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Guidelines

Guidelines for endoscopic diagnosis of early gastric cancer

Kenshi Yao, Noriya Uedo, Tomoari Kamada, Toshiaki Hirasawa, Takashi Nagahama, Shigetaka Yoshinaga, Masashi Oka, Kazuhiko Inoue, Katsuhiro Mabe, Takashi Yao, Masahiro Yoshida, Isao Miyashiro, Kazuma Fujimoto and Hisao Tajiri

Japan Gastroenterological Endoscopy Society, Tokyo, Japan

The Japan Gastroenterological Endoscopy Society developed the Guideline for Endoscopic Diagnosis of Early Gastric Cancer based on scientific methods. Endoscopy for the diagnosis of early gastric cancer has been acknowledged as a useful and highly precise examination, and its use has become increasingly more common in recent years. However, the level of evidence in this field is low, and it is often necessary to determine recommendations based on expert consensus only. This clinical practice guideline consists of the following sections to provide the current guideline: [I] Risk stratification of gastric cancer before endoscopic examination, [II] Detection of early gastric cancer, [III] Qualitative diagnosis of early gastric cancer, [IV] Diagnosis to choose the therapeutic strategy for gastric cancer, [V] Risk stratification after endoscopic examination, and [VI] Surveillance of early gastric cancer.

Key words: diagnosis of early gastric cancer, endoscopic examination, guideline

INTRODUCTION

BASIC PRINCIPLES ARE necessary to ensure the safe and accurate implementation of the endoscopic diagnosis of early gastric cancer. Although guidelines for the endoscopic treatment of gastric cancer and screening for gastric cancer not necessarily using endoscopy have been published to date, no guidelines specialized for the endoscopic diagnosis of early gastric cancer have been developed. In this background, the Japan Gastroenterological Endoscopy Society (JGES) Guideline Committee decided to develop a new guideline for the endoscopic diagnosis of early gastric cancer based on scientific findings. This guideline is applied to all adults who may undergo endoscopic examinations of the stomach and is aimed at facilitating the accurate diagnosis of early gastric cancer by endoscopy to improve mortality and quality of life (QOL) of patients with gastric cancer. To this end, we have assembled and interpreted the available evidence to provide recommendations for appropriate clinical decisions according to the personal values of individual patients (Table 1).

This guideline was prepared using evidence-based medicine (EBM), a common and international standard method. More specifically, we followed the Minds Handbook for Clinical Practice Guideline Development 2014[1] (Table 2). The guideline is written in the form of reviews with statements. Because there was insufficient high-level evidence in this field, we had to attach weight to expert consensus opinions. We expect that this guideline will serve as a useful standard for the endoscopic diagnosis of early gastric cancer.

Corresponding: Kenshi Yao, Japan Gastroenterological Endoscopy Society, 4th Floor, Shin-Ochanomizu Urban Trinity Building, 3-2-1 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan. Email: yao@fukuoka-u.ac.jp

All authors are belonging to Japan Gastroenterological Endoscopy Society Committee Guideline for Endoscopic Diagnosis of Early Gastric Cancer

Each author's contribution is shown in Table 3 in the text.

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GUIDELINE DEVELOPMENT

Committee members

THE JGES COMMITTEE on Guideline for Endoscopic Diagnosis of Early Gastric Cancer comprised a development panel of six gastroenterological endoscopists in charge of developing the guideline. There was also an internal evaluation panel comprising three

Table 1 Guideline for endoscopic diagnosis of early gastric cancer: list of statements

Statement no.	Statement	Strength of recommendation	Level of evidence	Page no.
[I] Risk stratification of gastric cancer before endoscopic examination				
1-1	Several factors such as *Helicobacter pylori (H. pylori)* infection, atrophy of the gastric mucosa, hereditary disease, and smoking have been cited as obvious risk factors for gastric cancer. Other factors reported as possible risk factors include diet, lifestyle preferences, and Epstein–Barr (EB) viral infection	Background knowledge	C	6
1-2	The risk of gastric cancer can be stratified before endoscopic examination. A beneficial economic effect can be expected from this risk stratification. However, issues about the optimal method remain	Background knowledge	C	11
1-3	A combination of serum *H. pylori* antibody and serum pepsinogen may be useful for risk stratification of gastric cancer. However, false negative results can occur in cases of severe atrophy and past infection in *H. pylori* antibody titer measurement and cut-off value, interpretation of pepsinogen (PG) levels, and PG I/PG II ratio cut-off value	2	C	12
[II] Detection of early gastric cancer				
2-1	The use of gastric peristalsis-inhibiting drugs should be considered in cases in which observation is difficult because of intense peristalsis	None	D	13
2-2	The use of mucolytic agents to dissolve and remove the gastric mucosa and defoaming agents is strongly recommended because improved visibility of the mucosa leads to the detection of early gastric cancer	1	D	14
2-3	Sedatives and analgesics may be used with caution for possible adverse reactions in subjects who have strong anxiety or in whom observation is difficult because of reflex or body movements	None	D	15
2-4	The observation duration of the stomach is associated with the detection of early gastric cancer. The stomach should be observed taking sufficient time	1	D	16
2-5	The stomach should be systematically observed to detect early gastric cancer	1	D	17
2-6	The usefulness of image-enhanced endoscopy for the detection of early gastric cancer is under discussion	None	D	18
[III] Qualitative diagnosis of early gastric cancer (differential diagnosis of cancer and non-cancer)				
3-1	Image-enhanced endoscopy is useful for the qualitative diagnosis of early gastric cancer; thus, its use is recommended	2	A	20
[IV] Diagnosis to choose the therapeutic strategy for gastric cancer				
4-1	A close pretreatment endoscopic examination is necessary for determining the therapeutic strategy in cases of early gastric cancer	1	D	25
4-2	Diagnosis of the histologic type of cancer should be performed comprehensively by endoscopic diagnosis and histopathological diagnosis using biopsy specimens	2	D	26
4-3	Although a rough estimation of lesion size can be obtained by endoscopy, an endoscopic diagnosis should be made on the premise that the lesion size should finally be judged after obtaining histopathological findings of the resected specimen	Background knowledge	D	22
4-4	In principle, conventional white-light endoscopy should be used for determining the depth of invasion of early gastric cancer. If this is difficult, endoscopic ultrasonography may be a useful adjunctive diagnostic tool	2	C	27
4-5	In principle, conventional white-light endoscopy should be used for determining the presence/absence of active ulcers and ulcer scars associated with early gastric cancer	2	D	28
4-6	Image-enhanced endoscopy is useful for diagnosing the extent of invasion	1	B	29
[V] Risk stratification after endoscopic examination				
5-1	Atrophy, intestinal metaplasia, goose bumps, swelling of the plica, and gastric xanthoma are endoscopic findings related to the risk of gastric cancer	Background knowledge	B	30

Table 1 (*Continued*)

Statement no.	Statement	Strength of recommendation	Level of evidence	Page no.
5-2	Risk stratification of gastric cancer may be implemented based on endoscopic findings of *H. pylori*-negative status and gastric mucosal atrophy. Thus, risk stratification using these two items is proposed	2	C	32
[VI] Surveillance of early gastric cancer				
6-1	A surveillance endoscopic examination is recommended for patients with risk factors for gastric cancer (clinical and endoscopic findings)	1	B	34

Table 2 Strength of recommendation and level of evidence

Strength of recommendation
1: Strongly recommended
2: Weakly recommended (proposed)
None: A definite recommendation cannot be made, or its strength cannot be decided
Level of evidence
A: Based on strong evidence
B: Based on moderate evidence
C: Based on weak evidence
D: Based on very weak evidence

gastroenterological endoscopists, one pathologist, one doctor in charge of guideline development methodology, and one epidemiologist. Three external evaluation panel members were also asked to conduct an evaluation (Table 3).

Strength of recommendation, level of evidence, and statement

The development panel members set up the following seven items: definition of early gastric cancer and significance of diagnosing early gastric cancer by endoscopy; risk stratification of gastric cancer prior to implementation of endoscopic examination; detection of early gastric cancer; qualitative diagnosis of early gastric cancer (differential diagnosis of cancer and non-cancer); diagnosis to choose the therapeutic strategy of gastric cancer; risk stratification after endoscopic examination; and surveillance of early gastric cancer. Because the definition of early gastric cancer and significance of diagnosing early gastric cancer by endoscopy represent the major premise on which this guideline is formulated, this item is not presented as a statement, but is rather described in the guideline's preamble. Consequently, clinical questions (CQs) were prepared for the other six items, and modifications were made in reference to opinions of the internal evaluation panel to make 19 statements. On the other hand, basic issues important to the understanding of clinical practice for patients with early gastric cancer (such as clinical and epidemiological features, pathological conditions, overall diagnosis and treatment course, and current standard method of the diagnosis and treatment) were managed separately as "background knowledge." More specifically, "background knowledge" includes the latest information, whereas CQs were managed separately for the development and presentation of recommendations through a systematic review. The policy underlying this act was derived from "Proposal from Minds: What are clinical questions in clinical practice guidelines?" (http://minds4.jcqhc.or.jp/minds/guideline/pdf/Proposal4_ver.1.0.pdf). For each CQ, a systematic literature search of PubMed, Cochrane, and Igaku Chuo Zasshi was conducted from database inception to February 2017. A detailed description of key words and search formulas was given for each statement. Additionally, a manual search was also performed for insufficient studies. The retrieved articles were evaluated by type: randomized controlled trials, observational studies (cohort or case–control studies), and meta-analyses. If these articles were insufficient, case series studies were also examined. Animal experiments and genetic studies were excluded from these articles, and the statement and expository writing were prepared for each CQ. The development panel members determined the level of evidence for each article of the field in their charges and the strength of recommendation and the level of evidence for each statement according to the Minds Handbook for Clinical Practice Guideline Development 2014.

Using the prepared statements and commentaries, the guideline in a review form was developed. For the proposed statements, a total of 12 people, comprising the development panel members and the internal evaluation panel members, voted according to the modified Delphi method, which uses a scoring system (1–3, non-consensus; 4–6, dissatisfaction; 7–9, consensus), and the proposed statements were adopted as statements when the score was 7 or higher. The proposed statements with a score of 6 or less were modified or the strength of recommendation was amended through discussion, and voting was repeated until a score of 7 or higher

Table 3 Committee on endoscopic diagnosis of early gastric cancer guideline development

JGES Guideline Committee	
President	Hisao Tajiri (Department of Innovative Interventional Endoscopy Research, The Jikei University School of Medicine)
Director in charge	Kazuma Fujimoto (Department of Internal Medicine, School of Medicine, International University of Health and Welfare)
Chairperson	Kazuma Fujimoto (Department of Internal Medicine, School of Medicine, International University of Health and Welfare)
JGES Committee on Guideline for Endoscopic Diagnosis of Early Gastric Cancer	
Chairperson	Kenshi Yao (Department of Endoscopy, Fukuoka University Chikushi Hospital)
Development panel chairperson	Kenshi Yao (Department of Endoscopy, Fukuoka University Chikushi Hospital)
Development panel members	Noriya Uedo (Department of Gastrointestinal Oncology, Osaka International Cancer Institute) Tomoari Kamada (Department of Health Care Medicine, Kawasaki Medical School General Medical Center) Toshiaki Hirasawa (Department of Gastroenterology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research) Takashi Nagahama (Department of Gastroenterology, Fukuoka University Chikushi Hospital) Shigetaka Yoshinaga (Endoscopy Division, National Cancer Center Hospital)
Evaluation panel chairperson	Masashi Oka (Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University)
Evaluation panel members	Kazuhiko Inoue (Junpukai Long Life Hospital) Katsuhiro Mabe (Department of Gastroenterology, National Hospital Organization Hakodate National Hospital) Takashi Yao (Department of Human Pathology, Juntendo University Graduate School of Medicine) Masahiro Yoshida (Department of Hemodialysis and Surgery, Ichikawa Hospital, International University of Health and Welfare) Isao Miyashiro (Cancer Control Center, Osaka International Cancer Institute)
External evaluation panel members	Takeo Nakayama (Department of Health Informatics, Kyoto University Graduate School of Medicine and Public Health; specialized area: guideline development methodology) Shogo Kikuchi (Department of Public Health, Aichi Medical University School of Medicine. Specialized area: public health, screening, surveillance) Hisao Tajiri (Department of Innovative Interventional Endoscopy Research, The Jikei University School of Medicine; specialized area: endoscopic medicine)
Collaborating societies	Japanese Gastric Cancer Association, Japanese Society of Gastrointestinal Cancer Screening, Japanese Society of Gastroenterology, Japanese Gastroenterological Association, Japanese Society for *Helicobacter* Research, Japanese Society of Pathology, Japan Society of Ningen Dock

Each member's facility was shown according to the information when the guideline was developed.

was achieved. The completed draft guideline was evaluated by external evaluation panel members and disclosed to the JGES members to elicit public comment. The draft was amended after discussion on the results of these procedures to finalize the guideline.

Targets

The assumed target of this guideline is healthcare professionals (for example, doctors, nurses, clinical engineers and technicians) engaged in the clinical practice of gastroenterological endoscopy. This guideline provides standard policies that should be used flexibly according to individual patients, patient age, complications, social situations, and facility circumstances.

Authors' Conflicts of Interest Related to the Context of this Article

(1) Disclosure: Each of the guideline development and evaluation panel members were asked to disclose all matters that applied to the following condition: concerning companies or organizations from which the panel member, as an individual, received any remuneration such as reward (1,000,000 yen or more), stock profit (1,000,000 yen [or 5%] or more), patent royalty (1,000,000 yen or more),

speaking honoraria (500,000 yen or more), manuscript fee (500,000 yen or more), research fund or grant (1,000,000 yen or more), scholarship (encouragement) donation (1,000,000 yen or more), donated fund laboratory provided by a company (1,000,000 yen or more), and offering that had no direct relationship with the study (50,000 yen or more).

Kenshi Yao (Speaking honorarium: Olympus Corporation), Masashi Oka (Speaking honorarium: Mylan EPD), Kazuhiko Inoue (Speaking honoraria: Takeda Pharmaceutical Company Limited; Eisai Co., Ltd.; AstraZeneca; Daiichi Sankyo Company, Limited; Otsuka Pharmaceutical Co., Ltd.), Katsuhiro Mabe (Speaking honoraria: Takeda Pharmaceutical Company Limited; Eisai, Co., Ltd.; and Donated fund laboratory: Eisai Co., Ltd.), and Takashi Yao (Speaking honorarium: Takeda Pharmaceutical Company Limited).

Other authors have no COI to disclose.

(2) Management: To manage conflicts of interest, each panel member was required to disclose academic as well as the above-mentioned financial conflicts of interest. Panel members who had conflicts of interest abstained from voting on the recommendation strengths.

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REVISION

THIS GUIDELINE WILL be revised in about 5 years with the JGES Guideline Committee taking a central role, in the light of the accumulation of new evidence and advances in devices and techniques.

THE GUIDELINE FOR ENDOSCOPIC DIAGNOSIS OF EARLY GASTRIC CANCER

Preamble to the guideline; definition of early gastric cancer and significance of diagnosing early gastric cancer endoscopically

EARLY GASTRIC CANCER is defined as gastric cancer occurring in the gastric mucosa and confined to the mucosa or submucosa irrespective of lymph node metastasis.[1]

Whether the detection of early gastric cancer and its subsequent treatment can decrease mortality rates should be judged only from the results of observational studies because it is realistically impossible to perform a randomized controlled trial to compare patients undergoing endoscopy and those not undergoing endoscopy in terms of mortality as the outcome. Although no reports directly presented evidence that treatment of endoscopically detected early gastric cancer can decrease mortality, it is a promising idea, considering the following available evidence: (i) population-based endoscopic screening is effective in decreasing the mortality rate of gastric cancer (early and advanced), (ii) there is an indirect outcome that early gastric cancer accounts for a high proportion among gastric cancer cases detected by population-based screening, and (iii) death is less common in patients with detected and treated early gastric cancer than in those without treatment.

1. As a result of a literature search using PubMed for screening and the mortality rate of gastric cancer, articles documenting two case–control studies[2,3] and two cohort studies[4,5] were retrieved. According to a cohort study in subjects who underwent a screening program for gastric cancer in South Korea,[6] the odds ratio (OR) for death from gastric cancer among subjects who underwent endoscopic examination of the stomach was 0.53 (95% confidence interval [CI] 0.51–0.56), suggesting that endoscopic screening for gastric cancer contributes to a decrease in mortality rates of gastric cancer. In another case–control study, a 30% decrease in OR was found in subjects who underwent gastric endoscopic screening within 36 months before a diagnosis of gastric cancer was made compared to those who did not undergo such screening.[2] Another case–control study reported that the OR for death from gastric cancer was 0.206 (95% CI 0.044–0.965) in subjects who underwent gastric endoscopic screening compared to those who did not undergo such screening.[3]
2. Although lead-time bias should be taken into consideration when the outcome is not mortality rate, a meta-analysis of comparative studies of people, who underwent screening for gastric cancer and those who did not, revealed that the percentage of early gastric cancers to all gastric cancers found in patients who underwent screening was 73%, which was significantly higher than the corresponding percentage (43%) obtained in those who did not undergo screening.[7]
3. Regarding the question of whether treating early gastric cancer decreases its mortality rate, a retrospective observational study revealed that the hazard ratio of the mortality rate of gastric cancer in patients who received treatment was 0.51, lower than that of those who did not receive treatment.[8]

Considering findings (1), (2), and (3), it is inferred that, if early gastric cancer detected by endoscopy is treated, deaths from gastric cancer will decrease.

As for the adverse events of endoscopy, a multicenter collaborative prospective study conducted by the JGES showed that the incidence of accidental events associated with upper gastrointestinal endoscopy was 0.171% among 11,081 endoscopic observations (0.667% among 3447 biopsied cases), but there were no cases of death.[9] There is insufficient evidence to enable a risk–benefit comparison. The perceived benefits and patients' preference for endoscopic examinations vary among patients, and burdens of endoscopic examination also differ depending on patients' perception.[10] No study has reported on the health economics related to the endoscopic detection of early gastric cancer in the Japanese population as a whole. This issue requires further investigation. However, in Japan, endoscopic examinations are relatively inexpensive and covered by health insurance and implemented in the form of population-based screening; in that sense, a benefit comparable to the cost is obtained. Human resources are considered adequate because the JGES membership is 34,258 (as of February 2018). A large number of early gastric cancers have been detected by health insurance-covered endoscopy implemented in symptomatic patients for purposes other than screening for gastric cancer. Therefore, health insurance-covered endoscopy is currently considered to be appropriate to resources. Population-based screenings were recently adopted (in 2016); therefore, manpower is not currently evaluable.

There may be variation in the content of this guideline in relation to the subject's age and *H. pylori* infection rate.

This guideline prescribes the following six major items in chronological order of actual clinical practice: [I] Risk stratification of gastric cancer before endoscopic examination, [II] Detection of early gastric cancer, [III] Qualitative diagnosis of early gastric cancer (differential diagnosis of cancer and non-cancer), [IV] Diagnosis to choose the therapeutic strategy for gastric cancer, [V] Risk stratification after endoscopic examination, and [VI] Surveillance of early gastric cancer. The major feature of this guideline is its proposal of an algorithm for the endoscopic practice of diagnosing early gastric cancer derived from these statements.

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[I] RISK STRATIFICATION OF GASTRIC CANCER BEFORE ENDOSCOPIC EXAMINATION

Statement 1-1

SEVERAL FACTORS SUCH as *H. pylori* infection, atrophy of the gastric mucosa, hereditary disease, and smoking have been cited as obvious risk factors for gastric cancer. Other factors reported as possible risk factors include diet, lifestyle preferences, and Epstein–Barr (EB) viral infection.

Evaluation by the modified Delphi method: Not performed (background knowledge)
Level of evidence: C

Commentary

There is a known strong association between *H. pylori* infection and gastric cancer;[1,2] thus, the International Agency for Research on Cancer (IARC) cites *H. pylori* as

a group 1 carcinogen. The prevalence of *H. pylori* infection is more than 50% of all population in Africa, Latin American and Asian regions, and that in Japan is 51.7%.[3] On the other hands, that of Europe, North America and Oceania is <50%. Some *H. pylori* species have the pathogenic protein CagA; a meta-analysis demonstrated a strong association of CagA with the occurrence of gastric cancer.[4,5] Although the correlation between *H. pylori* infection rate and incidence of gastric cancer varies among races,[6] a reason for this variation seems to be the difference in CagA type possessed by *H. pylori*. The prevalence of gastric cancer is significantly higher in people infected with *H. pylori* with East Asian-type CagA than in those infected with *H. pylori* with non-East-Asian-type CagA.[7] The percentages of different CagA types in *H. pylori* vary among different races within multiethnic countries such as Malaysia[8] and among different Asian countries.[9] These findings may explain the differences in the incidence of gastric cancer among different races. In addition, the presence or absence of the vacuolating toxin VacA, which is responsible for vacuolar degeneration in the gastric mucosal epithelium caused by *H. pylori*, is reportedly associated with the occurrence of gastric cancer.[10,11] Similar to CagA, VacA has a structural polymorphism; a combination of s1/m1-type VacA and CagA is strongly associated with the occurrence of gastric cancer.[12,13]

The presence or absence of atrophy of the gastric mucosa is strongly associated with the occurrence of gastric cancer, similar to *H. pylori* infection.[14–16] Serum pepsinogen (PG) is used as an indicator of atrophic gastritis. In particular, the PG I/PG II ratio, i.e., the ratio of PG I, produced only from the region of the fundic gland, to PG II, produced from both the fundic and pyloric glands, is reported to be correlated with the degree of atrophy.[17] A long-term prospective large-scale cohort study,[18] a systematic review,[19] and a meta-analysis[20] have shown that low PG I/PG II ratios (i.e. <3.0), are correlated with the occurrence of gastric cancer.

When other risk factors for gastric cancer are considered, congenital factors include gene polymorphism, hereditary disease, sex, and race. Gene polymorphism has both positive and negative data, and its relationship with gastric cancer varies among races and histological types, requiring further investigations.[21–24]

Hereditary diseases include hereditary diffuse gastric cancer (HDGC) and gastric cancer associated with Lynch syndrome, familial adenomatous polyposis (FAP), Peutz–Jeghers syndrome, and Li-Fraumeni syndrome.[25] HDGC inherits in the form of autosomal dominant inheritance, causing undifferentiated gastric cancer.[25,26] Mutation of *CDH1* as the cause may be observed. The presence of this gene mutation results in the development of gastric cancer before the age of 40 years in most carriers. Furthermore, mutation of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in the germ cell line is present in patients with Lynch syndrome, and their gastric cancer development risk is 6–13%.[27] Familiar adenomatous polyposis is included in APC-associated polyposis occurring due to *APC* mutation, and the incidence of gastric cancer in patients with FAP is 10-fold higher than that in the general population in Japan and South Korea.[28] The risk of developing gastric cancer is reportedly also high in patients with similar disease, gastric adenocarcinoma, and proximal polyposis of the stomach.[28] The risk of gastrointestinal cancer is high in patients with Peutz–Jeghers syndrome and Li-Fraumeni syndrome, and the risk is increased by 1.5–3.5 times in the presence of a familial history (especially first-degree relatives) of gastric cancer.[29–31] The presence or absence of familial history, including genetic predisposition, is considered an important factor. Regarding sex, the incidence of gastric cancer is higher in women than in men,[32] and the possibility that estrogen in women decreases the incidence of gastric cancer has been suggested.[33] Regarding race, although gastric cancer is more common in Asia, particularly East Asia,[6] a prospective cohort study Malaysia, a multiethnic country, revealed that gastric cancer was more common in dwellers of the Chinese origin than in those of the Indian origin despite the high rate of *H. pylori* infection in all ethnic groups, indicating that the incidence of gastric cancer varies among races even in the same geographic area.[34]

Factors cited as acquired risk factors for gastric cancer include diet, lifestyle preferences, disease, drugs, occupation, exercise, and *H. pylori* infection. Although it has occasionally been reported that eating fruits and vegetables decreases the risk,[35,36] some researchers have reported variations in such effect in relation to fruit or vegetable type,[37–39] while others have reported negative results.[40] Thus, further investigations are required. The relationship between the intake of fish and risk of gastric cancer is unclear,[41] whereas the possibility that the intake of processed red meat increases the risk of gastric cancer has been suggested.[42] The impact of the intake of high-fat dairy products is controversial; some views state that they increase the risk of gastric cancer, whereas others recognize no such correlation.[35,43] Another meta-analysis suggested that the intake of fats may increase the risk of gastric cancer. However, there was also inconsistency in the subgroup analysis results. More specifically, saturated fatty acids increased the risk, polyunsaturated fatty acids and plant fats decreased the risk, and monounsaturated fatty acids and animal fats were not associated with the risk.[44] In addition, a meta-analysis regarding the intake of food preserved with

salt and risk of gastric cancer showed that the risk of gastric cancer increased by 50%.[45] In a prospective cohort study that examined salt intake, there was an association between the intake of salt and increased risk of gastric cancer, particularly in patients with atrophic gastritis accompanied by *H. pylori* infection.[46] Regarding the role of vitamin C, the possibility that it contributes to a decreased risk of gastric cancer was suggested by a large-scale multinational multicenter study,[47] but controversy persists.[48–50] Regarding the relationship between body mass index (BMI) and gastric cancer, a meta-analysis showed that an increased BMI was associated with an increased risk of gastric cancer.[51] On the other hand, another meta-analysis found a relationship with gastric cardiac cancer but not with non-cardiac cancer.[52] In contrast to the strong association between BMI and esophageal or gastric cardiac cancer,[53] this issue remains controversial. A systematic review of the Japanese population and another meta-analysis showed no relationship between alcohol drinking and the risk of gastric cancer, and a planned study using a standardized method is considered necessary on this matter.[54,55] Although some researchers have a negative view of the relationship between smoking and an increased risk of gastric cancer,[56] others have an affirmative view,[57,58] and the IARC refers to smoking as a carcinogen with sufficient evidence. Three meta-analyses on the intake of coffee and risk of gastric cancer showed inconsistent results: one suggested that the intake of coffee is related to a decrease in the risk of gastric cancer,[59] another showed no correlation,[60] and the remaining one showed no correlation but suggested involvement in an increased risk of gastric cardiac cancer.[61] Similar results were obtained for the intake of green tea. A systematic review showed the possibility of the intake of green tea to decrease the risk of gastric cancer in Japanese women,[62] whereas other meta-analyses showed no correlation.[63,64] A case–control study that examined lifestyle in patients with gastric cancer and age, race, and sex-matched subjects found that the increased risk of gastric cancer was associated with a dinner-to-bed time of <3 h and a lack of walking after a meal, increasing expectations for further investigation.[65] Regarding the relationship between gastric cancer and other diseases, diabetes mellitus is reported to be strongly associated with an increased risk of gastric cancer,[66–69] although a systematic review showed no such association in men.[66] Among oral medicines, nonsteroidal anti-inflammatory drugs,[70,71] particularly aspirin, have been reported to decrease the risk of gastric cancer. However, the dose was not consistent among different studies, requiring further investigation.[72,73] A decreased risk of gastric cancer by statin drugs was also suggested by a meta-analysis, but further investigations are also required on this issue because many remain unclear, such as in terms of differences related to drug type and long-term prognosis.[74] In addition, a meta-analysis showed that occupational exposure to asbestos increased the risk of gastric cancer,[75] and the IARC refers to asbestos as a group 1 carcinogen, although the evidence is limited. EB virus has been observed in about 10% of gastric cancer tissues,[76,77] and its correlation with the risk of gastric cancer has been demonstrated.[78,79] However, although a strong association was found by *in situ* hybridization assay, the results of polymerase chain reaction assay alone were inconclusive.[78] More than 90% of adults have latent EB viral infection,[77] and there is difference in the actual positivity rate in patients with gastric cancer. Therefore, EB virus is considered a carcinogen under limited evidence by the IARC; there is still room for argument of its weight as a risk factor.

Thus, various factors affect the risk of gastric cancer as described above. However, these factors are related in a complex manner,[40,43,51,80] and a certain consensus has not been reached to date except for strongly associated factors such as *H. pylori* infection, atrophy of the gastric mucosa, genetic predisposition, and smoking. Readers are encouraged to refer to the websites of the IARC and the National Cancer Center, which also provides information on risk factors for gastric cancer.[81,82]

The Cochrane and PubMed databases were searched using the term gastric cancer combined with other key words such as risk factor, atrophy, smoking, drinking, alcohol, salt, preserved meat, vegetable, fruit, CagA, Gastrin 17, sex, age, family history, (past history, gastric cancer), (past history, gastric adenoma), (past history, esophageal cancer), *H. pylori* antibody, (*H. pylori* antibody, risk stratification), serum pepsinogen, and (serum pepsinogen, risk stratification). As a result, the search yielded 546 articles, including 34 systematic reviews and 76 meta-analyses (overlapping present). Excluding the overlapping, nine systematic review, 30 meta-analyses, and other articles related to risk factors for gastric cancer were cited. During the discussion in the guideline committee, 70 articles (overlapping present) were retrieved from PubMed using the term gastric cancer combined with EB virus, systematic, and meta-analysis. Excluding the overlapping, two systematic reviews related to risk factors for gastric cancer were cited. Another 21 articles obtained from among the cited references in the literature and by a manual search of PubMed were also added.

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Statement 1-2

The risk of gastric cancer can be stratified before endoscopic examination. A beneficial economic effect can be expected from this risk stratification. However, issues about the optimal method remain.

Evaluation by the modified Delphi method: Not performed (background knowledge)
Level of evidence: C

Commentary

A nested case–control study with risk stratification of gastric cancer using the serum PG level and serum *H. pylori* antibody titer was performed in Japan,[1] and a large-scale cohort study was performed with risk stratification using the serum *H. pylori* antibody titer, which was a multinational study including Japan.[2] The possibility of risk stratification of gastric cancer using the serum PG level and serum *H. pylori* antibody titer was suggested by a meta-analysis of four cohort studies, but the concrete method of risk stratification remains unclear because there are issues in grouping-related interpretation and difference in the measuring method.[3] Reports from Singapore documented a significant cost-decreasing effect of endoscopic surveillance in high- and low-risk groups of patients with gastric cancer.[4,5] However, this finding cannot be directly extrapolated to risk stratification before endoscopic examination in Japan because of differences between Singapore and Japan regarding the prevalence of gastric cancer and rate of *H. pylori* infection in the population.

For this literature search, five articles retrieved from the relevant literature for statement 1-1 and retrieved by manual search were cited.

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Statement 1-3

A combination of serum *H. pylori* antibody and serum pepsinogen may be useful for the risk stratification of gastric cancer. However, false negative results can occur in cases of severe atrophy and past infection. In addition, the cut-off value and measuring method of *H. pylori* antibody titers, interpretation of the PG level, and cut-off value of the PG I/PG II ratio have been investigated.

Evaluation by the modified Delphi method: Median, 9; Minimum, 7; Maximum, 9
Strength of recommendation: 2
Level of evidence: C

Commentary

Considering the evidence presented for Statements 1-1 and 1-2, it is likely that determination of the *H. pylori* infection status and measurement of serum PG are useful for risk stratification of gastric cancer risk. The culture method, microscopic examination, and urea breath test can be used to determine the *H. pylori* infection status. Measurement of serum *H. pylori* antibody titers is simple and proven useful for the risk stratification of gastric cancer.[1] Serum PG level is also proven useful for screening of risk of gastric cancer,[2] and so-called ABC screening by which subjects are divided into four groups according to measurement of serum *H. pylori* antibody titer and serum PG level has been advocated.[3] Using this screening method, a combination of PG I and the PG I/PG II ratio as well as serum *H. pylori* (Hp) antibody titer is used to distinguish among groups A [Hp (−)],), PG (−)], B [Hp (+), PG (−)],)], C [Hp (+), PG (+)], and D [Hp (−)],), PG (+)] to stratify the risk of gastric cancer. Group A was assumed to be never infected with *H. pylori*. Group B, C and D were infected with *H. pylori*. Group B was assumed to have mild gastric atrophy and group C was assumed to have severe gastric atrophy. Group D was assumed to have the most severe gastric atrophy, and serum *H. pylori* antibody became negative because of severe atrophy or eradication. The usefulness of this method was proven by a prospective cohort study in which the risk of gastric cancer development was 6.0-fold higher in group C and 8.2-fold higher in group D than in group A.[3] However, there is the view that risk stratification in a population with a high *H. pylori* infection rate is useless.[4] There are also other issues such as the following: group A includes cases with prior or current *H. pylori* infection,[5] while a systematic review has shown that dividing subjects into three groups, i.e., groups A, B, and C+D, rather than four, would be more appropriate.[6] In this context, the cut-off value and measuring method of *H. pylori* antibody titers, interpretation of the PG level, and cut-off value of the PG I/PG II ratio have been investigated.[7–9]

Among the factors referred to in statement 1-1, it is possible to determine genetic predisposition by screening for family history in all but the index case. Therefore, taking a family history may be useful for risk stratification.

For this literature search, one article retrieved for statement 1-1 and eight other articles comprising relevant articles, references cited for statement 1-2, and articles retrieved by manual search were used.

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[II] DETECTION OF EARLY GASTRIC CANCER

Statement 2-1

THE USE OF antispasmodics should be considered in cases in which observation is difficult because of intense peristalsis.

Evaluation by the modified Delphi method: Median, 8; Minimum, 6; Maximum, 9
Strength of recommendation: None
Level of evidence: D

Commentary

The stomach performs active peristalsis, particularly at the antrum, which may interfere with endoscopic observation. Therefore, antispasmodics may be used as premedication before upper gastrointestinal endoscopic examinations.[1] Antispasmodics include injectable drugs (butylscopolamine bromide, 10–20 mg intramuscularly or intravenously; glucagon, 1 mg intravenously)[2] and local sprays (peppermint oil and its major component, l-menthol, 20 mL of 0.8% directly sprayed).[2,3] Hiki *et al*. showed the inhibitory effect of l-menthol on gastric peristalsis in a randomized controlled trial.[3]

Butylscopolamine bromide is contraindicated for patients with glaucoma, prostatic hyperplasia, serious heart disease, and paralytic ileus. Adverse reactions to butylscopolamine bromide include cardiac palpitation, dysuria, thirst, and visual accommodation disorder; therefore, it is difficult to use this drug in elderly individuals.[4] Glucagon is contraindicated for patients with pheochromocytoma and uncontrolled diabetes. Attention to possible delayed hypoglycemic attack as an adverse reaction is needed. Glucagon has a lower influence on the cardiovascular system than butylscopolamine bromide.[5] Peppermint oil and l-menthol cause no adverse reactions; thus, they can be used with relative safety.[2,3]

Inhibiting peristalsis facilitates endoscopic observations, but no study has clearly shown that antispasmodics facilitate the detection of early gastric cancer. However, because it is speculated that securing a better field of view increases the detection rate of early gastric cancer, the use of antispasmodics should be considered in cases of intense peristaltic movements that make observation difficult. The drug cost is the highest for glucagon, followed by l-menthol products and butylscopolamine bromide.

In the recommendation decision meeting of the guideline development panel, the use of antispasmodics was weakly recommended in cases in which the observation is limited by intense peristaltic movements rather than the strength of recommendation not being specified.

Databases used for this literature search were PubMed and Igaku Chuo Zasshi. For PubMed, the following search formula was used: (gastroscopy OR esophagogastroduodenoscopy) AND (antidiarrheals OR antiperistaltic OR “cholinergic antagonists” OR “scopolamine hydrobromide” OR “scopolamine butylbromide” OR glucagon OR peppermint) Filters: Human; English; Japanese. A total of 288 articles were retrieved. The search formula used for Igaku Chuo Zasshi was: ((((蠕動/TH or 蠕動運動/AL) or (薄荷/TH or ハッカ/AL) or cholinergic/AL and antagonists/AL or (“Scopolamine Hydrobromide”/TH or scopolamine/AL) or (Glucagon/TH or glucagon/AL))) and ((内視鏡/TH or 内視鏡/AL) or 上部消化管内視鏡検査/AL)) and (PT=会議録除く), meaning in English: ((((peristalsis/TH or peristaltic movement/AL) or (peppermint *in kanji*/TH or peppermint *in katakana*/AL) or cholinergic/AL and antagonists/AL or (“Scopolamine Hydrobromide”/TH or scopolamine/AL) or (Glucagon/TH or glucagon/AL))) and ((endoscopy/TH or endoscopy/AL) or upper gastrointestinal endoscopic examination/AL)) and (PT=excluding conference proceedings). A total of 153 articles were retrieved. These articles were narrowed down to those relevant to this statement; some other articles obtained in the manual search were added.

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Statement 2-2

The use of mucolytic and defoaming agents is strongly recommended because improved visibility of the mucosa leads to the detection of early gastric cancer.

Evaluation by the modified Delphi method: Median, 8; Minimum, 7; Maximum, 9
Strength of recommendation: 1
Level of evidence: D

Commentary

The foam and mucus attached to the mucosal surface interfere with the endoscopic observation and may lead to overlooking of minute findings in the mucosa. Therefore, mucolytic and defoaming agents are often used as preparation drugs to improve the visibility of the mucosa.[1] The available mucolytic agents are pronase and *N*-acetylcysteine. Pronase is approved as a mucolytic agent for dissolving and removing the gastric mucus for gastroscopy in Japan. Several randomized controlled trials have shown improved visibility of the mucosa after the pronase administration.[2–4] This agent is reportedly useful for chromoendoscopy and magnifying narrow-band imaging (NBI) endoscopy.[5,6]

Dimethicone is used for defoaming. A randomized controlled trial that compared dimethicone and placebo showed that the amount of foam in the stomach was significantly smaller after dimethicone administration, and the defoaming effect was particularly strong in patients with a remnant stomach.[7] Dimethicone administration reportedly reduces the examination time[8] and improves endoscopist satisfaction.[9]

A meta-analysis showed that dimethicone administration alone resulted in better improvement in endoscopic visibility than pronase or *N*-acetylcysteine alone. The combined use of dimethicone with pronase or *N*-acetylcysteine yielded limited improvement in endoscopic visibility.[10]

No study has clearly shown that mucolytic or defoaming agents facilitate the detection of early gastric cancer. However, the use of mucolytic and defoaming agents is strongly recommended in Japan because it is speculated that improved visibility of the mucosa leads to the detection of early gastric cancer. Dimethicone and pronase are easily usable drugs because they are inexpensive and associated with low frequencies of adverse reactions. However, pronase may lead to bleeding from the affected area along with mucus removal; therefore, it requires careful administration in patients with suspected intragastric bleeding.

In Japan, the formula is 100 mL water with 20,000 U pronase (Kaken Pharmaceutical, Tokyo, Japan), 1 g sodium bicarbonate and 10 mL dimethylpolysiloxane (20 mg/mL; Horii Pharmaceutical, Osaka Japan). However, as pronase is not available worldwide, an alternative mixture is 100 mL water mixed with 2 mL acetylcysteine (200 mg/mL Parvolex; Celltech, Berkshire, UK or Mucomyst; Bristol-Myers Squibb, New York, NY, USA), and 0.5 mL (40 mg/mL) activated dimethicone (Infacol; Forest Laboratories, Dartford, UK).[1,11]

The guideline development panel determined that the use of mucolytic and defoaming agents should be strongly recommended due to the strong evidence of improved visibility of the mucosa and because these agents are inexpensive and easily available with minimal adverse reactions and a low burden to patients, despite a lack of evidence that they directly promote the detection of early gastric cancer.

The PubMed and Igaku Chuo Zasshi databases were searched. PubMed was searched using the following search formula: ((gastroscopy OR esophagogastroduodenoscopy) AND (expectorants[pa] OR pronase OR "antifoaming agents" OR defoaming OR Simethicone OR Octoxynol))Filters: Humans; English; Japanese. As a result, 93 articles were retrieved. The search formula used for the Igaku Chuo Zasshi search was: (((内視鏡/TH or 内視鏡/AL) or 上部消化管内視鏡検査/AL) and ((粘液溶解/AL or (去痰剤/TH or 去痰剤/AL) or (Pronase/TH or pronase/AL) or (Pronase/TH or プロナーゼ/AL) or (消泡剤/TH or 消泡剤/AL))) and (PT=会議録除く), meaning in English: (((endoscopy/TH or endoscopy/AL) or upper gastrointestinal endoscopic examination/AL) and ((mucolysis/AL or (expectorant/TH or expectorant/AL) or (Pronase/TH or pronase/AL) or (Pronase/TH or pronase *in katakana*/AL) or (defoaming agent/TH or defoaming agent/AL))) and (PT=excluding congress proceedings). Ultimately, 130 articles were retrieved. These articles were narrowed down to those relevant to this statement; some other articles obtained by a manual search were added.

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Statement 2-3

Sedatives and analgesics may be used with caution for possible adverse reactions in subjects with strong anxiety or in whom observation is difficult because of reflex or body movements.

Evaluation by the modified Delphi method: Median, 8; Minimum, 7; Maximum: 9
Strength of recommendation: None
Level of evidence: D

Commentary

Sedatives alleviate patient anxiety and discomfort, while analgesics reduce pain without decreasing consciousness. Sedatives and analgesics improve patient acceptability and satisfaction with endoscopic examinations increase rates of requesting re-examination.[1–5] In addition, for endoscopists, these drugs are also useful for improving the quality of endoscopic examination and satisfaction of endoscopists.[1,5] Adverse reactions to sedatives and analgesics include respiratory depression, circulatory depression, bradycardia, arrhythmia, anterograde amnesia, disinhibition, and hiccups. Because serious accidental events including death have also been reported, it is important to secure adequate personnel distribution and practice setting to enable monitoring when sedatives and analgesics are used. It is also necessary to continue monitoring post-endoscopy until the patient awakens.[1]

No study to date has clearly shown that sedatives and analgesics would contribute to the detection of early gastric cancer. However, sedatives and analgesics may be used in patients who have strong anxiety or in whom pain or body movements interfere with the observation. When using sedatives or analgesics, the facility must be equipped to provide countermeasures for the aforementioned adverse reactions and accidental events.

The guideline development panel initially released the following statement: "The use of sedatives or analgesics should be considered with caution regarding adverse reactions in subjects with strong anxiety or in whom observation is difficult because of reflexes or body motion." However, voting by the modified Delphi method resulted in a median value of 7 (range, 7–9); therefore, another discussion was held. Consequently, the expression "the use. . . should be considered" was revised to "may be used" because there are limitations in personnel distribution and practice settings that allow the use of sedatives and analgesics throughout Japan and because the development of endoscopic instruments, including thin endoscopes, and advances in endoscopic techniques will be able to reduce the use of sedatives and analgesics.

Since concepts and medical circumstances regarding sedation vary among countries, districts and societies, the relevant guideline (for example: JGES guideline[1]) should be referred to for using sedatives and analgesics prior to upper gastrointestinal endoscopic examinations.

Meanwhile, the relevant JGES guideline should be referred to for the administration of sedatives and analgesics prior to upper gastrointestinal endoscopic examinations.[1]

The PubMed and Igaku Chuo Zasshi databases were searched. From PubMed, 42 articles were retrieved using the following search formula: ("stomach neoplasms" AND Hypnotics and Sedatives [Pharmacological Action]) Filters: Humans; English; Japanese. Another 12 articles were also retrieved using the following formula: "stomach neoplasms/diagnosis" AND analgesics[Pharmacological Action] Filters: Humans; English; Japanese. In the case of Igaku Chuo Zasshi, 72 articles were retrieved using the formula: (((胃腫

瘍/TH or 胃腫瘍/AL)) and ((催眠剤と鎮静剤/TH or 催眠剤と鎮静剤/AL))) and (PT=会議録除く), meaning in English: (((gastric tumor/TH or gastric tumor/AL)) and ((sedative and analgesic/TH or sedative and analgesic/AL))) and (PT=excluding congress proceedings). Another 64 articles were retrieved using the formula: ((((胃腫瘍/TH or 胃腫瘍/AL)) and (((SH=診断的利用, 診断, 画像診断, X線診断, 放射性核種診断, 超音波診断) or (診断/TI)))) and ((鎮痛剤/TH or 鎮痛剤/AL))) and (PT=会議録除く), meaning in English: ((((gastric tumor/TH or gastric tumor/AL)) and (((SH=diagnostic use, diagnosis, diagnostic imaging, diagnostic radiography, diagnostic radionuclide imaging, diagnostic ultrasound) or (diagnosis/TI)))) and ((sedative/TH or analgesic/AL))) and (PT=excluding congress proceedings). A manual search of the literature yielded no study examining the contribution of sedatives or analgesics to the detection of early gastric cancer.

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Statement 2-4

The observation duration of the stomach is associated with the detection of early gastric cancer. The stomach should be observed taking sufficient time.

Evaluation by the modified Delphi method: Median, 8; Minimum, 7; Maximum, 9
Strength of recommendation: 1
Level of evidence: D

Commentary

Three studies on the duration of upper gastrointestinal endoscopic examination and detection of early gastric cancer have been reported to date. Teh *et al*.[1] reported that, in 837 cases of endoscopic examination, endoscopists who took a mean <7 min from endoscope insertion to removal did not detect early gastric cancer, whereas those who took a mean of 7 min or more detected four (0.9%) lesions of early gastric cancer. Kawamura *et al*.[2] analyzed 15,763 endoscopic examinations and found that the detection rate of early gastric cancer tended to be lower among endoscopists who took a mean duration of examination (from endoscope insertion to removal) of <5 min (0.2%) than among those who took a mean duration of 5 min or more (0.4%). Part *et al*. [3] classified 111,962 cases of endoscopic examination into two groups according to whether the mean pure duration of observation in the stomach, excluding the time of insertion to duodenum and cleaning the lumen, was 3 min or less (fast endoscopist group) or more than 3 min (slow endoscopist group). The detection rate of early gastric cancer was 0.06% in the fast endoscopist group and 0.09% in the slow endoscopist group, showing a significantly higher detection rate in the slow endoscopist group ($P = 0.0455$). The mean examination and observation durations in these three studies were calculated from data in subjects who underwent no biopsy.

Thus, it is suggested that false negative cases occur frequently among endoscopists who take a short time for examination. However, no definite conclusion has been drawn regarding the exact time needed for observation in individual subjects.

The PubMed and Igaku Chuo Zasshi databases were searched. The PubMed search used the following formula: “stomach neoplasms/diagnosis” AND (“examination time”[tiab] OR “observation time”[tiab] OR “time factors”) AND (endoscopy OR endoscopic). Ultimately, 194 articles were retrieved. In the Igaku Chuo Zasshi search, the following formula used was: ((((胃腫瘍/TH or 胃腫瘍/AL)) and (((SH=診断的利用, 診断, 画像診断, X線診断, 放射性核種診断, 超音波診断) or (診断/TI)))) and (((観察/TH or 観察/AL) or 経過観察/AL) and ((時間/TH or 時間/AL) or (時間因子/TH or 時間因子/AL)))) and (PT=会議録除く), meaning in English: ((((gastric tumor/TH or gastric tumor/AL)) and (((SH=diagnostic use, diagnosis, diagnostic imaging, diagnostic radiography, diagnostic radionuclide imaging, diagnostic ultrasound) or (diagnosis/TI)))) and (((observation/TH or observation/AL) or follow up/AL) and ((time/TH or time/AL) or (time factor/TH or time factor/AL)))) and (PT=excluding congress proceedings). Ultimately, 68 articles were retrieved. These articles were narrowed down to those relevant to this statement; some other articles obtained by a manual search were added.

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Statement 2-5

The inside of the stomach should be systematically observed to detect early gastric cancer.

Evaluation by the modified Delphi method: Median, 9; Minimum, 7; Maximum: 9
Strength of recommendation: 1
Level of evidence: D

Commentary

Hosokawa *et al*. defined a false negative case as gastric cancer registered within 3 years after an endoscopic examination in which no cancer was detected and reported a rate of 25.8%. In addition, the false negative rate among endoscopists with <10 years' endoscopic experience was 32.4%, whereas the corresponding rate was 19.5% among those with 10 or more years' experience. Thus, the false negative rate was significantly higher for less experienced endoscopists.[1] A meta-analysis including overseas studies showed a false negative rate of 11.3% based on the same definition.[2] Thus, false negative cases account for a substantial proportion of endoscopic examinations.

A reason for overlooking gastric cancer is insufficient observation of the inside of the stomach. Because the stomach has a wide curved lumen, there are blind spots even in a thorough observation, leading to overlooking of gastric cancer. In particular, observation is likely to be difficult in the anterior and posterior walls of the gastric body in the tangential direction and the area from the angulus to the posterior wall of the antrum, which barely allows a sufficient field of vision because of proximity. In addition, the lesser curvature in the cardia is in the tangential direction on antegrade view and behind the endoscope on retroflex view, resulting in poor observation.[3] The greater curvature in the gastric body should be observed while being extended because lesions may remain hidden behind folds with low-air insufflation.

No study has examined the method of endoscopic observation of the stomach and detection of early gastric cancer. Although the method of observation currently varies among different institutions and operators, it is necessary to conduct a thorough and systematic observation of the inside of the stomach to prevent the occurrence of false negative cases of early gastric cancer. Yao advocates a systematic screening protocol for the stomach.[4] It has also been reported that operator training improves the detection rate of gastric cancer.[5,6] Therefore, sufficient training for endoscopists is necessary.

The PubMed and Igaku Chuo Zasshi databases were searched. A total of 176 articles were retrieved from PubMed using the following search formula: "stomach neoplasms/diagnosis"[majr] AND ("gastric mucosa/pathology" OR observ*[tiab]) AND (endoscopy OR endoscopic) AND methods[sh] Filters: Humans; English; Japanese. In the Igaku Chuo Zasshi search, the following formula was used: ((((胃腫瘍/TH or 胃腫瘍/AL)) and (((SH=診断的利用, 診断, 画像診断, X線診断, 放射性核種診断, 超音波診断) or (診断/TI)))) and ((観察/TH or 観察/AL)) and ((内視鏡/TH or 内視鏡/AL)) and (((胃粘膜/TH or 胃粘膜/AL)) and (SH=病理学))) and (PT=会議録除く), meaning in English: ((((gastric tumor/TH or gastric tumor/AL)) and (((SH=diagnostic use, diagnosis, diagnostic imaging, diagnostic radiography, diagnostic radionuclide imaging, diagnostic ultrasound) or (diagnosis/TI)))) and ((observation/TH or observation/AL)) and ((endoscopy/TH or endoscopy/AL)) and (((gastric mucosa/TH or gastric mucosa/AL)) and (SH=pathology))) and (PT=excluding congress proceedings). Ultimately, 58 articles were retrieved. These articles were narrowed down to those relevant to this statement; some other articles obtained by a manual search were added.

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Statement 2-6

The usefulness of image-enhanced endoscopy for the detection of early gastric cancer is under discussion.

Evaluation by the modified Delphi method: Median, 8; Minimum, 6; Maximum, 9
Strength of recommendation: None
Level of evidence: D

Commentary

Endoscopic imaging is broadly divided into: (i) conventional (white light), (ii) image-enhanced, (iii) magnifying, (iv) microscopic, and (v) tomographic. Image-enhanced endoscopy is sub-divided into digital, optical-digital, and chromoendoscopy methods according to the image enhancement method (Fig. 1).[1–3]

In chromoendoscopy, indigocarmine has been used to enhance contrast for the endoscopic diagnosis of early gastric cancer. Indigocarmine stays in the concavities on the mucosal surface, thereby enhancing minute concavities and convexities of the mucosa and improving the visibility of the lesion.[4] However, no randomized controlled trial has shown the usefulness of indigocarmine for detecting early gastric cancer.

The digital method involves image enhancement through signal processing and the use of an image–processing algorithm. The flexible spectral imaging color enhancement (FICE), i-scan belong to this category. With the FICE system, an image at a freely selected wavelength is obtained from a conventional image by means of computerized processing. Some studies using ultraslim endoscopy with FICE were reported the usefulness of detecting early gastric cancer;[5,6] however, no randomized controlled trial has shown the usefulness of FICE for detecting early gastric cancer. I-scan has three adjustable modes of image

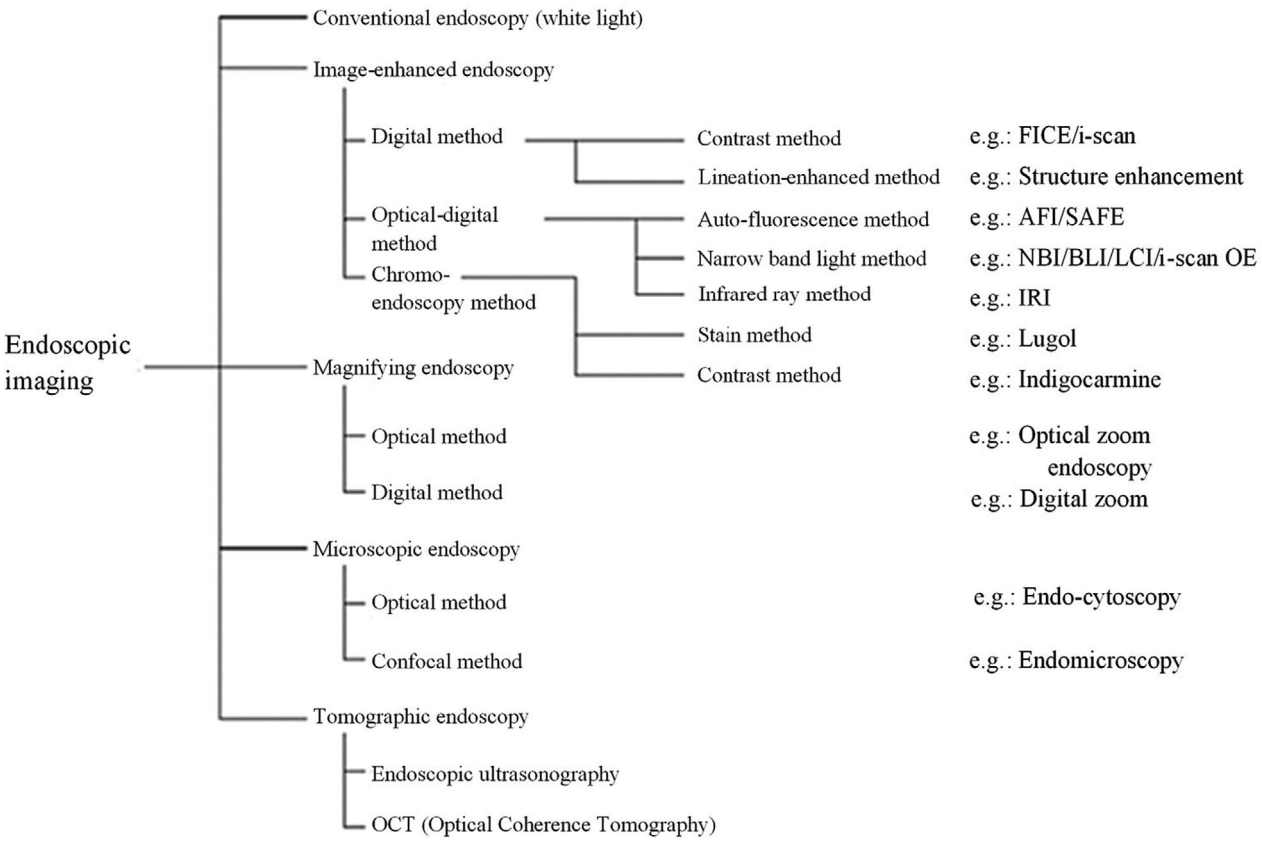

Figure 1 Classification of endoscopic techniques (Adapted from Ref. [3]).

enhancement, i.e. surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE).[7] SE enhances light dark contrast, and CE digitally adds blue color to relatively dark areas by obtaining luminance intensity data for each pixel. TE analyzes the individual red, green, and blue components of a normal image and recombines the color frequencies of each component to enhance minute mucosal structures with subtle color changes. The efficacy of i-Scan over that of white-light imaging for detecting gastric cancer was not shown.[8]

The narrow band light method uses irradiating light of wavelengths limited to a specific band. It is based on the principle that depth of penetration of light is wavelength dependent. This method includes narrow-band imaging (NBI), blue laser imaging (BLI), linked color imaging (LCI) and i-scan optical enhancement (OE). The NBI system involves a narrow-bandwidth NBI filter (415 ± 30 nm, 540 ± 30 nm) in the video endoscopy system. These two wavelengths are well absorbed by hemoglobin, the microvascular architecture of the mucosal surface can be visualized readily.[9] An overseas multicenter randomized controlled trial that examined non-magnifying NBI vs. conventional white-light endoscopy revealed that the detection rate of intestinal metaplasia was significantly higher for non-magnifying NBI but there was no significant difference in the detection of gastric cancer.[10] A similar multicenter randomized controlled trial is now underway in Japan (UMIN000014503). The BLI system involves a light source consisting of two types of lasers with wavelengths of 410 and 450 nm and fluorescent light which is useful for acquiring information about the mucosal surface, such as the patterns of surface blood vessels and structures. The combination of the two lasers and fluorescent light enables BLI, a brighter BLI (BLI-bright), and linked color imaging (LCI).[11,12] LCI is a color enhancement technology that provides slight color differences in mucosal color which are easy to recognize with sufficient brightness compared with BLI. Randomized controlled trials of the detection of early gastric cancer using BLI and LCI are also underway (UMIN 000011324, UMIN000023863). The i-scan OE have two modes: OE Mode 1 (OE1) and OE Mode 2 (OE2). The OE1 mode uses light emission at 415 and 540 nm, which are suitable for visualizing blood vessels on the mucosal surface and in the submucosa, respectively. On the other hand, the OE Mode 2 (OE2) uses red light emission as well as emission at 415 and 540 nm to increase the overall brightness of the image.[13] The OE1 had a significant advantage over the white light mode in demarcation of early gastric cancer;[14] however, there are no evidence of detection of early gastric cancer using OE1. The detection rate of early gastric cancer was no significant difference between OE2 and white light mode.[15]

Autofluorescence imaging (AFI), an optical-digital method, takes images with autofluorescence produced by irradiation of exciting light on the mucosa and provides a pseudo-color images.[16] This method is useful for observing lesions that are flat or have poor color variation, which are likely to be overlooked by white-light endoscopy. However, when AFI is used alone, its clinical usefulness is low because inflammatory and regenerative changes are considered false positive findings.[17] The use of white-light endoscopy combined with AFI and magnifying NBI endoscopy reportedly improves the diagnostic accuracy of gastric tumor.[18]

White-light endoscopy is the current basic method of endoscopically observing the stomach. The usefulness of image-enhanced endoscopy for detecting early gastric cancer currently remains unclear. In addition, image-enhanced endoscopy is not feasible in every institution.

The PubMed and Igaku Chuo Zasshi databases were searched. The PubMed searched used the following formula: "stomach neoplasms/diagnosis"[majr] AND (enhanced OR laser OR "linked color" OR autofluorescein* OR "narrow band") AND "sensitivity and specificity" Filters: Humans; English; Japanese. This search retrieved 27 articles. In the Igaku Chuo Zasshi search, the following search formula was used: ((((胃腫瘍/TH or 胃腫瘍/AL)) and (((SH=診断的利用, 診断, 画像診断, X線診断, 放射性核種診断, 超音波診断) or (診断/TI)))) and ((内視鏡法/TH or 内視鏡法/AL)) and (強調/AL or (蛍光/TH or 蛍光/AL) or (レーザー/TH or レーザー/AL)) and ((感度と特異度/TH or 感度と特異度/AL))) and (PT=会議録除く), meaning in English: ((((-gastric tumor/TH or gastric tumor/AL)) and (((SH=diagnostic use, diagnosis, diagnostic imaging, diagnostic radiography, diagnostic radionuclide imaging, diagnostic ultrasound) or (diagnosis/TI)))) and ((endoscopy/TH or endoscopy/AL)) and (enhancement/AL or (fluorescence/TH or fluorescence/AL) or (laser/TH or laser/AL)) and ((sensitivity and specificity/TH or sensitivity and specificity/AL))) and (PT=excluding congress proceedings). Ultimately, 22 articles were retrieved. These articles were narrowed down to those relevant to this statement; some other articles obtained by a manual search were added.

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[III] QUALITATIVE DIAGNOSIS OF EARLY GASTRIC CANCER (DIFFERENTIAL DIAGNOSIS OF CANCER AND NON-CANCER)

Statement 3-1

IMAGE-ENHANCED ENDOSCOPY IS useful for the qualitative diagnosis of early gastric cancer; thus, its use is recommended.

Evaluation by the modified Delphi method: Median, 8; Minimum, 7; Maximum, 9
Strength of recommendation: 2
Level of evidence: A

Commentary

When a lesion is detected, a qualitative diagnosis must be made to distinguish between cancer and non-cancer. Image-enhanced endoscopy, which enables the recognition of findings that are difficult to observe under white-light endoscopy, is often used for this purpose.

Chromoendoscopy (contrast method) using indigocarmine has been used for diagnosing early gastric cancer.[1] A spray of indigocarmine is often used for distinguishing between cancerous and non-cancerous lesions because it more obviously detects findings in the folds around and borders of the lesion and changes in the mucosal pattern. However, no randomized controlled trial has shown the usefulness of indigocarmine in the differential diagnosis of cancer and non-cancer.

Narrow-band imaging combined with magnifying endoscopy has occasionally been reported as useful for the qualitative diagnosis of early gastric cancer.[2–12] Ezoe *et al*. conducted a multicenter randomized controlled trial to distinguish between depressed gastric cancer and non-cancerous lesions measuring 1 cm or less and reported that the rates of accurate diagnosis, sensitivity, and specificity of magnifying NBI endoscopy for small depressed gastric lesions were 90.4%, 60.0%, and 94.3%, respectively, with the rate of accurate diagnosis and specificity being significantly better than those of white-light endoscopy.[5] However, it was difficult for magnifying NBI endoscopy to diagnose undifferentiated cancer with the remaining non-

cancerous epithelium on the mucosal surface.[6] Magnifying NBI endoscopy is also reported to be useful for the differentiation of cancer from adenoma among elevated lesions.[8–11] A meta-analysis that compared white-light endoscopy and magnifying NBI endoscopy regarding the ability of qualitative diagnosis showed the usefulness of magnifying NBI endoscopy.[12] It has also been reported that magnifying BLI endoscopy, another narrow band light method, is useful for the qualitative diagnosis of early gastric cancer similar to magnifying NBI endoscopy.[13,14] Dohi *et al*.[14] reported a prospective multicenter study to evaluated 114 gastric lesions examined using M-BLI, M-BLI-bright, and M-NBI. The demarcation line (DL), microvascular pattern (MVP), and microsurface pattern (MSP) were assesed. M-BLI, MBLI-bright, and M-NBI revealed a DL for 96.1%, 98.1%, and 98.1% and irregular MVP for 95.1%, 95.1%, and 96.2% of lesions, respectively, with no significant difference. Irregular MSP was observed by M-BLI, M-BLI-bright, and M-NBI in 97.1, %90.4%, and 78.8% of lesions, respectively, with significant differences ($P < 0.001$). They concluded M-BLI and M-BLI-bright provided excellent visualization of microstructures and microvessels similar to M-NBI. Irregular MSP might be frequently visualized using M-BLI and M-BLI-bright compared with using M-NBI.

The JGES, Japanese Society of Gastroenterology, and Japanese Gastric Cancer Association jointly advocate the magnifying endoscopy simple diagnostic algorithm for gastric cancer (MESDA-G; Fig. 2) based on the VS (vessels plus surface) classification system, VS classification system for the analysis of magnifying endoscopic findings was developed by Yao *et al*.[4,15]

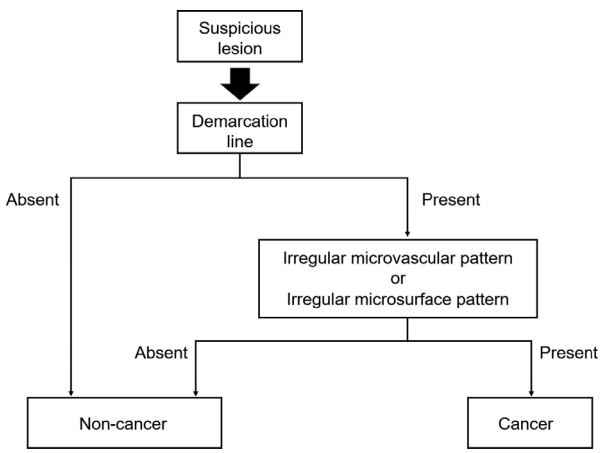

Figure 2 Magnifying endoscopy simple diagnostic algorithm for gastric cancer (MESDA-G; Adapted from Ref. [4]).

Anatomical terms are used to define the MV and MS patterns as visualized by magnifying endoscopy. The MV pattern is comprised of a subepithelial capillary (SEC), a collecting venule (CV), and pathological microvessels (MV), whereas the MS pattern is identified by a marginal crypt epithelium (MCE), a crypt opening (CO), and an intervening part (IP) between crypts (Fig. 3).[15]

According to the VS classification system, the characteristics magnifying endoscopic findings of EGC are the presence of a clear DL between non-cancerous and

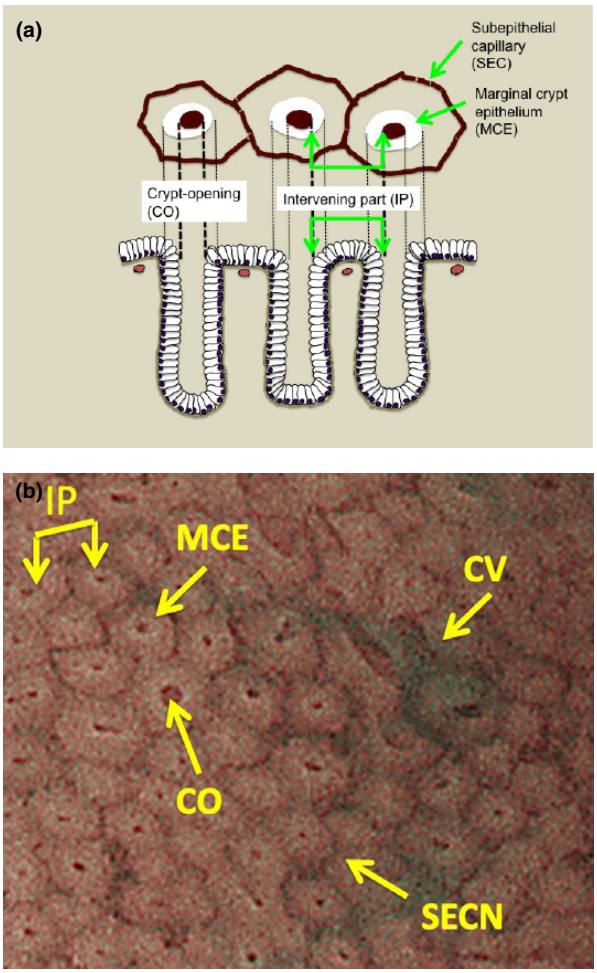

Figure 3 (a) Correlation between microanatomy (lower column) and endoscopic images (upper column) in the superficial part of gastric fundic gland mucosa. CO, crypt opening; IP, intervening part between crypts; MCE, marginal crypt epithelium; SEC, subepithelial capillary (Adapted from Ref. [16]). (b) Microanatomies which are visualized by M-NBI. MV pattern: subepithelial capillary network (SECN), collecting venule: (CV); MS pattern: marginal crypt epithelium (MCE), crypt opening (CO).

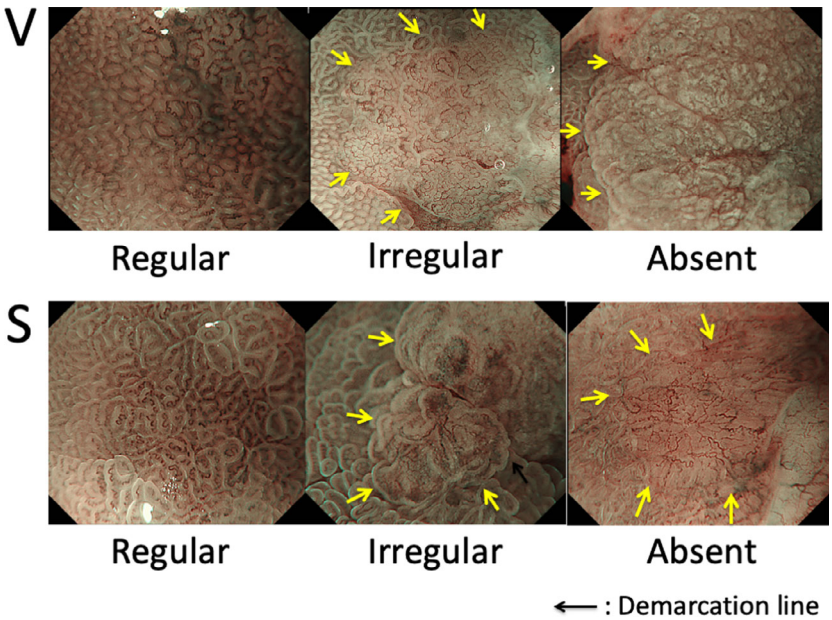

Figure 4 VS classification. Microvascular pattern (V) is classified as regular/irregular/absent; microsurface pattern (S) is classified as regular/irregular/absent. (Arrow shows a demarcation line; Adapted from Ref. [4]).

cancerous mucosa, and the presence of an irregular MV pattern and/or irregular MS pattern within the DL.

Accordingly, two criteria were set for making a diagnosis of high-grade dysplasia/EGC62:

1. An irregular MV pattern with a DL and/or
2. An irregular MS pattern with a DL.

If either or both criteria are fulfilled, an endoscopic diagnosis of EGC can be made.[15]

The definition of a DL is a border between the lesion and non-lesion areas, discernible through an abrupt change in MV and/or MS patterns.[15] Three categories of the MV and MS patterns are defined: regular, irregular, and absent (Fig. 4).[15] On principle, the MV and MS patterns need to be determined separately. In the regular MV pattern (Fig. 4), mucosal capillaries show closed-looped (polygonal) or open-looped with a homogeneous morphology, symmetrical distribution, and regular arrangement. In the irregular MV pattern (Fig. 4), the microvessels show closed-looped (polygonal), open-looped, tortuous, branched, or bizarrely shaped with heterogeneous morphology, asymmetrical distribution and irregular arrangement. If an MV pattern is not fully visualized due to presence of a white opaque substance (WOS) which obscures subepithelial microvessels (Fig. 4), the MV pattern is described as absent.[11] In cases in which the WOS is observed, rather than assessing the MVP, morphologic analysis of the WOS could be an alternative marker of MS pattern.[11] In the regular MS pattern (Fig. 2), the MCE represents a uniform curved, oval, or circular structure with homogeneous morphology, symmetrical distribution, and regular arrangement. In the irregular MS pattern (Fig. 3), the MCE demonstrates an irregular curved, oval, circular, or villous structure with heterogeneous morphology, asymmetrical distribution, and irregular arrangement. If the MS pattern is absent (Fig. 4), neither the marginal crypt epithelial structure nor WOS is visible by magnifying endoscopy.

Regarding the MESDA-G (Fig. 2), we first need to determine whether a DL is present between the mucosal lesion and the background mucosa. If DL is absent, the lesion is diagnosed as non-cancerous (Fig. 5). If DL is present, we should next evaluate if an irregular MV pattern and/or an irregular MS pattern are present. If both an irregular MV pattern and an irregular MS pattern is absent the lesion is diagnosed as non-cancerous (Fig. 6), If an irregular MV pattern and/or an irregular MS pattern are present, the lesion is diagnosed as cancerous (Fig. 7).

Thus, magnifying endoscopy using image enhancement is useful for the qualitative diagnosis of early gastric cancer, and as an optical biopsy method, it is expected to reduce the

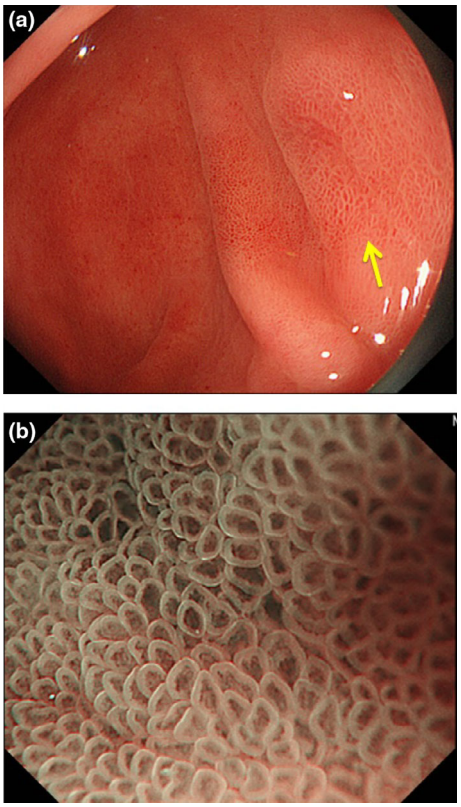

Figure 5 (a) Conventional endoscopic findings with white-light imaging. A slightly reddened depressed lesion (arrow) is noted at the gastric antrum. (Adapted from Ref. [4]). (b) Magnifying endoscopic findings with narrow-band imaging. When we observe the marginal part of the lesion, there is no demarcation line. According to the diagnostic algorithm, this lesion is diagnosed as non-caner. (Adapted from Ref. [4]).

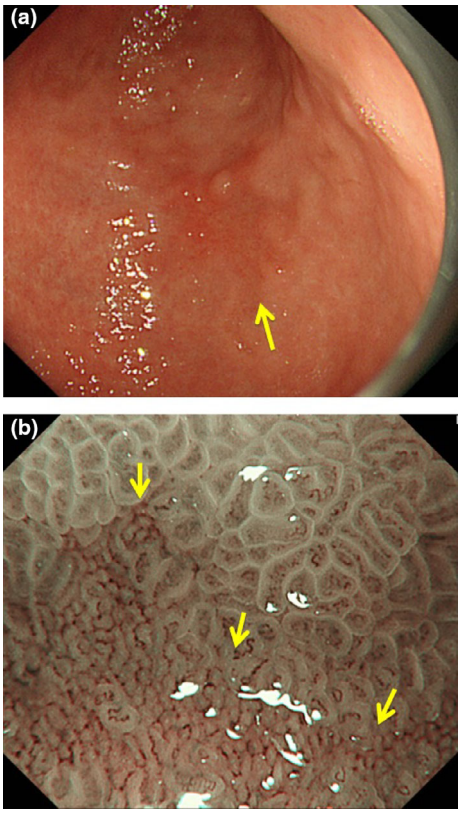

Figure 6 (a) Conventional endoscopic findings with white-light imaging. Slightly reddened depressed lesion is detected at the lower gastric body. (Adapted from Ref. [4]). (b) Magnifying endoscopic findings with narrow-band imaging. A clear demarcation line between the background mucosa and the lesion is detected. Inside the demarcation line, there are regular microvascular pattern and regular microsurface pattern. Since neither irregular microvascular nor irregular microsurface pattern is absent, this lesion is diagnosed as non-cancer. (Adapted from Ref. [4]).

implementation of biopsy.[6,17] However, facilities in which image-enhanced endoscopy is currently feasible are limited, and further spread of this technique is desired.

The guideline development panel concluded that the strength of the recommendation for image-enhanced endoscopy should be two because this technique is feasible in limited facilities despite strong evidence supporting its usefulness for the qualitative diagnosis of early gastric cancer.

The PubMed and Igaku Chuo Zasshi databases were searched. For PubMed, the search formula used was: "stomach neoplasms/diagnosis" AND ("image enhancement" OR "white light") AND (qualitative OR magnifying OR "blue laser" OR "linked color" OR autofluorescence OR "narrow band") Filters: Humans; English; Japanese. The search yielded 53 hits. For Igaku Chuo Zasshi, the following formula was used: (((胃腫瘍/TH or 胃腫瘍/AL)) and ((画像強調/TH or 画像強調/AL)) and ((質的研究/TH or 質的研究/AL) or 質的/AL)) and (PT=会議録除く), which means in English: (((gastric tumor/TH or gastric tumor/AL)) and ((image enhancement/TH or image enhancement/AL)) and ((qualitative study/TH or qualitative study/AL) or qualitative/AL)) and (PT=excluding congress proceedings). Ultimately, 24 articles were retrieved. These articles were narrowed down to those relevant to this statement; some other articles obtained by a manual search were added.

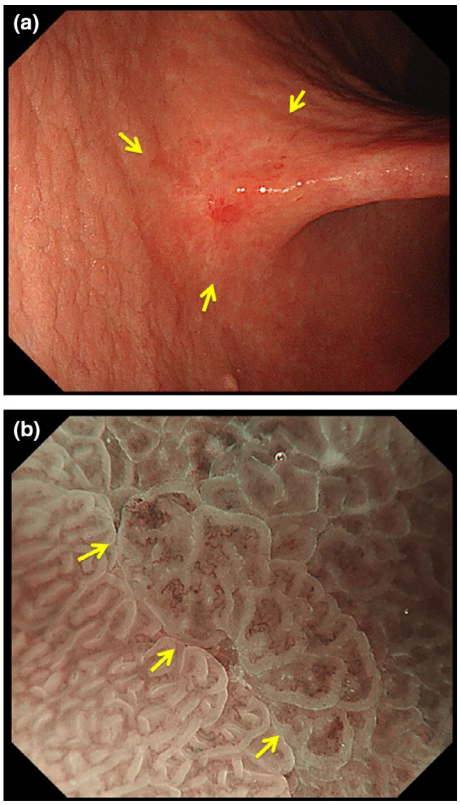

Figure 7 (a) Conventional endoscopic findings with white-light imaging. A slightly depressed lesion with some discoloration (arrow) is noted at the gastric incisura. (Adapted from Ref. [4]). (b) Magnifying endoscopic findings with narrow-band imaging. A clear demarcation line (arrow) is noted at the margin of the lesion. Since both irregular microvascular pattern and irregular microsurface pattern are present within the demarcation line, this lesion is diagnosed as cancer. (Adapted from Ref. [4]).

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[IV] DIAGNOSIS TO CHOOSE THE THERAPEUTIC STRATEGY FOR GASTRIC CANCER

Statement 4-1

A CLOSE PRETREATMENT endoscopic examination is necessary for determining the therapeutic strategy in cases of early gastric cancer.

Evaluation by the modified Delphi method: Median, 9; Minimum, 7; Maximum, 9
Strength of recommendation: 1
Level of evidence: D

Commentary

According to the fifth edition of the Japanese Gastric Cancer Treatment Guidelines, endoscopic or surgical treatment should be performed when a diagnosis of early gastric cancer is made.[1] Endoscopic treatment is less invasive and better preserves the stomach, achieving better patient QOL than surgical treatment. Therefore, in principle, endoscopic treatment is employed for lesions that have an extremely low probability of lymph node metastasis.[1] From this point of view, absolute indications for endoscopic mucosal resection/endoscopic submucosal dissection (ESD) are "macroscopic intramucosal cancer measuring 2 cm or less with UL0 (cT1a)," while those for ESD are "(i) cT1a measuring more than 2 cm with UL0, differentiated cancer, (ii) cT1a measuring 3 cm or less with UL1, differentiated cancer, and (iii) cT1a measuring 2 cm or less, undifferentiated cancer."[2–4] (Takizawa K, Ono H, Hasuike N *et al*. A non-randomized single-arm confirmatory trial of endoscopic submucosal dissection to expand ITS indication for early gastric cancer of undifferentiated type: Japan Clinical Oncology Group Study (JCOG1009/1010). Gastrointest Endosc. Accepted for publication. (Handsearch) (cohort study)). Therefore, to determine whether endoscopic treatment is indicated for a particular lesion, it is necessary to diagnose (i) histologic type, (ii) size, (iii) invasion depth, and (iv) ulcer presence or absence. In particular, because the lateral margin of the resected specimen positive for cancer cells indicates non-curative resection, it is necessary to determine the exact horizontal extent of invasion.[5–10] A close endoscopic examination prior to treatment should be performed at the same time as the detection of gastric cancer or on another occasion by a specialist if only an insufficient endoscopic diagnosis is obtained at the time of the detection of gastric cancer. Although the influence of intervention by close endoscopic examination on the radicality of treatment and mortality rate of gastric cancer remains unclear because of a lack of studies, it is inferred that an accurate endoscopic diagnosis contributes to the radicality of endoscopic treatment, patient QOL, and improvement of medical economics.

PubMed was searched using the following search formula: ("stomach cancer" OR "stomach neoplasms" OR "gastric cancer") AND (detection OR diagnosis) AND ("histological type" OR burden OR depth OR invasion OR cicatrix). Ultimately, 30 articles in English were retrieved. Some other relevant articles obtained by a manual search were added.

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Statement 4-2

Diagnosis of the histologic type of early gastric cancer should be performed comprehensively by endoscopic diagnosis and histopathological diagnosis using biopsy specimens.

Evaluation by the modified Delphi method: Median, 9; Minimum, 8; Maximum, 9
Strength of recommendation: 2
Level of evidence: D

Commentary

Morphological differences between differentiated and undifferentiated early gastric cancers as observed under endoscopy were reported long ago,[1,2] and this classification has been used clinically since then. Among macroscopic type lesions, protruding (0-I) and superficial elevated (0-IIa) lesions are frequently differentiated cancers, with a low frequency of undifferentiated cancer.[2] Among superficial depressed (0-IIc) lesions, undifferentiated cancer lesions are characterized by clear precipitous margins of the depressed area, granules of various sizes present in the depressed area,[2] and a discolored tone.[1,3,4] Lesions having concentrated folds show sharp thinning and/or discontinuation of the mucosal folds.[2] In addition, the mucosa around the lesion is usually the intestinal metaplastic mucosa in differentiated cancers but is often the gastric proper glandular mucosa in undifferentiated cancers. Therefore, the determination of the nature of the background mucosa of the lesion helps achieve a histological diagnosis.[2]

In recent years, characteristic features of differentiated and undifferentiated early gastric cancers on magnifying NBI endoscopy have been reported. Differentiated cancer lesions have an irregular microvascular pattern with a demarcation line,[5] and a fine-network pattern is often present.[6] On the other hand, undifferentiated cancer lesions often show a reduced or eliminated regular subepithelial capillary network pattern that is present around the cancerous region,[5] an irregular corkscrew pattern,[6–8] and absent microsurface pattern.[7,9]

However, all the above-mentioned studies were retrospective single-center studies. Therefore, evidence of a sufficiently high level has not been obtained for the endoscopic diagnosis of the histological type. In addition, there are currently limitations to the endoscopic diagnosis of cancers having both differentiated and undifferentiated elements. An endoscopic examination is advantageous in that it allows the diagnosis of the lesions as a whole. On the other hand, a histopathological diagnosis using biopsy specimens is restricted to the tissue from a particular site and not necessarily reflective of the histological type of the whole lesion. Therefore, when diagnosing the histological type of a cancerous lesion, it is necessary to make the diagnosis based on a comprehensive judgment of the results of endoscopic and histopathological diagnoses using biopsy specimens.

PubMed was searched using the following formula: "stomach neoplasms/pathology"[majr] AND early AND (endoscopy OR endoscopic OR gastroscopy) AND (histolog* OR histopathol*) Filters: Humans; English; Japanese. Ultimately, 320 articles in English and 16 in Japanese were retrieved. These articles were narrowed down to those relevant to this statement, and some articles obtained by a manual search were added.

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Statement 4-3

Although a rough estimation of lesion size can be obtained by endoscopy, an endoscopic diagnosis should be made on the premise that the lesion size should finally be judged after obtaining histopathological findings of the resected specimen.

Evaluation by the modified Delphi method: Not performed (background knowledge)
Level of evidence: D

Commentary

No report has systemically examined the diagnostic accuracy concerning the lesion size of early gastric cancer. In actual clinical practice, lesion size is estimated by comparison of the lesion and the diameter of the endoscope or biopsy forceps or by measurement using a measuring disc or measuring forceps.[1–5] However, the measurement of ulcers using biopsy forceps results in underestimation of lesion size by 26.5 ± 5.7% to 41.8 ± 3.3%.[2] Endoscopic measurement of the lesion vary among and within endoscopists.[5] Thus, there are errors among size measurements obtained by endoscopic visual evaluation in relation to the observation distance and angle.[1–5] The tumor diameter indicated for endoscopic treatment was prescribed based on the histopathological findings. Therefore, it is a general rule that the use of endoscopic treatment is determined according to the endoscopically estimated lesion size, but the final lesion determination should be made based on the histopathologically determined size of the resected specimen.

PubMed was searched using the following formula: "stomach diseases"[mesh] AND (endoscopy OR endoscopic OR gastroscopy) AND (measurement OR measuring OR size) NOT (resection OR surgery[sh]) Filters: Humans; English; Japanese. Ultimately, 752 articles in English were retrieved, narrowed down to those relevant to this statement, and some other articles obtained by a manual search were added.

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Statement 4-4

In principle, conventional white-light endoscopy should be used for determining the depth of invasion of early gastric cancer. If this is difficult, endoscopic ultrasonography may be a useful adjunctive diagnostic tool.

Evaluation by the modified Delphi method: Median, 8; Minimum, 7; Maximum, 9
Strength of recommendation: 2
Level of evidence: C

Commentary

For choosing a therapeutic strategy for early gastric cancer, it is necessary to distinguish between the depths of invasion of mucosal (cT1a) and submucosal (cT1b) cancers. Conventional white-light endoscopy is the most common endoscopic examination for determining the depth of invasion. Indicators of cancers at least 0.5 mm deeper from the submucosa (pT1b2) on white-light endoscopy include hypertrophy or fusion of concentrated folds,[1,2] tumor size at least 30 mm,[3] marked redness,[3] an irregular surface,[1,3,4] marginal elevation,[2] submucosal tumor-like raised margins,[3,4] and non-extension sign (Fig. 8).[5,6] The positive predictive value for diagnosing cT1b2 cancer using these indicators is reported to be about 63–89%.[6–9] A number of reports have indicated the usefulness of ultrasonography (EUS) for determining the depth of invasion of early gastric cancer.[7–11] However, in observational studies (non-randomized controlled trials) that compared the rates of accurate diagnosis of the depth of invasion by EUS and conventional endoscopy, Choi *et al*.[2] observed that conventional endoscopy was superior to EUS (73.7% vs. 67.4%, $P < 0.001$), while Yanai *et al*.[12] found no significant difference in diagnostic accuracy between the two techniques (63% vs. 71%, no significance). Therefore, it is proposed that the conventional white-light endoscopy should be performed to determine the depth of invasion of early gastric cancer and that EUS should be used as an auxiliary method for lesions diagnosed as cT1b by conventional endoscopy.[4,6,7]

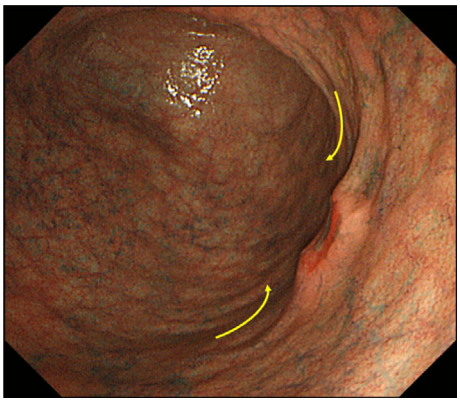

Figure 8 An example of chromoendoscopic findings of early gastric cancer (superficial elevated plus depressed (0-IIc + IIa) type) invaded down into the deeper part of the submucosa (T1b2). When the gastric wall is strongly extended by insufflation of a large amount of air, the T1b2 cancer is not extended and forms a trapezoid elevation, Mucosal folds converge and become elevated at the T1b2 cancer area (arrows). This is a so-called "non-extension sign" which is characteristic for the T1b2 cancer. (Adapted from Ref. [6]).

PubMed was searched using the following formula: "stomach neoplasms"[mesh] AND early AND ("Neoplasm Invasiveness" OR invasi* OR depth) AND (endoscopy OR endoscopic) Filters: Humans; English; Japanese. Ultimately, 887 articles in English and 124 in Japanese were retrieved. These articles were narrowed down to those relevant to this statement, and some other articles obtained by a manual search were added.

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Statement 4-5

In principle, conventional white-light endoscopy should be used for determining the presence/absence of active ulcers and ulcer scars associated with early gastric cancer.

Evaluation by the modified Delphi method: Median, 8; Minimum, 8; Maximum, 9
Strength of recommendation: 2
Level of evidence: D

Commentary

To decide the indication for endoscopic treatment, it is necessary to determine the presence or absence of ulcers (UL) prior to the operation. In principle, the presence/absence of UL should be determined according to whether there are findings of evident ulcer activity or scarring in the lesion on conventional endoscopy. An active ulcer is an open ulcer accompanied by a deep white coat with a mucosal defect, excluding shallow erosion. Because UL in the healing and scarring stages within the lesion are morphologically characterized by folds convergency, it is

necessary to distinguish these folds from concentrated folds associated with deep submucosal invasion.[1] Conventional white-light endoscopy combined with chromoendoscopy (indigocarmine contrast method) allows clearer observation of minute converging folds.[1–3] EUS is reportedly useful for diagnosing not only the presence/absence but also the depth of UL, which is linked to difficulty in ESD.[4]

PubMed was searched using the following formula: "stomach neoplasms"[majr] AND ("stomach ulcer" OR cicatrix OR scar) AND (endoscopy OR endoscopic) AND pathology[sh] Filters: Humans; English; Japanese. Ultimately, 274 articles in English and 83 in Japanese were retrieved. These articles were narrowed down to those relevant to this statement, and some other articles obtained by a manual search were added.

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Statement 4-6

Image-enhanced endoscopy is useful for diagnosing the extent of invasion.

Evaluation by the modified Delphi method: Median, 9; Minimum, 8; Maximum, 9
Strength of recommendation: 1
Level of evidence: B

Commentary

In the surgical or endoscopic resection of early gastric cancer, a strict diagnosis of the extent of invasion is necessary to achieve local radicality by avoiding positive lateral margins.[1–3] White-light endoscopy combined with indigocarmine chromoendoscopy has been widely used to diagnose the extent of invasion of early gastric cancer. Indigocarmine chromoendoscopy enhances changes in the surface structure of the gastric mucosal epithelium; therefore, it is useful for determining borders between cancerous and non-cancerous mucosae.[4,5] However, it reportedly cannot be used to determine the circumferential borders of early gastric cancer in 18.9–21.6% of cases.[6–9] Therefore, it fails to diagnose the extent of invasion in about 20% of cases, even when modern high-resolution endoscopy is used.

It was recently reported that the VS classification system[10] using magnifying NBI endoscopy has high diagnostic capability for determining the extent of invasion of early gastric cancer,[6–9,11,12] showing accuracy in 72.6% of lesions in which indigocarmine chromoendoscopy failed.[13] Among various studies that directly compared indigocarmine chromoendoscopy and magnifying NBI endoscopy, a randomized single-center controlled trial covering ESD cases alone showed significantly better results with magnifying NBI endoscopy (89.4% vs. 75.9%, $P = 0.007$),[6] whereas a randomized multicenter controlled trial that examined ESD and surgical cases found no superiority of magnifying NBI endoscopy (88.0% vs. 85.7%, $P = 0.63$).[13]

PubMed was searched using the following formula: "stomach neoplasms"[mesh] AND early AND ("neoplasm invasiveness" OR invas* OR extent OR margin OR horizontal) AND (endoscopy OR endoscopic OR gastroscopy) NOT (surgery[sh] OR resection PR dissection) Filters: Humans; English; Japanese. Ultimately, 265 articles in English and 182 in Japanese were retrieved. These articles were narrowed down to those relevant to this statement, and some other articles obtained by a manual search were added.

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[V] RISK STRATIFICATION AFTER ENDOSCOPIC EXAMINATION

Statement 5-1

ATROPHY, INTESTINAL METAPLASIA, nodularity, enlarged fold, and gastric xanthoma are endoscopic findings related to the risk of gastric cancer.

Evaluation by the modified Delphi method: Not performed (background knowledge)
Level of evidence: B

Commentary

Although atrophy and intestinal metaplasia have long been known as risk factors for differentiated gastric cancer, most studies on this issue were based on histological findings,[1–4] whereas few have evaluated the relationship between endoscopic findings and the risk of gastric cancer. Uemura *et al*.[5] performed endoscopic observations in 1246 persons infected with *H. pylori* and 280 uninfected persons for a mean 7.8 years and reported that 36 cases of gastric cancer occurred from the infected persons, showing that severe atrophy (endoscopic diagnosis), corpus predominant gastritis, and intestinal metaplasia (histological diagnosis) were significant risk factors. Regarding the relationship between the risk of gastric cancer and spread of endoscopic gastric mucosal atrophy evaluated by the Kimura-Takemoto classification, the risk of gastric cancer was reported to increase with progression of atrophy; the risk was 1.7 (95% CI 0.8–3.7) for cases of moderate atrophy and 4.9 (95% CI 2.8–19.2) for cases of severe atrophy when the risk for cases of absent or mild atrophy was set at 1. Masuyama *et al*.[6] registered 27,777 individuals who underwent endoscopic examinations (including 272 with early gastric cancer and 135 with advanced gastric cancer) and retrospectively analyzed the prevalence of gastric cancer and severity of endoscopic gastric mucosal atrophy (CI-OIII). The prevalence of gastric cancer was 0% (0/4506) for CI 0.25% (9/3660) for CII, 0.71% (21/2960) for CIII, 1.32% (75/5684) for OI, 3.70% (140/3780) for OII, and 5.33% (160/3004) for OIII. Thus, they reported that the frequency of gastric cancer increased significantly with the progression of endoscopic gastric mucosal atrophy, the same finding as that reported by Uemura *et al*. In a Korean study, endoscopic findings in 75 patients with gastric cancer detected from among 60,261 patients who underwent endoscopy were retrospectively analyzed; endoscopically observed atrophy (OR 8.47; 95% CI 4.65–15.40; $P < 0.001$) and intestinal metaplasia (OR 5.80; 95% CI 3.24–10.35; $P < 0.001$) were independent risk factors on a multivariate analysis.[7] Sugimoto *et al*.[8] studied 932 patients with *H. pylori* gastritis, 189 with early gastric cancer, and 79 gastric cancer after *H. pylori* eradication and retrospectively analyzed the relationship between gastric cancer and atrophy, intestinal metaplasia, enlarged fold, nodularity, and diffuse redness according to the endoscopic score of the Kyoto Classification of Gastritis.[9] They reported that the scores for atrophy and intestinal metaplasia in early gastric cancer were significantly higher than those in *H. pylori* gastritis; the significant risk factors found by multivariate analysis were intestinal metaplasia (OR 4.453; 95% CI 3.332–5.950; $P < 0.001$) and male sex.

Kamada *et al*.[10] retrospectively compared the risk of gastric cancer in patients with nodular gastritis aged 29 years or less and sex- and age-matched patients with *H. pylori* gastritis (case–control study). The rate of detection of gastric cancer among patients with nodular gastritis was 4.7% (7/150), which was significantly higher than the corresponding rate of 0.08% (3/3939) among controls (OR

64.2), suggesting that nodular gastritis is strongly associated with undifferentiated gastric cancer. In a prospective cohort study, Watanabe *et al*.[11] found that the incidence of gastric cancer among patients with enlarged fold gastritis on endoscopic examination (1749 cases/100,000 population/year) was significantly higher than the corresponding rate (43 cases/100,000 population/year) among patients without enlarged fold. In a gastric radiological study, Nishibayashi *et al*.[12] found that the risk of gastric cancer was 35.5-fold higher in cases with a fold width of at least 7 mm than in those with a fold width of 4 mm or less in the gastric corpus and pointed out that the fold width in the gastric corpus was a risk factor for undifferentiated gastric cancer occurring in the gastric corpus. Yamamichi *et al*.[13] also found the occurrence of five cases of gastric cancer in 3-year prospective observation of 1253 patients with enlarged fold gastritis and reported that enlarged fold was a predictor of gastric cancer.

Sekikawa *et al*.[14] prospectively followed 1823 individuals who underwent endoscopic examinations to determine the association between the presence/absence of gastric xanthoma and occurrence of gastric cancer. They reported that 29 cases of early gastric cancer occurred among the subjects during the study period and that endoscopic open type atrophy (OR 7.19; 95% CI 2.50–20.83; $P < 0.0001$) and xanthoma (OR 5.85; 95% CI 2.67–12.82; $P < 0.0001$) were independent risk factors of gastric cancer.

Thus, endoscopic findings associated with the risk of gastric cancer are atrophy, intestinal metaplasia, enlarged fold, and xanthoma. It is important to be fully aware of these risk factors for gastric cancer when performing endoscopic examinations. However, although specific intestinal metaplasia can be diagnosed by white-light endoscopy, non-specific intestinal metaplasia is difficult to diagnose under white light. In contrast, image-enhanced endoscopy, particularly by NBI[15] or LCI,[16] is useful for diagnosing non-specific intestinal metaplasia.

In Europe, the use of operative link on gastritis assessment,[17] which comprehensively assesses the risk of gastric cancer using a combination of severities of histological atrophy of biopsy specimens from fixed points of the gastric antrum and corpus, and operative link on gastric intestinal metaplasia assessment,[18] which assesses the risk of gastric cancer based on the degree of histological intestinal metaplasia, instead of atrophy, has been proposed. In recent years, findings on image-enhanced endoscopy have been well correlated with the histologically determined risk.[19] If risk stratification of gastric cancer based on endoscopic findings is possible, it is advantageous since it can reduce the cost of multiple biopsies and bleeding risk. From the viewpoint of the ability of endoscopy to diagnose histological atrophy and intestinal metaplasia, it is important to compare endoscopic and histological findings. However, only articles that examined the relationship between endoscopic findings and the occurrence of gastric cancer were used to prepare this statement.

Because this statement is provided as background knowledge, the strength of this recommendation was not evaluated.

PubMed was searched using the following formula: ("stomach neoplasms/diagnosis"[majr] OR gastritis[majr]) AND ("risk stratification" OR "risk assessment") AND (endoscopy OR endoscopic). Ultimately, 105 articles were retrieved. These articles were narrowed down to those relevant to this statement, and some other articles obtained by a manual search were added.

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Statement 5-2

Risk stratification of gastric cancer may be implemented based on endoscopic findings of *H. pylori*-negative status and gastric mucosal atrophy. Thus, risk stratification using these two items is proposed.

Evaluation by the modified Delphi method: Median, 9; Minimum, 7; Maximum, 9
Strength of recommendation: 2
Level of evidence: C

Commentary

The risk stratification of gastric cancer is currently performed using a combination of the serum anti- *H. pylori* antibody titer and serum PG level.[1] The possibility of implementing a risk stratification based on endoscopic findings is questioned. Statement 5-1 describes that atrophy, intestinal metaplasia, nodularity, enlarged fold, and gastric xanthoma are associated with the risk of gastric cancer. The Kimura-Takemoto classification[2] evaluates the extent of gastric mucosal atrophy based on the appearance of visible net-like or dendritic blood vessels and discoloration of the mucosa as observed on endoscopic examination (Fig. 9).

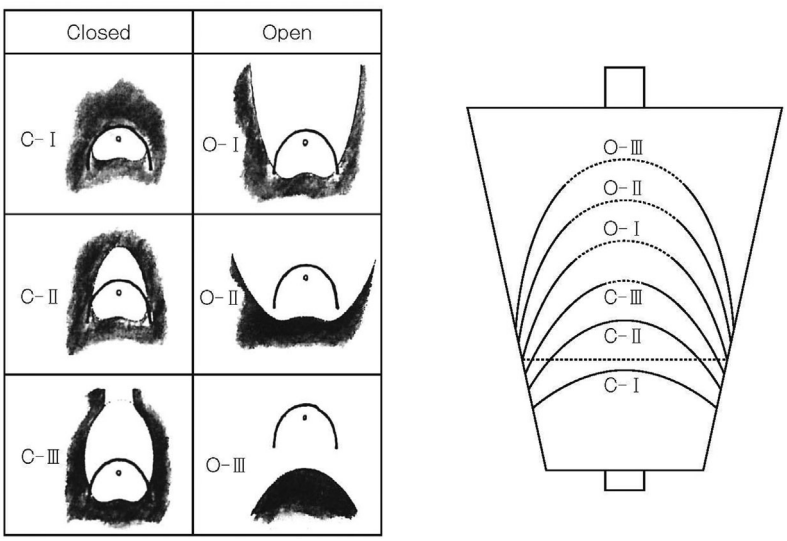

Figure 9 Illustration for endoscopic gastric mucosal atrophy (Kimura-Takemoto classification). Atrophic mucosa is limited to the antrum in C-I; limited to the lesser curvature of lower corpus in C-II; limited to the upper corpus in C-III, limited to the surroundings of the gastric cardia in O-I, atrophy is present in the entire stomach in O-III, and O-II is an intermediate type between O-I and O-III. (Adapted from Ref. [2]).

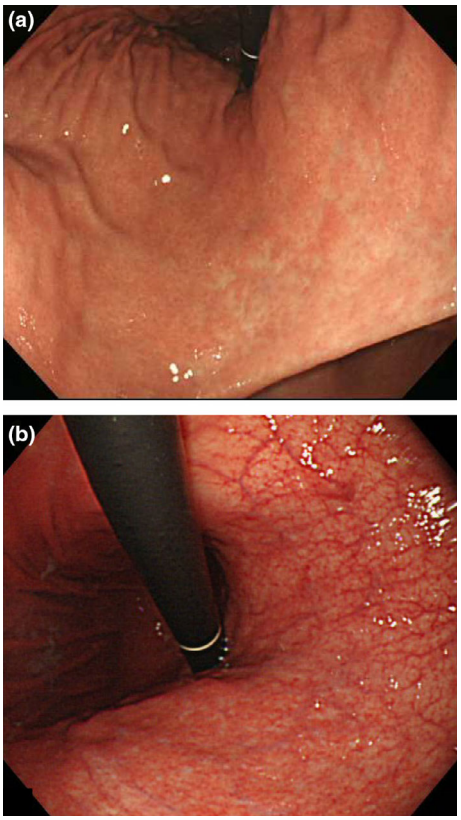

Figure 10 Endoscopic pictures of gastric mucosal atrophy. (a) Closed type (C-III): Atrophic discolored mucosa is limited to the lesser curvature of the upper corpus. (b) Open type (O-II): Visible vessels extend beyond the lesser curvature of gastric cardia to anterior and posterior wall. However, the folds of greater curvature in the corpus are not disappeared.

Figure 10 shows the typical endoscopic gastric mucosal atrophy. However, the appearance of visible blood vessels varies according to the degree of air insufflation; therefore, this parameter lacks objectivity. Statement 5-1 stated that the studies of Uemura *et al*.[3] and Masuyama *et al*.[4] indicated that risk stratification of gastric cancer is practical to some extent by evaluating the degree of gastric mucosal atrophy using the following Kimura-Takemoto classification: CI–CII (mild atrophy), CIII–OI (moderate atrophy), and OII–OIII (severe atrophy). Regarding risk stratification of gastric cancer in terms of intestinal metaplasia, all studies were based on histological findings[5–8] rather than endoscopic findings because white-light endoscopy cannot facilitate an accurate diagnosis of intestinal metaplasia. In addition, no studies have reported on risk stratification using a combination of atrophy and intestinal metaplasia. However, because image-enhanced endoscopy using NBI[9,10] or LCI[11] facilitates the diagnosis of intestinal metaplasia, the risk stratification of gastric cancer is feasible based on endoscopic findings of intestinal metaplasia. Further investigations on this matter are awaited.

Although the presence/absence of nodularity,[12] enlarged fold,[13] and gastric xanthoma was separately examined for a relationship with the risk of gastric cancer,[14] no reports have detailed these findings in a risk stratification of gastric cancer. On the other hand, the regular arrangement of collecting venules in the gastric corpus has been reported to be indicative of *H. pylori*-uninfected status,[15] i.e., an extremely low risk of gastric cancer.[1] Thus, it is speculated that the use of the finding of *H. pylori*-uninfected status and endoscopically observed gastric mucosal atrophy (Kimura-Takemoto classification) makes it possible to stratify the risk of gastric cancer into low or high. The production of sufficiently high levels of evidence is expected in the future.

PubMed was searched using the following formula: ("stomach neoplasms"[majr] OR gastritis[majr]) AND (endoscopy OR endoscopic) AND findings AND "risk factors" AND "gastric mucosa/pathology"). Ultimately, 188 articles were retrieved. These articles were narrowed down to those relevant to this statement, and some other articles obtained by a manual search were also added.

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[VI] SURVEILLANCE OF EARLY GASTRIC CANCER

Statement 6-1

A SURVEILLANCE ENDOSCOPIC examination is recommended for patients with risk factors (clinical and endoscopic findings) for gastric cancer.

Evaluation by the modified Delphi method: Median, 9; Minimum, 6; Maximum, 9
Strength of recommendation: 1
Level of evidence: B

Commentary

Screening is a strategy used in a population to identify individuals with an unrecognized target disease or predict the development of the target disease using common examinations, whereas surveillance is a strategy that aims to prevent and manage a particular disease through continuous investigations and monitoring of its occurrence.

The efficiency of detecting a disease using an examination is greatly associated with the risk (pretest probability) of the disease. Risk factors related to the occurrence of gastric cancer include several endoscopic (Statement 5-1) and clinical (Statement 1-1) findings, and the risk of gastric cancer in a target patient can be determined after endoscopic examination based on both findings. The continuation of an endoscopic examination (surveillance endoscopy) after the initial endoscopy is recommended for persons with risk factors for gastric cancer (clinical and endoscopic findings). In Japan, the percentage of *H. pylori*-infected persons among those who underwent endoscopic examinations was 74.7% in the 1970s vs. 35.1% in the 2010s.[1] Along with this decrease, there were similar changes in the prevalence of atrophy and intestinal metaplasia of the gastric corpus mucosa, which are high-risk factors for gastric cancer; the prevalences were 82% and 32%, respectively, in the 1970s vs. 19% and 4.7%, respectively, in the 2010s.[1] Thus, the current Japanese population is not entirely a high-risk population for gastric cancer; rather, it consists of a mixture of high- and low-risk populations. Therefore, the recommendation of surveillance endoscopy for a properly selected high-risk population can promote the efficiency of gastric cancer detection and reduce endoscopy-related harms (cost, burden, risk of adverse events).

There is little high-level evidence that directly demonstrates the effectiveness of surveillance endoscopy and its appropriate intervals for reducing gastric cancer mortality rates in a population at high risk of developing gastric cancer. In Japan and South Korea, where the prevalence of *H. pylori* infection is high and the majority (≥70%) of infected people have high-risk gastric mucosal changes, i.e., mucosal atrophy and intestinal metaplasia,[1] the implementation of a nationwide gastric cancer screening program has been recommended. Results of studies that investigated the association between the intervals of screening endoscopy and occurrence of gastric cancer in these countries may provide useful information for the efficacy and appropriate intervals of surveillance endoscopy in high-risk populations. A large-scale case–control study showed a 47% reduction in gastric cancer mortality among individuals who participated in the Korean National Gastric Cancer Screening Program, and in people aged 40–69 years, a statistically significant mortality reduction was observed even when the examination interval was 4 years or more.[2] A Japanese case–control study indicated a 30% reduction in the gastric cancer mortality rate in individuals who underwent endoscopic screening within the past 2–4 years, but the statistically significant effect was only seen in those who underwent an endoscopic examination within the prior 3 years.[3] A South Korean cross-sectional study investigated the association

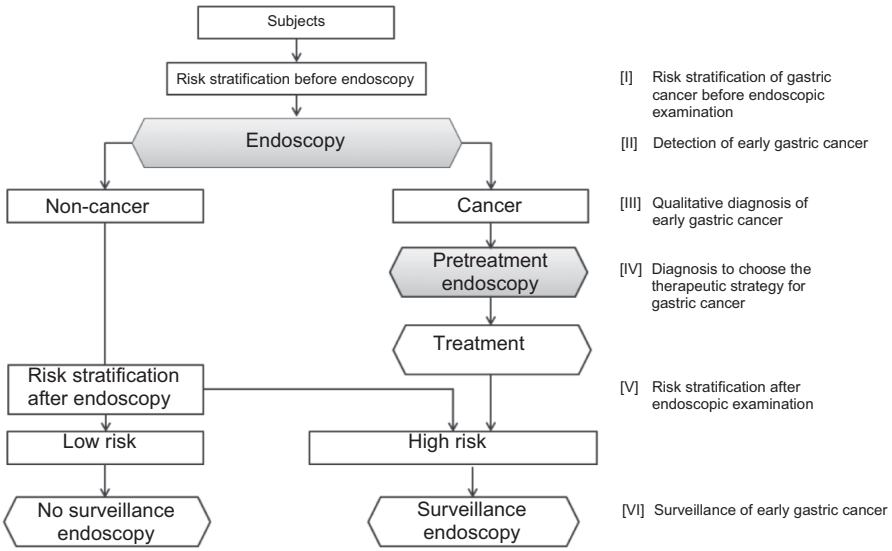

Figure 11 Algorithm of diagnostic and therapeutic strategy for early gastric cancer. In each subject, the risk of gastric cancer is assessed before endoscopic examination by clinical information [I]. With appropriate preparation and observation method, suspicious lesions for early gastric cancer are detected [II]. The detected lesions are differentiated whether they are cancerous or non-cancerous by endoscopic findings [III]. The differential diagnosis should be confirmed by targeted biopsy. Cancerous lesions are further examined for histological type, size, depth of invasion, and presence or absence of ulcer/scar to determine indication of treatment including endoscopic resection [IV]. The risk of gastric cancer is assessed again in accordance with endoscopic findings [V], and surveillance endoscopy is recommended according to the risk [VI].

between the interval of endoscopic examination and stage of the detected gastric cancer, and the percentage of stage I diagnoses was consistently about 70% when the examination interval was 1–3 years, whereas it was significantly lower, 60%, when the examination interval was 4 years or more.[4] It has also been reported that the proportion of intramucosal carcinoma was 75% among those who underwent an annual endoscopic examination, whereas it was significantly lower, 57%, among those who underwent a biannual examination.[5] Thus, the appropriate interval of endoscopic examination surveillance for persons at high risk of gastric cancer is suggested to be 1–3 years considering the inhibitory effect on gastric cancer mortality, but shorter intervals are preferable if the detection of endoscopically resectable early gastric cancer is intended. However, further investigations of the optimal surveillance endoscopy interval are required in terms of examination purpose (mortality reduction or avoidance of gastric surgery) and cost-effectiveness.

In a Japanese cohort study (1603 patients with peptic ulcer, gastric polyp, functional dyspepsia followed for a mean 7.8 years), no cases of gastric cancer developed among 280 patients without *H. pylori* infection.[6] In addition, a cross-sectional study of 3161 patients with gastric cancer revealed that 0.66% were *H. pylori*-uninfected.[7] These data indicate that the incidence of gastric cancer among *H. pylori*-uninfected persons was extremely low even in Japan, which is known for its high incidence of gastric cancer. Considering the processing capacity, cost, burden, and potential risk of adverse events, surveillance endoscopy is not recommended for *H. pylori*-uninfected persons who have no structural disorders. However, this recommendation should not conflict with the performance of population-based screening or implementation of endoscopic examinations in symptomatic patients. Further investigations are required of risk factors for gastric cancer other than *H. pylori* infection (autoimmune gastritis, EB viral infection, hereditary diffuse gastric cancer).[8]

Among patients who received endoscopic treatment for early gastric cancer, metachronous multiple gastric cancer occurs frequently (cumulative 3-year incidence, 5.9%). Because its incidence remains the same even after 5 years,[9] long-term surveillance endoscopy is indispensable. A Japanese cohort study reported that annual surveillance endoscopy yielded endoscopic curative resection in almost all (≥95%) cases of detected metachronous gastric cancer.[9] However, a subsequent study on a large number of patients

in the same institution reported gastric cancer deaths of metachronous multiple gastric cancer, indicating the need for long-term careful examinations.[10]

PubMed and the Cochrane Library were searched using the following formula: ("stomach cancer" OR "stomach neoplasms" OR "gastric cancer") AND (endoscopy OR endoscopic) AND surveillance AND (period OR interval). Ultimately, 61 articles were retrieved and then narrowed down to those 15 relevant to this statement; some other articles obtained by a manual search were also added.

Algorithm for endoscopic diagnosis of EGC is proposed based on the statements of this guideline (Fig. 11).

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