REVIEW

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CLINICAL ENDOSCOPY

Recent advancement in endoscopic diagnosis for risk stratification of gastric cancer

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Approximately 90% of cases of gastric cancer (GC) are caused by *Helicobacter pylori* infection, and screening esophagogastroduodenoscopy is effective for secondary prevention of GC. Endoscopic findings of the stomach due to *H. pylori* infection vary widely, and the risk of GC varies according to each finding. GC risk is evaluated by combining endoscopic and histopathological findings. In the operative link on gastritis assessment and operative link on gastric intestinal metaplasia assessment staging, GC risk is determined by histopathological evaluation. In the endoscopic grading of gastric intestinal metaplasia, Kyoto classification, and modified Kyoto classification, the risk is considered based on endoscopic findings. However, evaluating endoscopic findings is challenging because the evaluation varies depending on the skill of the endoscopist. Similarly, histopathological findings can be assessed differently by different pathologists. Histopathological evaluation by biopsy carries a risk of bleeding; thus, simpler and less-invasive risk stratification methods are desirable. Artificial intelligence for risk stratification, which has the potential for improved accuracy and consistency, has been developed for endoscopic and histopathological evaluations. Appropriate GC risk stratification would benefit the economy and patients, and further evaluation of surveillance intervals tailored to individual risks is warranted.

Keywords: Classification; Early detection of cancer; Neoplasms; Secondary prevention; Stomach neoplasms

INTRODUCTION

According to Global Cancer Observatory 2022, gastric cancer (GC) is the fifth most diagnosed and fifth deadliest cancer worldwide.[1] Approximately 90% of cases of GC are due to long-term infection with *Helicobacter pylori*, and the risk of GC varies greatly depending on the infection status (uninfected, currently infected, or post-eradication).[2] Compared with that in individuals without infection, the risk of GC in individuals with current infection is estimated to be more than 20 times higher.[3] Successful eradication will decrease the GC risk; however, it remains 10 times higher than that of individuals without infection.[4] While the 5-year relative survival rate for patients with stage I GC is as high as 94.7%, it decreases to 80.9% and 9.4% in patients with stage II and IV GC, respectively.[5] Primary prevention of GC is possible with eradication for *H. pylori*-infected gastritis, while secondary prevention through screening is also important.[5] However, only a few countries have guidelines on GC screening. With the goal of ensuring the quality of GC diagnosis and screening worldwide, current national or international guidelines were collected, presenting seven recommendations for screening and diagnosis of GC with the consensus of experts in each country.[6] These seven recommen-

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dations include (1) identification of patients at high risk of GC before esophagogastroduodenoscopy (EGD), (2) patients who need surveillance of GC, (3) method to ensure quality of EGD for GC detection, (4) individual GC risk assessment by EGD, (5) identification of patients at high risk of GC after EGD, (6) qualitative or differential diagnosis of GC by EGD, and (7) endoscopic assessment to choose the therapeutic strategy for GC. Because performing EGD on all individuals is challenging owing to the manpower of endoscopists and cost-effectiveness, the ABC classification method has been developed to identify patients at high risk before EGD. In this method, patients are classified into four groups, A–D, according to their serum anti-*H. pylori* IgG antibody and pepsinogen values, in which the prevalence of GC is highest in group D and lowest in group A.[7,8] Although the number of patients with current *H. pylori* infection has decreased with widespread *H. pylori* eradication in Japan, the ABC method is a useful tool for GC risk stratification.[9] Appropriate risk stratification is important for efficient screening and decreasing the cost and human resources for EGD. In this review, we summarize the endoscopic findings related to risk diagnosis and stratification of GC.

ENDOSCOPIC FINDINGS RELATED TO *H. PYLORI* INFECTION AND EACH RISK FOR GC

Atrophic gastritis

Atrophy is characterized by pathological and endoscopic atrophy. Pathological atrophy is defined as a decrease in the number of gastric glands, and endoscopic atrophy is diagnosed using the Kimura-Takemoto classification.[10-12] Atrophic gastritis is rated in six categories (closed 1–3 to open 1–3) according to the extent of atrophy. The presence of atrophy is a risk for diffuse GC, and severe atrophy is a risk for intestinal-type GC.[13] The incidence of GC increases as atrophy progresses.[14] Previous cohort studies showed that the GC incidence increased with atrophy from 0.04% to 0.10% per year for C0–C1, 0.12% to 0.34% for C2–C3, and 0.31% to 1.60% for O1–O3 (Fig. 1A).[15-17]

Intestinal metaplasia

Intestinal metaplasia (IM) is defined as the replacement of the gastric mucosa by intestinal epithelium. IM can be recognized as whitening when sprayed with an acetic acid indigo carmine mixture, which is useful in diagnosing the presence of IM.[18] IM has an odds ratio of 5.0 for GC and is associated with intestinal-type GC.[19,20] Compared with conventional white-light imaging, image-enhanced endoscopy (IEE) yields a higher diagnostic rate for IM. An endoscopic finding called light blue crest (LBC) is a blue-white tinted line bordering the margins of IM observed with magnifying endoscopy with narrow band imaging (M-NBI).[21] The diagnostic performance of LBC for histologic IM is as high as 89% sensitivity, 93% specificity, and 91% accuracy.[22,23] Another endoscopic finding called white opaque substance (WOS) in the epithelium of tumors and IM was reported, which makes the subepithelial microvasculature invisible with M-NBI.[24,25] Histopathological studies have demonstrated that WOS is microscopic fat droplets, which decrease along with the decrease in intragastric pH.[26] The diagnostic performance of WOS for histologic IM is 50% sensitivity, 100% specificity, and 70% accuracy. The diagnostic performance for histologic IM was increased to 87.5% sensitivity, 93.8% specificity, and 90% accuracy with a combination of LBC and WOS.[27] Marginal turbid band (MTB) is another endoscopic finding related to IM, which is observed as a cloudier white epithelium than the normal marginal foveolar epithelium.[28] The diagnostic performance of MTB for histologic IM is 100% sensitivity, 66% specificity, and 82% accuracy. The relative risk of developing GC is 6.4 for patients with IM compared with that for patients without IM.[13] In particular, the presence of IM is a risk factor for intestinal-type GC (Fig. 1B–D).[29]

Map-like redness

Map-like redness is considered to be the manifestation of small intestinal-type IM as the eradication improves the inflammation and the redness of the background mucosa diminishes.[30] Although map-like redness is a risk for post-eradication GC, map-like redness is sometimes difficult to distinguish from type 0–IIc post-eradication GC.[31] Therefore, biopsy should be considered by assessing the ease of bleeding, intensity of color change, and unevenness of the mucosal surface (Fig. 1E).[32]

Enlarged fold

The highly active inflammation induced by *H. pylori* causes an enlarged fold (EF). It remains in the greater curvature of the corpus and is defined as ≥5 mm folds that do not flatten with air insufflation. Inflammation-induced DNA methylation is involved in the carcinogenesis of gastritis with EF.[33] A positive association was reported between the width of EF and the incidence of GC.[34] Severely EFs (≥10 mm) are more strongly associated with submucosal invasion GC than slightly EFs (5–9

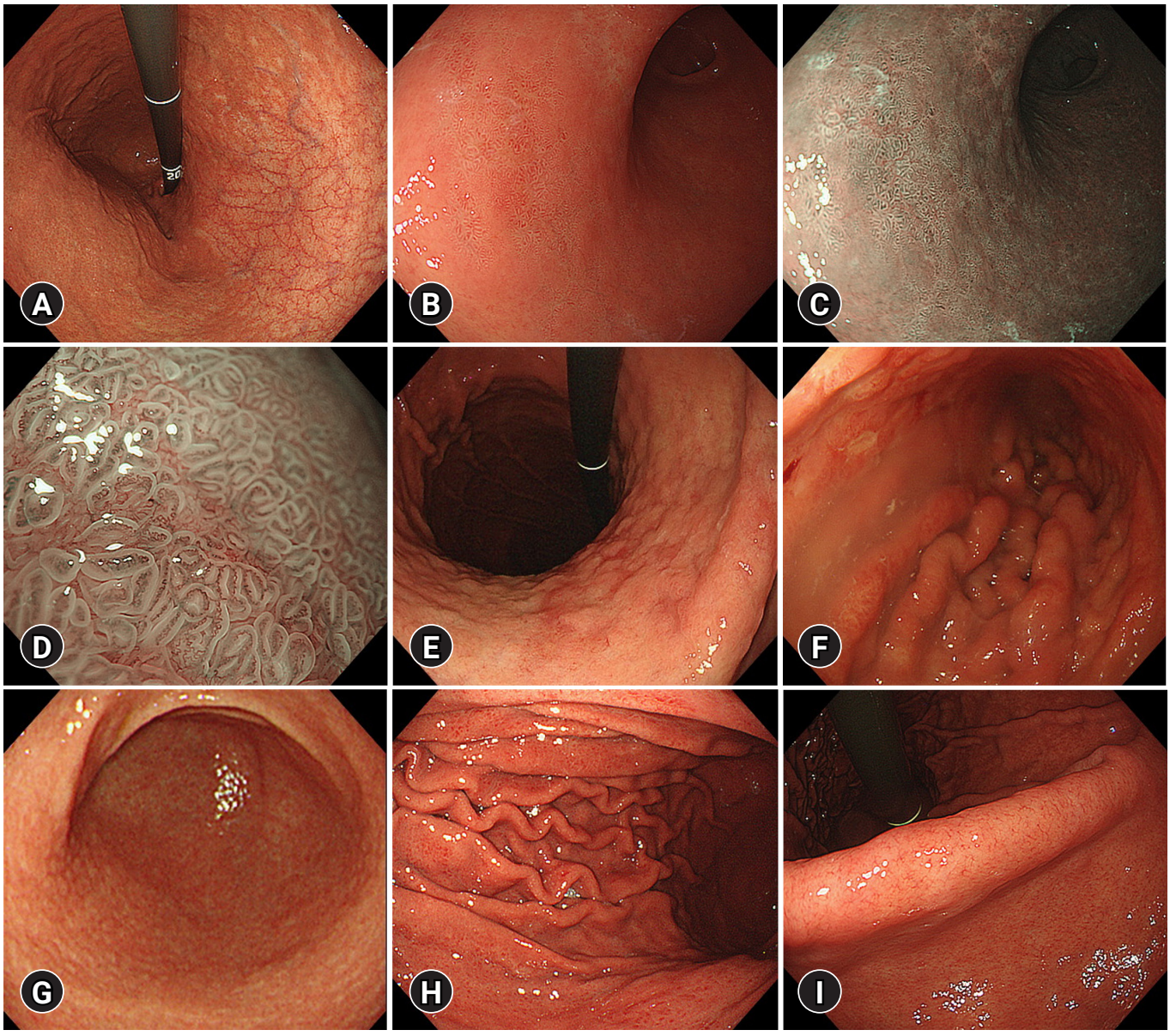

Fig. 1. Typical images of (A) atrophic gastritis, (B) intestinal metaplasia observed with conventional white light endoscopy, (C) intestinal metaplasia observed with image-enhanced endoscopy (IEE) without magnification, (D) intestinal metaplasia observed with IEE with magnification, (E) map-like redness, (F) enlarged fold, (G) nodularity, (H) diffuse redness, and (I) regular arrangement of collecting venules on the lesser curvature of the angulus.

mm).[35] In particular, the presence of EF is a risk for diffuse-type GC (Fig. 1F).[29]

Nodularity

Nodularity refers to relatively uniform multiple nodules that resemble goose bumps and is caused by an excessive immune response due to *H. pylori* infection. Nodularity is observed mainly in the antrum. Nodularity is associated with pathologic inflammation (neutrophil activity and chronic inflammation) and high *H. pylori* antibody titer (>50 U/mL).[36] Additionally, in immunohistochemistry, nodularity is associated with decreased E-cadherin and increased p53.[37] The odds ratio for GC is 13.9 and is associated with diffuse-type GC.[38] In particular, nodularity is strongly associated with diffuse-type GC in young patients.[39] However, some reports have suggested that nodularity does not correlate with the development of GC.[17,29] The number

of diffuse-type GC is lower than that of intestinal-type GC. The risk of intestinal-type GC increases with age, while diffuse-type GC is more common in young individuals. These factors may counteract the correlation between GC and nodularity. However, this association remains controversial (Fig. 1G).

Diffuse redness

Diffuse redness (DR) is a uniform erythematous tone of the mucosa, observed mainly in the non-atrophic mucosa of the corpus. DR is reduced by eradication[40] but sometimes persists after eradication.[41] The more severe the DR, the higher the incidence of GC (Fig. 1H).[17]

Xanthoma

A xanthoma is a white to yellowish flat or sessile lesion with a granular surface. It is considered to be the aggregation of lipid-phagocytosing histiocytes and to be caused by a high degree of inflammation.[42] The presence of xanthomas is associated with the presence of GC.[43]

Regular arrangement of collecting venules

A regular arrangement of collecting venules (RAC) refers to an image of regularly arranged collecting venules in the fundic gland region of the stomach. Originally reported as a typical endoscopic image of the *H. pylori*-uninfected normal stomach, it can also be seen in the stomach after eradication.[44] Therefore, the lesser curvature of the angulus is the ideal location to identify RAC for detecting *H. pylori*-uninfected stomach.[45] RAC has shown a negative correlation with GC, with an odds ratio of 0.4 (Fig. 1I).[46]

HISTOPATHOLOGICAL DIAGNOSIS FOR RISK STRATIFICATION OF GC

Updated Sydney system

The updated Sydney system (USS) is an international notation for gastritis consisting of histological and endoscopic sections. The USS uses a visual analog scale to grade five items: (1) *H. pylori* density, (2) neutrophil activity, (3) chronic inflammation, (4) glandular atrophy, and (5) IM. The protocol recommends a 5-point biopsy including the lesser curvature of the antrum and corpus, greater curvature of the antrum and corpus, and lesser curvature of the angulus. However, given its invasiveness, some authors believe that a 2-point biopsy including the greater curvature of the corpus (8 cm from the cardia) and the greater curvature of the antrum (2–3 cm from the pylorus), avoiding any lesion, is adequate.[47] Consideration must be given to patients taking antiplatelet and anticoagulant medications and older adults. The topographic distribution of neutrophil activity is strongly correlated with the risk of GC. According to activity distribution, gastritis is classified as follows: no gastritis, antrum-predominant gastritis, pangastritis, or corpus-predominant gastritis. When antrum-predominant gastritis was considered as the control, the risk of pangastritis was 16, that of corpus-predominant gastritis was 35.[13] Corpus-predominant gastritis is related to intestinal-type GC, and that of pangastritis is related to diffuse-type GC.

OPERATIVE LINK ON GASTRITIS ASSESSMENT STAGING AND OLGIM STAGING

The operative link on gastritis assessment (OLGA) staging and operative link on gastric intestinal metaplasia (OLGIM) assessment staging have been reported in Europe, both of which assess GC risk according to the degree of pathological atrophy and IM in the antrum and the corpus (Tables 1, 2).[48,49] According to the OLGA staging, five biopsies are taken: two from the antrum, one from the angulus, and two from the corpus.[48] The pathologist evaluates these biopsies based on the USS, and the results of the antrum and the corpus are combined for staging. A prospective study reviewed 439 cases for OLGA staging and stated that 21 cases were classified as stage III or IV, which were considered high-risk stages, and five cases with GC were classified as stage III or IV, suggesting the usefulness of OLGA

Table 1. Operative link on gastritis assessment staging

Antrum and angulus	Corpus			
	No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
No atrophy (score 0)	Stage 0	Stage I	Stage II	Stage II
Mild atrophy (score 1)	Stage I	Stage I	Stage II	Stage III
Moderate atrophy (score 2)	Stage II	Stage II	Stage II	Stage IV
Severe atrophy (score 3)	Stage III	Stage III	Stage IV	Stage IV

Table 2. Operative link on gastric intestinal metaplasia assessment staging

Antrum and angulus	Corpus			
	No IM (score 0)	Mild IM (score 1)	Moderate IM (score 2)	Severe IM (score 3)
No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
Moderate IM (score 2)	Stage II	Stage II	Stage II	Stage IV
Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

IM, intestinal metaplasia.

staging.[48] However, the pathological diagnosis of atrophy can differ by pathologists, and the kappa value is low.[50] Thus, OLGIM staging has been proposed. The OLGIM staging replaced the evaluation of atrophy with that of IM.[49] According to the OLGIM staging, 12 biopsies are taken: four from the antrum and two each from the lesser curvature of the angulus, the lesser curvature of the corpus, the greater curvature of the corpus, and the cardia. Performing 12 biopsies differs from the protocol of the USS, and debates remain on whether five biopsies are sufficient for an adequate diagnosis of IM and dysplasia.[49] Patients with GC have been reported to have a higher prevalence of corpus-predominant gastritis and OLGIM stage II–IV, but not OLGA stage II–IV, than the controls.[51] However, both stagings require many biopsies and are difficult to use in patients taking antiplatelet and anticoagulant medications and in older adults.

ENDOSCOPIC DIAGNOSIS FOR RISK STRATIFICATION OF GC

Endoscopic grading of gastric intestinal metaplasia

To eliminate the risk of bleeding from biopsies, endoscopic grading of gastric intestinal metaplasia (EGGIM) was advocated (Table 3). EGGIM assesses four areas (lesser and greater curvatures of the antrum and lesser and greater curvatures of the corpus) and scores endoscopic findings of IM such as LBC, WOS, and ridge/tubulovillous surface structure as 0 (no IM), 1 (focal ≤30%), and 2 (extensive >30%) using high-definition endoscopy without magnification. The EGGIM score was calculated as the sum of these four scores, ranging from 0 to 10 points.[52] A prospective study showed that the EGGIM classification indicated a higher diagnostic performance than OLGIM staging and that biopsies could be avoided for surveillance EGD using the EGGIM score.[53]

Kyoto classification

The Kyoto classification is used to quantify gastritis findings

Table 3. Endoscopic grading of gastric intestinal metaplasia staging

	No IM	≤30% IM	>30% IM
Lesser curvatures of the antrum	0	1	2
Greater curvatures of the antrum	0	1	2
Incisura	0	1	2
Lesser curvatures of the corpus	0	1	2
Greater curvatures of the corpus	0	1	2

IM, intestinal metaplasia.

(Table 4). The Kyoto score is calculated as the sum of 0 to 8 points, with atrophy, IM, EF, nodularity, and DR. The score for DR is also evaluated by RAC. Kyoto score is associated with GC risk.[17] Above all, a Kyoto score of 4 or higher is rated as a risk for GC.[40] *H. pylori* eradication has been reported to improve the Kyoto score from 3.90 to 2.78, with EF, nodularity, and DR contributing to this improvement but not atrophy and IM.[54] Patients with multiple GCs had higher Kyoto scores than those with a single GC (5.1 vs. 3.8) and tended to have endoscopic open-type atrophy and IM in the corpus.[55] Patients with early GC and *H. pylori* infection had a higher Kyoto score of 4.8 than those without GC (3.8). In detail, patients with early GC had higher atrophy and IM scores, lower nodularity scores, and no significant difference in EF and DR scores compared with those without GC.[19] In addition, individuals who had prostate stem cell antigen, a single nucleotide polymorphism associated with GC, had a significantly higher Kyoto score (4.87 vs. 3.87).[56]

Because diffuse-type and intestinal-type GC have different risks, an evaluation score that considers the type of GC is desirable in the future. A retrospective case-control study that compared diffuse-type and intestinal-type GC reported that patients with intestinal-type GC were older, had a higher proportion of males, had more severe atrophy, had more extensive IM, had milder EF, and had slighter nodularity than those with diffuse-type GC.[29] Given the aforementioned discussion on nodularity, nodularity should be considered separately in GC risk stratification.

Table 4. Kyoto classification

	Kyoto score 0	Kyoto score 1	Kyoto score 2
Atrophy	C0–C1	C2–C3	O1–O3
Intestinal metaplasia	No	Antrum	Corpus and antrum
Enlarged fold	No	Yes	
Nodularity	No	Yes	
Diffuse redness	No (RAC [+])	Mild (partially visible RAC)	Severe (RAC [–])

RAC, regular arrangements of collecting venules.

The Kyoto classification does not require pathological evaluation. Endoscopic and pathological diagnoses have been reported to be consistent with atrophy and IM among individuals positive for *H. pylori*.[57] Another report showed that risk evaluation for GC yielded comparable outcomes when conducted by endoscopic or histologic assessment, which would eliminate the necessity for biopsies.[58]

In China, Li's score was developed, which is based on clinical and laboratory data consisting of age, sex, presence of *H. pylori* infection, pepsinogen value, and gastrin-17 value.[59] Comparing Li's score to the Kyoto score, the sensitivity was 57.6% vs. 85.3%, and the specificity was 75.4% vs. 83.6%. Although the Kyoto score is more sensitive than Li's score, Li's score has the advantage of assessing the risk of GC without endoscopy. The combination of clinical and laboratory data and the Kyoto score may provide a more appropriate risk stratification for GC.

Modified Kyoto classification

A multicenter study assessed the Kyoto classification, atrophy, EGGIM, OLGA, and OLGIM and showed that OLGIM stage III or IV, high EGGIM score, and open-type atrophy significantly increased the risk of GC in Japanese patients.[60] The modified Kyoto classification was proposed, which consisted of the disappearance of RAC in the angulus (score 2), open-type atrophy (1), IM in the corpus (>30%) with IEE (1), and map-like redness in the corpus (1). Compared with scores of 0 to 1, the odds ratio for GC increased to 8.6 (2.6–26.7) for scores of 2 to 3 and 28.0 (8.7–88.7) for scores of 4 to 5 (Table 5). As IEE is used to evaluate IM, the evaluation may vary depending on the skill of the endoscopist. In addition, because map-like redness appears after eradication, the score may increase with eradication.[61]

Table 5. Modified Kyoto classification

	Score
Disappearance of RAC in the angulus	2
Open-type atrophy	1
IM in the corpus (>30%) with IEE	1
Map-like redness in the corpus	1
Diffuse redness	1

RAC, regular arrangement of collecting venules; IM, intestinal metaplasia; IEE, image-enhanced endoscopy.

RISK STRATIFICATION WITH ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) refers to the ability of a computer to achieve human performance on cognitive tasks. Compared with human performance, in which errors can be introduced through fatigue, stress, or limited capability, AI has the advantages of greater accuracy, consistency, and higher speed. AI can also prevent human error and compensate for limited capabilities and experience. The first AI system for the diagnosis of *H. pylori* gastritis was developed in 2017.[62] A convolutional neural network was constructed, which provided a higher accuracy and a significantly shorter time for the diagnosis of *H. pylori* gastritis than endoscopists.

A computerized system for image analysis of endoscopic images to assess the risk of GC was reported in 2019.[63] The system was trained using images that were classified as high-risk (patients with GC), moderate-risk (patients with current or past *H. pylori* infection or gastric atrophy), and low-risk (patients with no history of *H. pylori* infection or gastric atrophy). In total, 12,824 images (454 patients) were analyzed in 345 s. In this analysis, the risk of GC significantly increased in the moderate- and high-risk groups.

An AI system based on a deep convolutional neural network algorithm for the diagnostic pathology of IM was developed in 2023.[64] The system assessed hematoxylin and eosin-stained slides and evaluated the degree of IM. The diagnostic performance of IM was 97.7% sensitivity and 94.6% specificity, and its performance in classifying the degree of IM was 98.5% sensitivity and 94.9% specificity. In addition, the minimal IM areas that

pathologists overlooked during the review were identified using AI. This system may reduce costs, the burden on pathologists, and the variability subject to pathologists.

AI is also being developed for endoscopic findings. AI diagnosed the degree of atrophy according to the Kimura-Takemoto classification as well as experts and more accurately than non-experts.[65] Regarding Kyoto classification, a deep learning system that evaluates atrophy, DR, EF, IM, and nodularity had significantly higher accuracy, specificity, recall, and F1 score than experts.[66]

CONCLUSIONS

Various risk stratification methods for GC exist, including endoscopic imaging and histopathological evaluation of atrophy and IM. Advances in less-invasive and simpler stratification are desirable. Further studies are required to evaluate the optimal surveillance intervals according to risk stratification. Appropriate risk stratification will make it possible to provide optimal follow-up intervals for endoscopy for each patient, which will also produce economic benefits.

Conflicts of Interest

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Author Contributions

Conceptualization: TH, NK; Data curation: TH; Formal analysis: TH; Investigation: TH, NK; Methodology: TH; Project administration: NK; Resources: NK; Software: TH, NK; Supervision: MF; Validation: all authors; Visualization: TH; Writing–original draft: TH; Writing–review & editing: all authors.

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