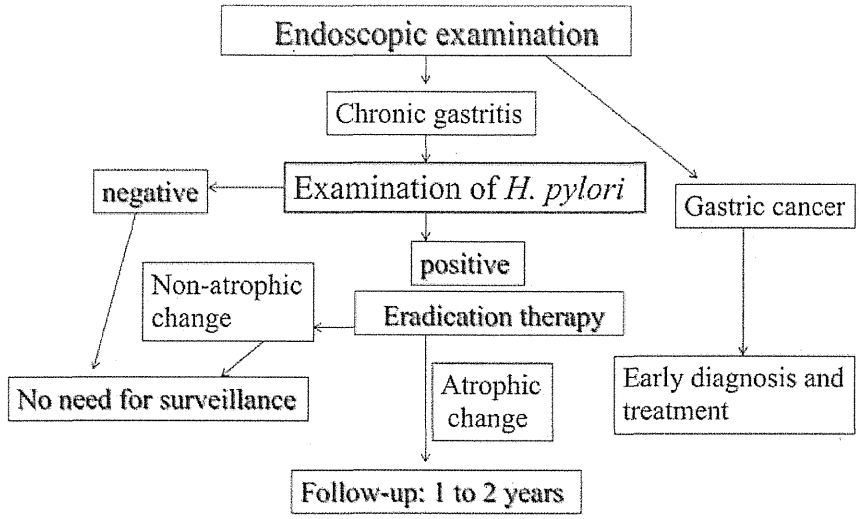

Fig. 3. Strategy for elimination of gastric cancer deaths in Japan.[5]

H. pylori in adolescents achieves nearly 100% prevention of gastric cancer, while the incidence of this cancer increases with advancing age.[34),35)] We recommend a screen-and-treat approach as the strategy for adolescents, which would involve testing for *H. pylori* infection in junior high school and high school followed by immediate eradication therapy if there was a positive result. Eradication of this infection in adolescents should prevent *H. pylori*-related diseases such as gastric ulcer and gastric polyps, as well as preventing nearly 100% of gastric cancers. In the future, it should be possible to reduce the prevalence of most *H. pylori*-related gastric diseases in Japan, including gastric cancer and gastric ulcer, which is likely to attract attention from around the world. It is estimated that approximately 5% of all teenagers in Japan are positive for *H. pylori*,[36)] suggesting that the cost of this approach would not be so high. Some local governments have already scheduled *H. pylori* screening for junior high school students. In Maniwa City of Okayama Prefecture, free *H. pylori* screening for junior high school students was initiated in August 2013 based on measurement of *H. pylori* antibodies in urine specimens. Students who are positive for *H. pylori* receive eradication therapy that costs 6,000 yen, and 80% of the cost is paid by Maniwa City out of an annual budget of 600,000 yen. Other municipal governments, such as Wakkanai City, Fukusima Town, Bihoro Town of Hokkaido Prefecture are starting to take a similar approach to Maniwa City. Because the diagnosis and treatment of *H. pylori*-associated gastritis is only covered by national health insurance for adults, these actions of municipal governments deserve appreciation.

The expansion of insurance cover for eradication therapy to include *H. pylori*-related gastritis allows more individuals with abdominal symptoms to undergo diagnosis and treatment of *H. pylori*-associated gastritis. To qualify for health insurance coverage, endoscopy must be performed first for diagnosis of gastritis, and most patients are likely to have chronic gastritis on endoscopy. Such mandatory endoscopy based on the national health scheme may also increase the detection of gastric cancer. All patients with endoscopic gastritis are then supposed to receive *H. pylori* eradication therapy. For patients with atrophic gastritis, periodic endoscopic follow-up is recommended every 1 or 2 years even after eradication therapy, while patients with no or mild atrophy and those who are negative for *H. pylori* can be followed by optional screening (such as complete medical check-up) instead of strategic screening[5)] (Fig. 3).

Although it is still not clear how effective eradication therapy will be at reducing the development of gastric cancer in patients with *H. pylori*-associated gastritis, prediction can be based on experience with gastric and duodenal ulcer for which *H. pylori* eradication therapy has been covered by the Japanese national health scheme since 2000. As a result, the incidence of gastric and duodenal ulcer has decreased dramatically by about 60% over 10 years.[5)] In particular, duodenal ulcer decreased to 50,000 cases per year in 2011, representing an almost 70% decrease of its incidence during the 10 years of

insurance coverage. In the near future, duodenal ulcer may disappear from Japan. The medical cost of treating gastric and duodenal ulcer also decreased by 47% during the same period. Now that insurance cover is available for *H. pylori* eradication therapy, providing eradication therapy (etiologic treatment) for *H. pylori*-associated gastritis is likely to lead to a long-term reduction in the incidence of gastric cancer, although it is unclear whether the outcome for gastric cancer will be comparable to that for gastric and duodenal ulcer. Eradication therapy for *H. pylori*-associated gastritis should reduce the development of gastric and duodenal ulcer and gastric polyp as well as gastric cancer, expecting that a greater reduction of medical costs will be achieved by expanding insurance cover to patients with *H. pylori*-associated gastritis than by offering insurance to patients with gastric and duodenal ulcer.

Because the baby boomer generation is a huge population that is turning 65 and entering the cancer-prone years, the number of gastric cancer deaths in Japan is likely to reach 60,000 in 2020 without any countermeasures. In contrast, if the gastric cancer elimination project is successful and even 50% of persons with *H. pylori* infection receive eradication therapy, the number of gastric cancer deaths will be reduced to about 30,000 in 2020.[5)]

The cost of gastric cancer treatment in Japan is currently around 300 billion yen per year and will exceed 500 billion yen annually if measures are not taken for a decade or so.[35)] However, if the incidence of gastric cancer is reduced by *H. pylori* eradication, medical costs should be lowered substantially.[37)] A good model may be peptic ulcer for which *H. pylori* eradication therapy was first covered by the Japanese national health scheme in 2000. Since then, the incidence of peptic ulcer has decreased dramatically by about 60% over 10 years. The medical costs of treating ulcers have decreased by no 47% during that period.[5)]

Conclusion

A gastric cancer elimination project that combines *H. pylori* eradication therapy and endoscopic examination is both appropriate and feasible for Japan, where excellent methods of diagnosis and endoscopic treatment for early gastric cancer are already available. In 2013, *H. pylori* eradication therapy for chronic gastritis was covered by the Japanese national health insurance scheme for the first time in the world, making a dramatic decrease of gastric cancer-related deaths more feasible.

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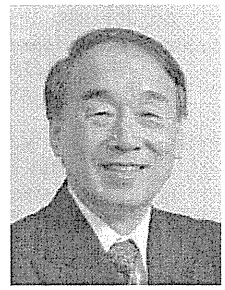
(Received May 2, 2014; accepted July 16, 2014)

Profile



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Pathology – Research and Practice 210 (2014) 440–443

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Short Communication

Human intestinal spirochetosis is significantly associated with sessile serrated adenomas/polyps

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ARTICLE INFO

Article history:
Received 1 July 2013
Received in revised form 25 February 2014
Accepted 5 March 2014

Keywords:
Human intestinal spirochetosis
Sessile serrated adenoma/polyps
Serrated lesion

ABSTRACT

It remains unclear whether or not human intestinal spirochetosis (HIS) has any associated symptoms or lesions. In this study, we assessed the prevalence of HIS in sessile serrated adenomas/polyps (SSA/Ps) and their possible association.

Following identification of early cecal cancer with SSA/P accompanied by a colonization of HIS, we went on to conduct a retrospective case-control study using endoscopically resected SSA/P specimens to examine the frequency of HIS infection in SSA/Ps.

Nineteen SSA/P cases and 172 controls were obtained. The rate of HIS infection was significantly higher at 52.6% (10/19) in the SSA/P cases compared to the controls at 8.1% (14/172).

Our SSA/P series were associated with a remarkably higher rate of HIS than controls or than previously reported. This is the first report to provide evidence for potential association between HIS and SSA/Ps.

Introduction

Among the heterogeneous group of colonic serrated lesions, sessile serrated adenomas/polyps (SSA/Ps) are reported to be associated with malignant alternations, despite their resemblance to hyperplastic polyps (HPs) in gross morphology, through the serrated pathway involving the mutation of the BRAF gene and DNA methylation [1], although the causal factors responsible for such mutation and methylation remain yet to be elucidated. On the other hand, while spirochetes are well-known causative pathogens of watery diarrhea in veterinary medicine [2], there are conflicting reports [3,4] as to whether human intestinal spirochetosis (HIS), which is mostly caused by *Brachyspira aalborgi* (*B. aalborgi*) or *B. pilosicoli*, is associated with symptoms of chronic diarrhea or irritable bowel syndrome. It is also reported that HIS may be responsible for colonic adenomas or hyperplastic polyps (HPs) [5], while its association with neoplasms remains largely unclear [3].

Following identification of a HIS-positive patient in whom both SSA/P and synchronous adenocarcinoma were present (Fig. 1), we conducted a retrospective case–control study using endoscopically resected SSA/P specimens to examine the prevalence of HIS in SSA/Ps and their association.

Subjects and methods

In this case–control study, SSA/P cases consisted of SSA/P lesions endoscopically removed at our hospital and affiliated institutions between January 2008 and December 2011, and controls consisted of colon biopsies endoscopically obtained from non-SSA/P patients

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http://dx.doi.org/10.1016/j.prp.2014.03.007
0344-0338/

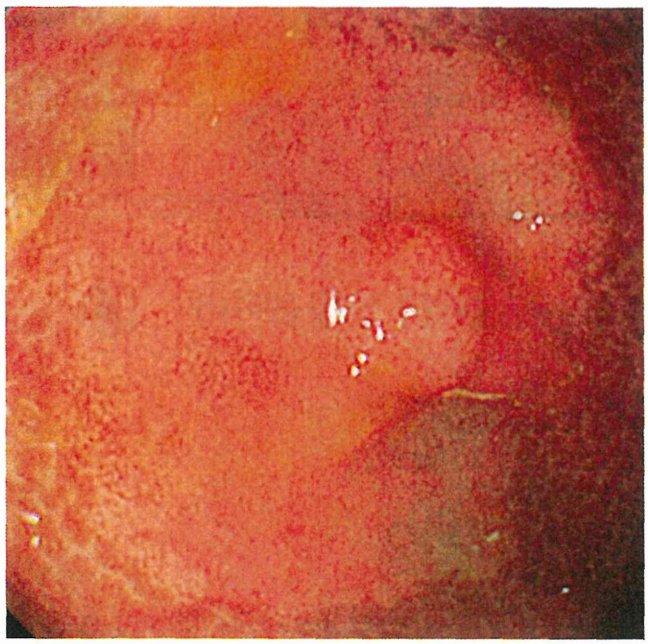

Fig. 1. Endoscopic photograph showing SSA/P with synchronous adenocarcinoma.

at our hospital between July and December 2011. All specimens were fixed in 10% formaldehyde for at least 24 h. Given that spirochetes are reported to attach themselves to the microvilli of the colon [6], control specimens were excluded if they had been taken from patients with advanced colorectal cancer, as they are thought likely to be associated with minimal endothelial microvilli, thus potentially contributing to a low HIS rate among the control specimens.

For all patients diagnosed with SSA/Ps at the participating institutions, endoscopic images, hematoxylin and eosin (HE)-stained and unstained histologic specimens of the lesions were collected for central review at Hokkaido University. Of these, those confirmed by two independent pathologists to be consistent with the findings characteristic of SSA/Ps [7] were included for analysis. In their diagnosis, attention was focused on whether the lesions were associated with two or more of the following: (1) crypt dilation; (2) irregular branching crypts; or (3) horizontally arranged basal crypts (inverted T- and L-shaped crypts) [8] (Fig. 2).

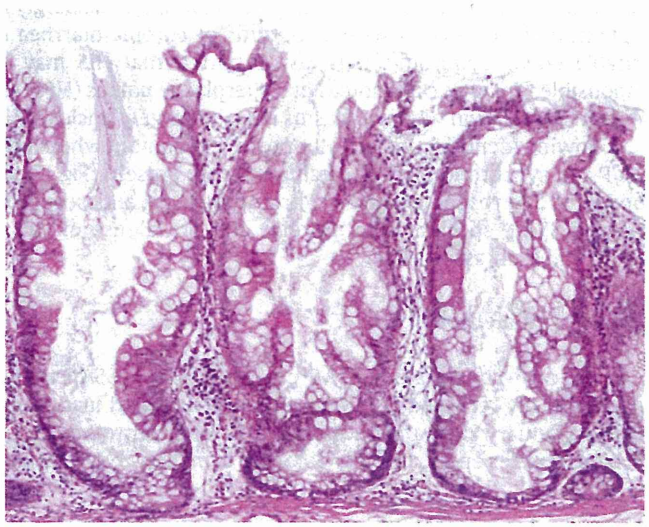

Fig. 2. Photomicrograph showing SSA/P (HE staining).

Table 1
Comparison of SSA/P cases and controls.

	SSA/Ps	Controls	*P* value
Number of cases	19	172	
Number of lesions	35	348	
Mean age (range)	62.3 (25–82)	54.5 (16–89)	ns*
Males/females	12:7	115:57	ns**

* *t*-Test.
** Fisher's exact test; ns, not significant.

All histologic specimens were examined for the presence of HIS by HE staining and immunostaining with anti-*Treponema pallidum* (TP) antibody, which is reported to present a cross reaction with the *Brachyspira* species (AbD Serotec, UK) [9]. Specimens were judged to be HIS-positive if the colonic brush border was found HIS-positive after immunostaining (Fig. 3A) and if the spirochetes were found to be present in the surface or crypt mucus (Fig. 3B).

Statistical analysis

Statistical analyses were performed to compare cases and controls by using Fisher's exact test. All statistical analyses were performed by using SPSS 20 (SAS Institute Inc., Cary, NC, USA). *P* values of < 0.05 were considered statistically significant.

Results

Thirty-five SSA/P cases (19 patients; men, 63.9%; mean age, 62.3 years) and 348 controls (172 patients; men, 66.9%; mean age, 54.6 years) were obtained and subjected to central review and analysis (Table 1). All SSA/Ps were shown to be flat, proximally located, and associated with multiple synchronous lesions, including HPs, adenomas and adenocarcinomas. Furthermore, 3 of the 10 HIS-positive SSA/P cases were associated with adenocarcinomas, with 2 found in the same sites as the SSA/Ps and 1 found in a different site.

All control specimens were biopsy samples, single or multiple, taken from the colon and rectum of the same control patients, and there was no difference in HIS infection rate between these biopsy sites at 7.3% in the right colon and at 8.1% in the left rectum (Fig. 4) ($P = 0.796$). Again, there was no significant difference in HIS infection rate, irrespective of whether single or multiple biopsies were taken from the same control patients (6.3% and 10.4%; 6/95 and 8/77, $P = 0.331$).

The rate of HIS infection was significantly higher at 52.6% (10/19) in SSA/P cases than in controls at 8.1% (14/172) ($P < 0.001$; Fisher's exact test) (Fig. 5).

Of the 14 HIS-positive controls, very few were associated with "fringe formations", thus failing to meet the diagnosis of HIS at the initial diagnosis based on HE staining alone. However, a more detailed examination of the controls involving immunostaining revealed that 9 of the 14 controls were associated with "fringe formations" on HE staining.

Of the 10 HIS-positive SSA/P patients, 4 patients were judged to be positive for HIS both on HE staining (i.e., "fringe formation" present) and on immunostaining, while the remaining 6 were judged to be positive for HIS based on immunostaining, while they showed no "fringe formation" on HE staining. Again, spirochetes were found to be present in both the SSA/P lesions and their background mucosa in 4 patients (40%), in the SSA/P lesions alone in 4 (40%), and in the background mucosa alone in 2 (20%). Spirochetes were found to be present on the surface of the mucosa that remained intact.

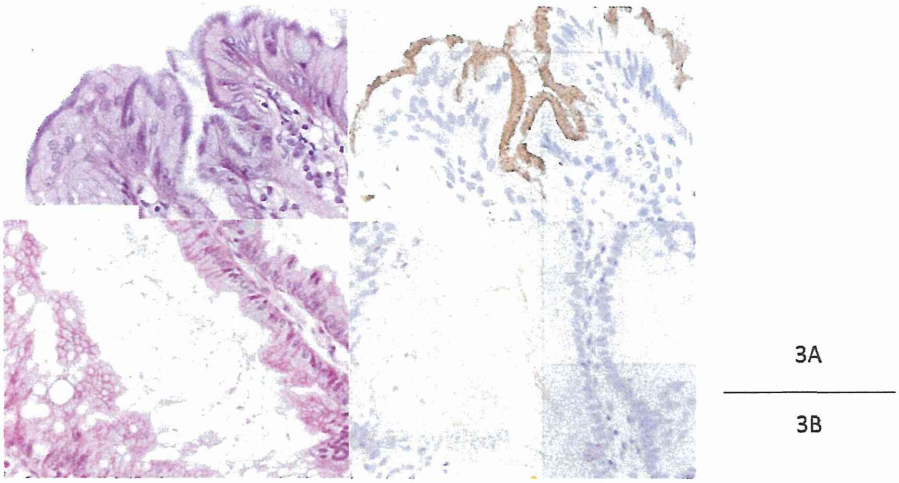

Fig. 3. (A) Photomicrograph showing a HIS-positive "fringe formation" (anti-TP antibody staining). (B) Photomicrograph of HIS-positive tissue with no "fringe formation" showing the spirochetes within the crypts that tested HIS-positive in anti-TP antibody staining.

There was no clear difference between the HIS-positive and -negative SSA/P cases in regard to the degree of lymphocyte infiltration in the background mucosa, amount of mucus on the surface mucosa, or crypt length and breadth (data not shown).

Discussion

Following identification of a case of SSA/P associated with multiple SSA/P lesions covered by mucus, we suspected and examined the presence of some bacterial infection which may account for the onset of SSA/Ps. Study results demonstrated that SSA/Ps as a potential causal factor for the onset of colon cancer are associated with a higher rate of HIS infection than controls, thus strongly suggesting an association between HIS infection and the onset of SSA/Ps.

In recent years, SSA/Ps have come to be characterized as the CpG island methylator phenotype-high (CIMP-high) associated with the mutation of the BRAF gene and regarded as precursor lesions of colorectal cancer. However, the causal factors responsible for such gene mutation or methylation remain largely unknown. In this regard, our results suggest that HIS may be implicated in the pathogenesis of SSA/Ps or their malignant alterations, while they fall short of providing definite evidence for their causal relationship.

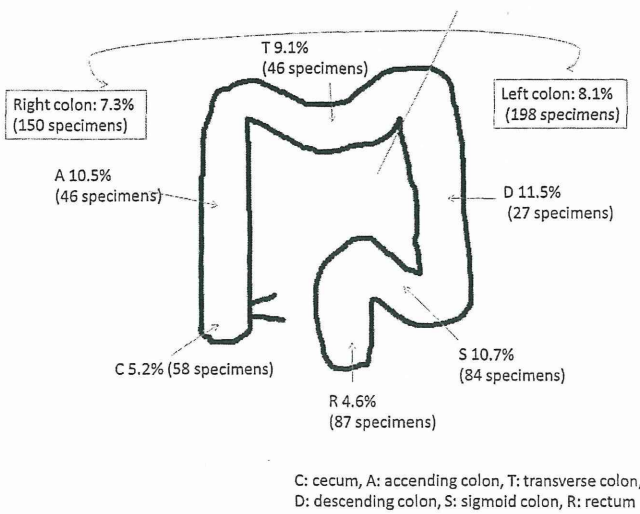

Fig. 4. Rates of HIS at each site in colon and rectum.

In gastric cancer in which *Helicobacter pylori* (*H. pylori*) infection-associated, aberrant methylation is shown to be implicated [10], eradication of *H. pylori* has been shown to reduce the risk of developing gastric cancer not only in animal studies, but also in a prospective, multicenter, randomized, controlled trial [11].

If HIS is to be implicated in the development of SSA/P and/or its malignant alterations, eradication of spirochetes may have a role in reducing the risk of developing colon cancer in a subset of patients, as with *H. pylori* eradication in gastric cancer. Therefore, further studies are warranted to confirm our findings.

In this study, all specimens were examined for the presence of HIS by using both HE staining and immunostaining, which detected HIS infection in a greater proportion of control specimens than was possible in an earlier Japanese report [9] and allowed detection of control specimens associated with a "fringe" formation along the colonic brush border, which may not be characterized as such by HE staining alone. However, our study has several limitations. First, the study involved a small sample size, and it was designed as a retrospective case–control study, although it may be difficult to prospectively investigate the association between HIS and SSA/Ps, given that SSA/Ps are less common in incidence than other colonic adenomas. Second, the endoscopically resected specimens and biopsy specimens differed in regard to their size and location, although this may not be too much of an issue, given that the incidence of HIS did not differ between the biopsy sites examined. In this regard, a comparison of another 10 SSA/P patients and their 10 tubular adenoma controls matched for sex, age, treatment phase, and lesion location/size showed that 9 of 10 (90%) SSA/P patients were found to be positive for HIS, and 4 of 10 (40%) tubular adenoma controls were found to be positive for HIS (no detailed data shown), suggesting that the HIS infection rate may not vary depending on the specimen size or location. Third, the study confined itself to evaluating HIS based on cytological and histological diagnosis alone. More in-depth analysis with PCR may be required to establish the rate of HIS infection and to identify the *B.* species involved, including *B. aalborgi* and *B. pilosicoli*. Again, *in vitro* studies involving cell cultures or animal experiments are required to elucidate the association between HIS and SSA/P-related gene mutations and/or methylation in order to provide further evidence for association between HIS and SSA/Ps.

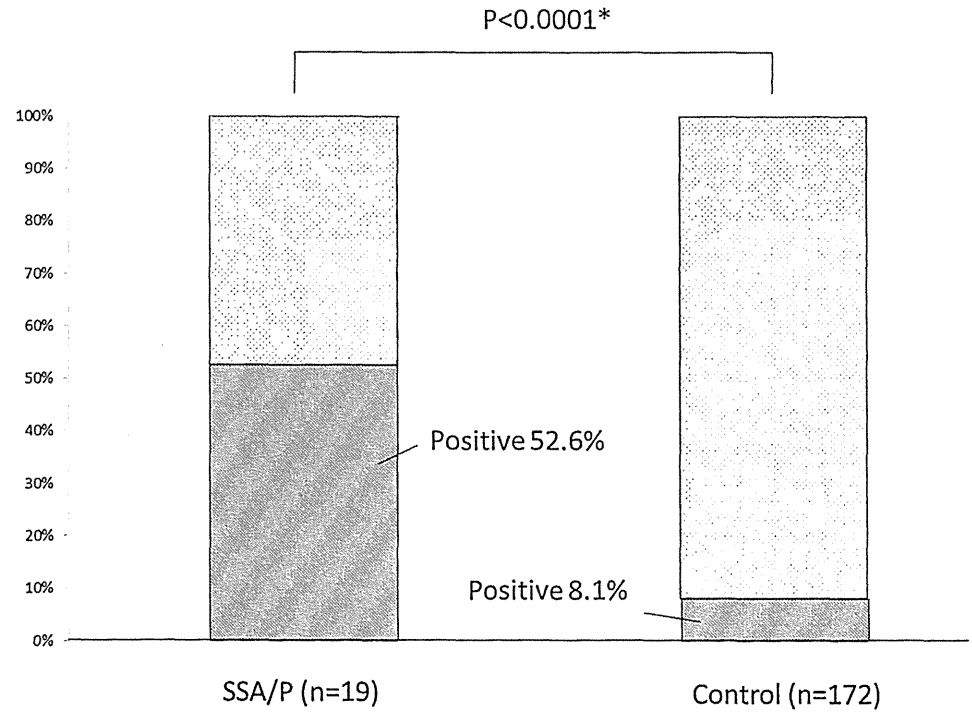

Fig. 5. Rates of HIS in SSA/Ps and controls. *Fisher's exact test

Conclusions

Our SSA/P cases were associated with a remarkably higher rate of HIS than controls or than previously reported. Study results suggest that HIS is among the factors responsible for the pathogenesis of SSA/Ps. To the best of our knowledge, this is the first report to provide evidence for a potential association between HIS and SSA/Ps. Further studies are warranted to examine HIS for an association with SSA/P-related gene mutations and/or methylation.

Take home message

SSA/P cases were associated with a remarkably higher rate of HIS than controls. Immunostaining using anti-*TP* antibody is useful for the detection of HIS.

Funding

None.

Competing interests

None.

Contributors

Study concept and design: KM, MK. Acquisition of data: SM, KM, MO, MM, MT, TY, SO, YS, NS, AS, SK, and TF. Analysis and interpretation of data: SO, KM, KH, MO, and AS. Drafting of the manuscript: SO, KM. Critical revision of the manuscript for important intellectual content: KH, SK, MK, MA, and NS. Administrative, technical or material support: MK, MA, and NS. Study supervision: KM, MK, MA, and NS. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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ORIGINAL ARTICLE

Annals of Gastroenterology (2014) **27,** 149-155

An educational intervention to improve the endoscopist's ability to correctly diagnose small gastric lesions using magnifying endoscopy with narrow-band imaging

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Abstract

Background Magnifying endoscopy with narrow-band imaging (ME-NBI) and a simple and systematic classification system based on microvascular and microsurface patterns, the "VS" classification system (VSCS), have been shown to be useful for the diagnosis of early gastric cancer. The aim of this study was to clarify whether an educational lecture about the VSCS improves performance with ME-NBI.

Methods Sixty-four gastrointestinal endoscopists took the 1st exam before receiving the lecture about the VSCS, the 2nd exam immediately after the lecture, and the 3rd exam 2 months after the lecture. We compared the VSCS-based diagnostic accuracy among the participants before and after the lecture.

Results The proportion of correct diagnoses was significantly higher, at 70.8% in the 2nd exam than in the 1st exam, at 53.1% (P<0.001). The correct diagnosis rate in the 3rd exam was significantly lower than that in the 2nd exam (60.9% vs. 70.8%; P<0.001) but was still higher than that in the 1st exam (60.9% vs. 53.1%; P<0.001). The difference in proportion of correct diagnosis between the 2nd and the 3rd exams was smaller among routine ME-NBI practitioners (n=6; 79.2% and 76.1%, respectively), compared to that among non-routine practitioners (n=34; 71.6% and 59.8%, respectively) or non-practitioners (n=24; 67.5% and 58.8%, respectively).

Conclusion This study revealed that an educational intervention increased correct diagnosis rate of small gastric lesions using the VSCS, diagnosis criteria based on ME-NBI and also showed that the routine use of the modality and the diagnosis criteria was necessary to maintain diagnostic skills.

Keywords Magnifying endoscopy, narrow-band imaging, gastric cancer, educational intervention, diagnostic performance

Ann Gastroenterol 2014; 27 (2): 149-155

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Conflict of Interest: None

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Received 16 July 2013; accepted 27 October 2013

Introduction

Gastric cancer represents the second leading cause of cancer death worldwide, with some 50,000 individuals dying annually from the disease in Japan, where early endoscopic detection of gastric cancer remains the cornerstone that contributes not only to a decrease in mortality from gastric cancer but also to optimization of care, with the use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) being reserved for a subset of patients with early gastric cancer. However, endoscopic diagnosis of gastric lesions, particularly differential diagnosis of small benign versus malignant lesions in the stomach, remains far more difficult than that in the colon and rectum with colonoscopy, due to the background presence of chronic inflammation associated with *Helicobacter pylori* infection [1].

To date, various modalities and image enhancement techniques have been developed to improve the accuracy of endoscopy-based diagnosis. Briefly, in addition to chromoendoscopy [2-4], acetic acid spray [5], and magnifying endoscopy [6], recently, narrow-band imaging (NBI) [7], autofluorescence imaging [8], and endocytoscope with a 450-fold magnification power [9], have been reported to have great promise in improving diagnostic accuracy. However, the usefulness of these novel diagnostic modalities involving the use of cutting-edge equipment has mainly been reported from tertiary care centers, such as university hospitals, with most of these modalities remaining still less readily available for clinical use in general hospitals and clinics.

Of these, the NBI and magnifying endoscopy have recently become available in a considerable number of hospitals in Japan, where the NBI has become established as a modality that allows recognition of squamous epithelial lesions in the laryngopharynx and esophagus as "brownish areas", as well as detailed, qualitative studies of the intraepithelial papillary capillary loops of the squamous mucosa when combined with magnifying endoscopy [10].

As it involves the use of an optical filter with narrow-band transmission, however, the NBI is less well suited for detection of lesions in the stomach with wide lumens. On the other hand, the NBI combined with magnifying endoscopy (ME-NBI) allows differential diagnosis of gastric lesions [11-15] as well as determination of gastric cancer margins [16-17], although ME-NBI still remains less well established among endoscopists, with disparate diagnostic classifications proposed for ME-NBI-guided diagnosis [11-15]. Of the classifications reported to date, the VS classification system (VSCS) proposed by Yao *et al* [14,15] as a simple yet comprehensive classification, appears to have great potential for widespread use.

However, no study has been conducted, to date, to investigate whether an educational intervention may result in improvements in diagnostic accuracy.

We therefore aimed in this study to investigate whether an educational lecture on the VSCS-based, ME-NBI-guided diagnosis might contribute to improvement in the accuracy of ME-NBI-guided diagnosis of benign lesions versus early gastric cancers among endoscopists who received the lecture in this study.

Materials and methods

The present study included gastrointestinal endoscopists who consisted of Japan Gastroenterological Endoscopy Society board-certified (specialist) and non-board-certified (non-specialist) endoscopists including trainees from the Hokkaido area, Japan, to receive a lecture on the VSCS in order to compare the accuracy of ME-NBI-based diagnosis of random, sample ME-NBI images of gastric lesions among the participants before and after the lecture.

The ME-NBI images of gastric lesions used for simulated diagnosis had been taken by the original advocate of the VSCS (K.Y.) from patients treated at Fukuoka University Chikushi Hospital and affiliated hospitals by using magnifying endoscopy (GIF-H260Z, GIF-240Z; Olympus Corporation, Tokyo, Japan) at maximum magnification (approximately x80), equipped with a soft black hood (MB-162 for GIF-Q240Z, MB-46 for GIF-H260Z; Olympus Corporation, Tokyo, Japan) and a light source (CV-260SL; Olympus Corporation, Tokyo, Japan) (ME-NBI), and the diagnosis of each lesion depicted by the ME-NBI had earlier been histologically confirmed based on biopsy or resected specimens.

In conjunction with the use of the ME-NBI images, it was ensured that all personal information, such as patient name, ID number, sex, and age, by which an individual could be identified, was omitted from the images. Approval was obtained from the institutional review board of the Hokkaido University Hospital for this study using ME-NBI images from patients treated at another tertiary care center to compare diagnostic outcomes.

Three sets of questions were developed by the instructor with each involving a total of 20 ME-NBI images of small gastric mucosal lesions (10 non-cancerous and 10 cancerous lesions). The exams consisted of multiple-choice questions that had to do with: 1) the demarcation line (DL); 2) the microvascular pattern; 3) the microsurface pattern; and 4) endoscopic diagnosis (1. benign; 2. potentially benign; 3. potentially malignant; 4. malignant; and 5. unknown) (Fig. 1). The participants were blinded to the content of the exam questions and the histological diagnosis of each lesion used during the exams.

The educational lecture was given by the advocate of the VSCS (K.Y.) on January 12, 2011, in which still ME-NBI images were used to illustrate the VSCS-based, ME-NBI-guided diagnosis. Prior to the lecture, the participants were given instructions about the exams and how to answer the exam questions. Participants took the 1st exam before receiving the lecture about VSCS, the 2nd exam immediately after the lecture, and the 3rd exam 2 months later to compare the accuracy of VSCS-based diagnosis among the participants (Fig. 2). Gastric cancers were diagnosed in the exams in accordance with the VSCS, i.e., in terms of the presence of an irregular microvascular pattern with a demarcation line or the presence of an irregular microsurface pattern with a demarcation line. All completed answer sheets for each exam were collected from the participants at the completion of the study.

Statistical analysis

The main outcome measure was the improvement in the proportion of correct diagnosis after the lecture. A correct diagnosis was judged to have been made in accordance with the VSCS in the exams if the diagnosis made was consistent with the findings identified on the demarcation line, the

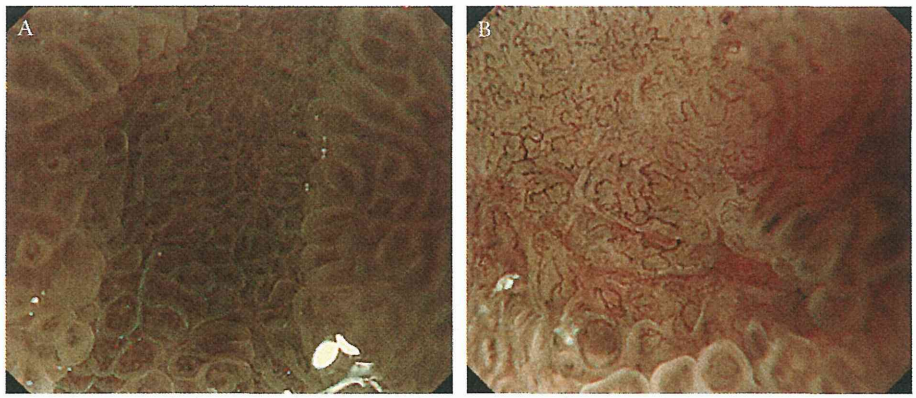

Figure 1 Examples of the magnifying endoscopy with narrow-band imaging images of gastric lesions used for the exams. (A) Non-cancerous lesion with a demarcation line but without an irregular microvascular or irregular microsurface pattern (intestinal mataplasia). (B) Gastric cancer with a demarcation line, irregular microvascular and microsuraface patterns

microvascular pattern, and the microsurface pattern, which represented the major diagnostic components of the VSCS, and thus met the VSCS criteria. In addition, it was calculated separately in malignant lesions and benign lesions. In detail, the proportion of correct diagnosis was individually calculated as the number of the correct diagnosis divided by the number of questions, and then their means were calculated. The means were compared by using the *t*-test (between unpaired two groups), ANOVA with *post hoc* Tukey Kramer test (between more than two unpaired groups), paired *t*-test (between two paired groups), or multiple paired *t*-test with Bonferroni's correction (between more than two paired groups). Other continuous variables were also compared by using the *t*-test. Categorical variables were compared by using Fisher's exact test or chi-square test. Ordinal variables were compared by using Mann-Whitney test. All statistical analyses were performed by using SPSS 20 (IBM). P values of <0.05 were considered statistically significant.

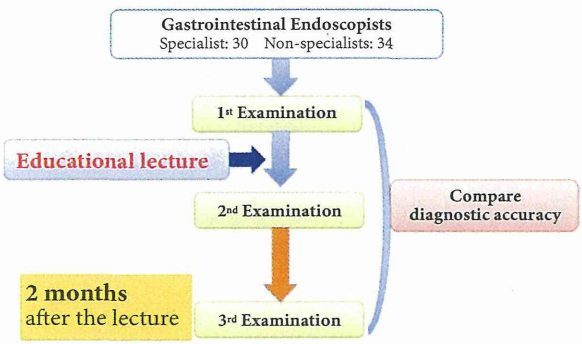

Figure 2 Protocol design of the study. A total of 64 endoscopists (34 specialists and 30 non-specialists) attended the lecture and completed all exams, and were eligible for analysis in this study. They took the 1st exam before receiving the lecture about the microvascular and microsurface classification system, the 2nd exam immediately after the lecture and the 3rd exam 2 months after the lecture

Results

A total of 64 endoscopists (34 specialists and 30 non-specialists) attended the lecture, completed all exams and were eligible for analysis in this study. The characteristics of participants are summarized in Table 1. There was a significant difference between the specialists and the non-specialists with regard to experience with endoscopy, magnifying endoscopy, and ESD. However, there was no difference between the groups with regard to their possession of textbooks describing the VSCS, participation in VSCS-related lectures, and frequency of use of magnifying endoscopy (Table 1).

The average proportion of correct diagnosis among the participants was significantly higher in the 2nd exam at 70.8% than in the 1st exam (before the lecture) at 53.1% (P<0.001), with significant improvement also noted in malignant lesions (2nd exam, 70.8%; 1st exam, 47.0%; P<0.001) and in benign lesions (2nd exam, 70.8%; 1st exam, 59.2%, P<0.001) (Table 2). A comparison of the diagnostic performance as stratified by board-certification status showed that the proportion of correct diagnosis in malignant and benign lesions were both significantly improved in the 2nd exam, compared to the 1st exam. Furthermore, although the proportion of correct diagnosis (total) was significantly different between the specialists (56.8%) and the non-specialists (49.0%) in the 1st exam (P=0.009), no significant difference was observed between the specialists (71.8%) and the non-specialists (69.7%) in the 2nd exam (P=0.597) (Table 2). Again, the proportion of correct diagnosis in the 3rd exam 2 months after the lecture was significantly lower at 60.9% than in the 2nd exam (P<0.001), but was higher than that in the 1st exam (53.1%) (P<0.001). No significant difference was observed between the specialists (60.4%) and the non-specialists (61.6%) in the 3rd exam (P=0.752) (Table 2, Fig. 3).

A comparison of the participants by frequency of use of magnifying endoscopy in their practice showed that there was a significant improvement among the participants in the 2nd exam, compared to the 1st exam, regardless of frequency of

Table 1 Characteristics of the participants in this study

	Non-specialists (n=30)	Specialists (n=34)	Total (n=64)	P value
Endoscopic experience (years)	4.9 ± 5.6	16.7 ± 6.9		<0.001*
Number of endoscopic procedures with magnifying endoscopy				
< 50	26	20	46	0.011†
51-100	2	4	6	
101-500	2	9	11	
> 501	0	1	1	
Experience with ESD				
No	17	10	27	0.042‡
Yes	13	24	37	
Possession of VSCS textbooks				
No	19	25	44	0.427‡
Yes	11	9	20	
Past participation in VSCS lectures				
No	13	10	23	0.301‡
Yes	17	24	41	
Frequency of use of magnifying endoscopy				
No, I do not use it	14	15	24	
Yes, I use it sometimes (for in-depth exams only)	15	19	34	
Yes, I routinely use it	1	5	6	0.080†

** t-test, † Mann-Whitney test, ‡ Fisher's exact test*
ESD, endoscopic submucosal dissection; VSCS, microvascular and microsurface classification system

use of magnifying endoscopy, while there was a significant decrease in the correct diagnosis rate in the 3rd exam among the participants except for the routine ME-NBI users, compared to that in the 2nd exam. Furthermore, while there was no significant difference in the correct diagnosis rate among the participants in both the 1st and 2nd exams, there was a significant difference in the correct diagnosis rate between the routine ME-NBI users and the other endoscopists. Of note, the difference in the proportion of correct diagnosis between the 2nd exam and the 3rd exam was much smaller among the routine ME-NBI users (n=6; 79.2% to 76.1%), compared to that among the non-routine users (n=34; 71.6% to 59.8%) or the non-users (n=24; 67.5% to 58.8%) (Table 3, Fig. 4).

Discussion

Early endoscopic diagnosis of gastric mucosal lesions, particularly differential diagnosis between non-cancerous and cancerous lesions, is critically important in determining or obviating the need for endoscopic biopsy or therapy.

Novel diagnostic approaches involving the use of chromoendoscopy, magnifying endoscopy, and new spectrum endoscopy have been reported to be useful in improving the accuracy of endoscopic diagnosis. In this regard, the ME-NBI has been reported to be useful in the diagnosis of gastric cancer [11-16], as well as in the recognition of gastric cancerous margins [17,18]. In a prospective study [19], the ME-NBI

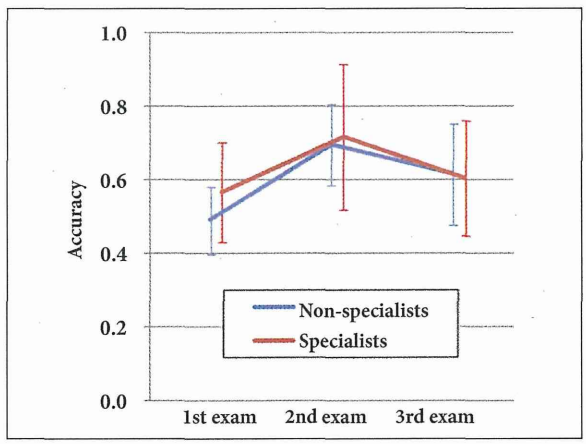

Figure 3 The difference of the accuracy between specialists and non-specialists before and after the lecture. This shows the accuracy as stratified by board-certification status. Accuracy was significantly different between the specialists (56.8%) and the non-specialists (49.0%) before the lecture but no significant difference was observed after the lecture

Table 2 The average proportion of correct diagnosis before and after the lecture

			1st		2nd		3rd		P value*		
		N	Mean	SD	Mean	SD	Mean	SD	1st vs. 2nd	1st vs. 3rd	2nd vs. 3rd
All endoscopists	Total	64	0.531	0.120	0.708	0.157	0.609	0.145	<0.001	0.001	<0.001
	In malignant lesions	64	0.470	0.183	0.708	0.226	0.618	0.220	<0.001	<0.001	0.002
	In benign lesions	64	0.592	0.204	0.708	0.197	0.601	0.177	0.002	1.000	<0.001
Non-specialists	Total	30	0.490	0.135	0.697	0.198	0.616	0.155	<0.001	0.002	0.004
	In malignant lesions	30	0.433	0.215	0.707	0.264	0.604	0.214	<0.001	0.004	0.010
	In benign lesions	30	0.547	0.224	0.687	0.229	0.627	0.181	0.028	0.360	0.286
Specialists	Total	34	0.568	0.091	0.718	0.110	0.604	0.138	<0.001	0.298	<0.001
	In malignant lesions	34	0.503	0.145	0.709	0.191	0.629	0.227	<0.001	0.023	0.158
	In benign lesions	34	0.632	0.179	0.726	0.166	0.578	0.173	0.072	0.470	<0.001
P value for difference between groups†	Total			0.009		0.597		0.752			
	In malignant lesions			0.130		0.970		0.654			
	In benign lesions			0.094		0.424		0.280			

** Multiple pairwise comparisons by paired t-test with Bonferroni's correction*
† Comparison between non-specialists and specialists in each test
SD, standard deviation

has also been reported to be more useful in the diagnosis of small depressed gastric lesions than magnifying endoscopy with a regular light source.

Commercially available NBI systems allow the endoscopists to alternate readily between normal white-light and NBI viewing modes simply by pressing a button on the handle of the endoscope. However, the ME-NBI has remained less well established as a diagnostic modality among the endoscopists, with various diagnostic classifications proposed for ME-NBI-guided diagnosis [11-15].

In this regard, the VS classification system (VSCS) proposed by Yao *et al* [14,15] is of particular interest, in that it draws on a combination of findings on 1) the demarcation line; 2) the microvascular pattern; 3) the microsurface pattern, where any lesion with a demarcation line and an irregular microvascular pattern or/and an irregular microsurface pattern is diagnosed as gastric cancer, with all other lesions which fail to meet these criteria diagnosed as non-cancerous lesions. While some of the proposed classifications are intended for in-depth diagnosis including the histological type of tumor, the VSCS represents a simple yet comprehensive diagnostic classification system which is readily available for widespread use among specialist and non-specialist endoscopists alike.

Our study findings showed that educational lectures on the VSCS improve the ability of both specialist and non-specialist endoscopists to correctly diagnose small gastric lesions using ME-NBI and this improvement appears to have been accounted for by improvement in VSCS-based diagnosis, demonstrating both the utility of the VSCS in the diagnosis of gastric lesions and the usefulness of educational lectures on the VSCS in improving diagnostic accuracy. This study also revealed that the routine use of ME-NBI and the VSCS was necessary to maintain high diagnostic accuracy after the educational lecture.

Although the VSCS and the ME-NBI were used for the differential diagnosis of small gastric lesions in this study, both the VSCS and the ME-NBI are also shown to be useful in the

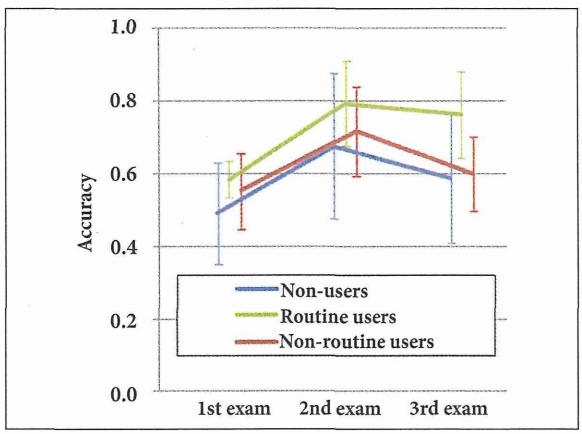

Figure 4 Proportion of correct diagnoses made in accordance with the VSCS by frequency of use of magnifying endoscopy in each exam. This figure shows the accuracy by frequency of use of magnifying endoscopy in each exam. The difference in diagnostic accuracy between the 2nd and the 3rd exams was smaller among routine magnifying endoscopy with narrow-band imaging practitioners (n=6; 79.2% and 76.1%, respectively), compared to that among non-routine practitioners (n=34; 71.6% and 59.8%, respectively) and non-practitioners (n=24; 67.5% and 58.8%, respectively)

Table 3 Diagnostic accuracy before and after the lecture by frequency of use of magnifying endoscopy in each exam

Frequency of use of magnifying endoscopy	1st			2nd		3rd		P value*		
	n	Mean	SD	Mean	SD	Mean	SD	1st vs. 2nd	1st vs. 3rd	2nd vs. 3rd
a. Non-users	24	0.490	0.141	0.675	0.199	0.588	0.180	<0.001	0.061	0.036
b. Non-routine users	34	0.551	0.104	0.716	0.122	0.598	0.103	<0.001	0.163	<0.001
c. Routine users	6	0.583	0.052	0.792	0.116	0.761	0.120	0.006	0.011	1.000
		Difference	P†	Difference	P†	Difference	P†			
a vs. b		0.062	0.123	0.041	0.540	0.011	0.956			
a vs. c		0.094	0.192	0.117	0.235	0.174	0.021			
b vs. c		0.032	0.812	0.075	0.520	0.163	0.027			

** Multiple pairwise comparisons by paired t-test with Bonferroni's correction*
† Multiple comparisons between groups in each test by Tukey Kramer test
SD, standard deviation

recognition of gastric cancer demarcation lines [15,17,18], which is particularly important for *en bloc* resection in ESD which allows resection of large lesions. In this regard, the educational lecture on the VSCS-based, ME-NBI-guided diagnosis as it was given in this study was also thought to assist in determining gastric cancerous margins.

The present study has some limitations. It is not an *in vivo* study. The diagnostic process can be divided into two steps, detection and characterization [20]. While endoscopic diagnosis in a real-world, clinical setting calls for ME-NBI-based imaging techniques, as well as the ability to perform real-time detection technique and diagnoses, in addition to the diagnostic capabilities evaluated in this study, the study used only still images taken by an expert endoscopist in comparing diagnostic performance. Indeed, a tailored training program is required to enable endoscopists to perform accurate ME-NBI-guided diagnoses, as shown in the ME-NBI-guided diagnosis of colorectal lesions [21,22]. Thus, this limitation needs to be taken into account when considering the study and its contributions.

On-site educational lectures by expert endoscopists may also have limited contributions to improvement in diagnostic performance. In this regard, web-based training programs have been reported to be useful [23], suggesting that future educational lectures may have greater contributions when presented in media that provide a larger number of physicians with the benefit of repeated learning and testing, such as web-based programs or DVDs.

In conclusion, an educational lecture about the VSCS improved the accuracy of ME-NBI-guided diagnosis of gastric mucosal lesions. The routine use of VSCS-based ME-NBI may be required to maintain high diagnostic performance as well as to obviate the need for biopsies to rule out malignancies and allow safe and early diagnosis of gastric cancer.

Summary Box

What is already known:

- Various modalities and image enhancement techniques have been developed to improve the accuracy of endoscopy-based gastric cancer diagnosis
- Magnifying endoscopy with narrow-band imaging (ME-NBI) has been shown to be useful for the differential diagnosis of gastric lesions as well as determination of gastric cancer margins
- The "VS" classification system (VSCS), one of the classifications for ME-NBI-guided diagnosis, has been shown to be useful for the diagnosis of early gastric cancer

What the new findings are:

- An educational intervention about the VSCS improved the accuracy of ME-NBI-based diagnosis among endoscopists, regardless of the board-certification status, suggesting that the VSCS may have potential for widespread use in conjunction with ME-NBI
- The routine use of VSCS-based ME-NBI may be required to maintain high diagnostic performance

Acknowledgments

The authors thank all endoscopists who attended the lecture and participated in the study

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