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Difficulty in distinguishing malignant gastric lymphoma from advanced gastric cancer

Focusing on endoscopic findings of the Borrmann type

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Abstract

Malignant gastric lymphoma (MGL) accounts for a small proportion (upto 5%) of gastric malignancies. However, unlike for advanced gastric cancer (AGC) that requires surgical treatment, the standard treatments for MGL are chemotherapy and radiotherapy. Hence, the initial impression of the endoscopist is critical for the differential diagnosis and for planning future treatment. The purpose of this study was to assess the endoscopic diagnostic accuracy and the possibility of distinguishing between AGC and MGL depending on the endoscopist's experience.

A total of 48 patients who had MGL, and 48 age and sex-matched patients who had AGC were assessed by endoscopic review at a tertiary referral hospital between June 2008 and February 2017. Two endoscopic specialists reviewed the endoscopic findings and divided these diagnoses into 5 groups: Borrmann type (1, 2, 3, and 4) and early gastric cancer-like type. After this, 7 experts and 8 trainees were asked to complete a quiz that was comprised of 6 images for each of the 96 cases and to provide an endoscopic diagnosis for each case. The test results were analyzed to assess the diagnostic accuracy according to the pathologic results, endoscopic subgroups, and endoscopists' experience. For inter-observer agreement was calculated with Fleiss kappa values.

The overall diagnostic accuracy of endoscopic findings by the experts was 0.604 and that by the trainees was 0.493 ($P = .050$). There was no significant difference in the diagnosis according to the final pathology (lymphoma cases, 0.518 vs 0.440, $P = .378$; AGC cases, 0.690 vs 0.547, $P = .089$, respectively). In the subgroup analysis, the experts showed significantly higher diagnostic accuracy for the endoscopic Borrmann type 4 subgroup, including lymphoma or AGC cases, than the trainees ($P = .001$). Inter-observer agreement of final diagnosis (Fleiss kappa, 0.174) and endoscopic classification groups (Fleiss kappa, 0.123–0.271) was slightly and fair agreement.

The experts tended to have a higher endoscopic diagnostic accuracy. Distinguishing MGL from AGC based on endoscopic findings is difficult, especially for the beginners. Even if the endoscopic impression is AGC, it is important to consider MGL in the differential diagnosis.

Abbreviations: AGC = advanced gastric cancer, B1 = Borrmann type 1, B2 = Borrmann type 2, B3 = Borrmann type 3, B4 = Borrmann type 4, DLBCL = diffuse large B-cell lymphoma, EGC = early gastric cancer, GIST = gastrointestinal stromal tumor, MGL = malignant gastric lymphoma.

Keywords: advanced gastric cancer, differential diagnosis, malignant gastric lymphoma

1. Introduction

The gastrointestinal tract is the most frequent site of extra-nodal involvement in lymphoma. Gastrointestinal lymphoma occurs most commonly in the stomach, followed by the small intestine and ileocecal region. Malignant gastric lymphoma (MGL) is an uncommon tumor accounting for less than 5% of all gastric malignancies.[1] Moreover, due to the ambiguity and diversity of endoscopic findings, MGL cannot be easily distinguished from advanced gastric cancer (AGC).

AGC is generally classified according to the Borrmann system of 1926, based on the endoscopic and pathologic findings.[2] However, there is no endoscopic classification for MGL. The diagnosis and treatment of AGC and MGL is also different. The preferred treatment for AGC is surgical resection, while the standard treatment for MGL is systemic chemotherapy. Therefore, the differential diagnosis between AGC and MGL is important. In clinical practice, the first step in differential diagnosis is endoscopic examination. Hence, assessment of the malignancy by skilled endoscopists is important. In this study, we aimed to assess the endoscopic diagnostic accuracy and the possibility of distinguishing between AGC and MGL, according to the endoscopists' level of experience.

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KJ and IHC have contributed equally to this study as first authors.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Materials and methods

2.1. Patients

Between June 2008 and February 2017, 48 patients diagnosed with MGL were reviewed by endoscopy experts (PMI and KSE), and the diagnosis was reclassified based on the Borrmann type. However, if the lesion did not meet the criteria of any of the 4 Borrmann types, 2 experts discussed the case and considered the possible diagnosis as early gastric cancer (EGC)-like AGC type. Based on MGL patients, there were 5 cases of Borrmann type 1, 3 cases of type 2, 24 cases of type 3, 12 cases of type 4, and 4 cases of EGC like AGC type. EGC-like AGC was defined as advanced gastric cancer with early gastric cancer-like gross appearance on endoscopy, according to the Japanese classification of gastric carcinoma and EGC criteria (type 0).[3,4] In addition to the detailed types of EGC such as superficial, elevated, or depressed lesions, the mixed types such as elevated lesions with depressed areas (IIa + IIc) were also included in the classification. Finally, the 5 types were reclassified as 4 Borrmann types and the EGC-like type. As the patients with gastric cancer had the same type of lesions as those with MGL according to the same experts, the 2 patient groups were matched for age and sex for inclusion in the study (Fig. 1).

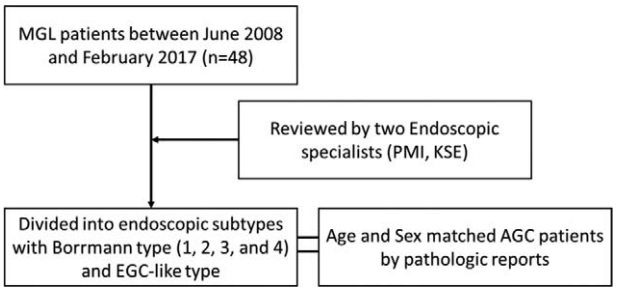

Figure 1. Flow chart of patients (MGL: malignant gastric lymphoma, AGC: advanced gastric cancer).

2.2. Endoscopic classification

First, a literature review was conducted to reclassify the endoscopic terms previously used to describe the gastric lymphomas.[2,5–8] The commonly reported abnormalities in the literature used the terms polypoid, nodular, fungating, mass-forming, ulcero-infiltrative, volcano craters, thickened folds, diffuse infiltrating, erosions, and superficial spreading. Later, based on the endoscopist's review, each term was reclassified as shown in Figure 2. Polypoid and nodular types were classified as Borrmann type 1, fungating and mass-forming as type 2, ulcero-infiltrative and volcano craters as type 3, thickened fold and diffuse infiltrating as type 4, and erosion and superficial spreading as EGC-like type (Fig. 2).

2.3. Test for classification by experts and trainees

Six endoscopic images of each of the 96 patients were used by the previously mentioned experts to create a test questionnaire. These 6 images were selected from various angles best representing the lesion, as shown in Figure 2. These images include forward view, J turn view for body or fundus lesion, close-up view, and the distance view with a glance at the entire lesion.

An expert group comprising 7 physicians with more than 3 years of endoscopic experience, and a trainee group comprising 8 endoscopists with less than 1 year of experience were asked to answer the same test questions. Physicians in the expert group

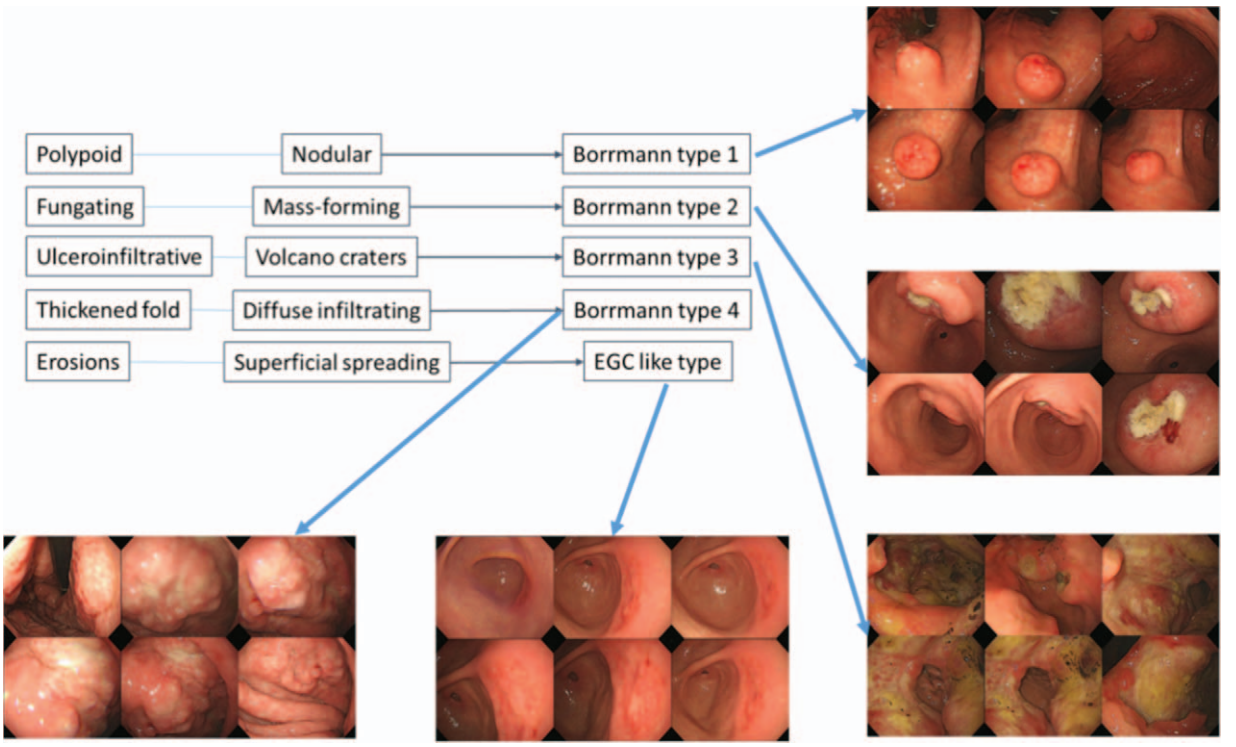

Figure 2. Classification and examples of endoscopic morphologic findings according to the Borrmann type and EGC-like type. (EGC = early gastric cancer).

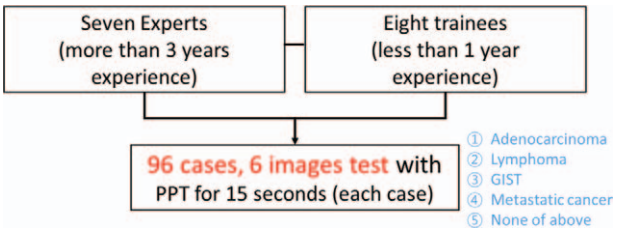

Figure 3. Test methods according to the experience of endoscopy.

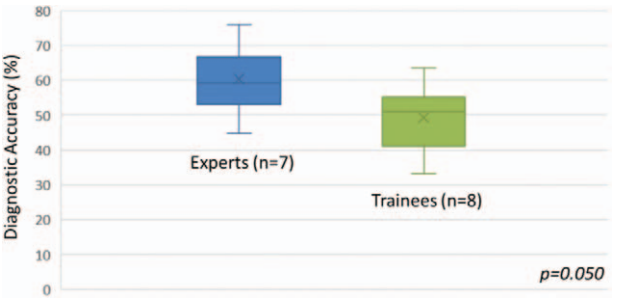

Figure 4. Overall diagnostic accuracy of endoscopic findings.

usually performed 3000 endoscopies annually and endoscopic screening of more than 10,000 cases. The trainee group members were first-year clinical fellows with an experience of less than 1000 endoscopic screening procedures. During the quiz, 6 images were displayed on a PowerPoint slide for 15 seconds, and the respondents were asked to choose the most likely endoscopic diagnosis. The answers included lymphoma, gastric adenocarcinoma, gastrointestinal stromal tumor (GIST), and metastatic gastric cancer, usually identified through endoscopic differentiation. If none of the 4 answers were found to be applicable, the respondents could choose to answer it as "none of the above" (Fig. 3). This study was approved by our Institutional Review Board (KUGH 2019-11-005), and written informed consent was obtained from all the endoscopists.

2.4. Statistical analysis

Statistical analysis was performed by comparing the rate of correct diagnosis of all cases by the expert and trainee groups. Subsequently, we compared the diagnosis rate by the Borrmann type classification. Categorical variables were assessed using the χ^2 test or the Fisher exact test. Inter-observer agreement was evaluated using Fleiss kappa coefficient.[9] A P value of $<.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY).

3. Results

3.1. Overall diagnostic accuracy

The overall diagnostic accuracy was 60.4% in the expert group and 49.3% in the trainee group. However, the difference between the groups was not statistically significant ($P=.050$, Fig. 4).

3.2. Accuracy of diagnosis according to final diagnosis

The diagnostic accuracy for malignant lymphoma was 51.8% ± 18.49 in the expert group and 44.0% ± 13.42 in the trainee group. Among cases of AGC, 69.0% ± 16.15 and 54.7% ± 13.49 were correctly identified by the expert and trainee groups, respectively. Although the expert group had a higher accuracy in diagnosing both, MGL and AGC cases, there was no significant difference between the groups in terms of accuracy according to the final pathologic diagnosis (MGL, 0.518 vs 0.440, $P=.378$; AGC, 0.690 vs 0.547, $P=.089$, respectively, Fig. 5). However, when comparing the overall accuracy of diagnosis by disease type, the accuracy was 61.4% ± 16.06 for AGC and 47.6% ± 15.90 for malignant lymphoma, indicating a high accuracy in diagnosing AGC.

3.3. Diagnostic accuracy according to endoscopic classification

When MGL and AGC were classified endoscopically into Borrmann types 1, 2, 3, and 4, and EGC type, the diagnostic accuracy was not different each MGL and AGC group by classification type. However, the subgroup analysis showed that the expert group had a significantly higher diagnostic accuracy for endoscopic Borrmann type 4, including MGL, or AGC cases, than that among the trainees (0.696 vs 0.474, $P=.001$, Fig. 6).

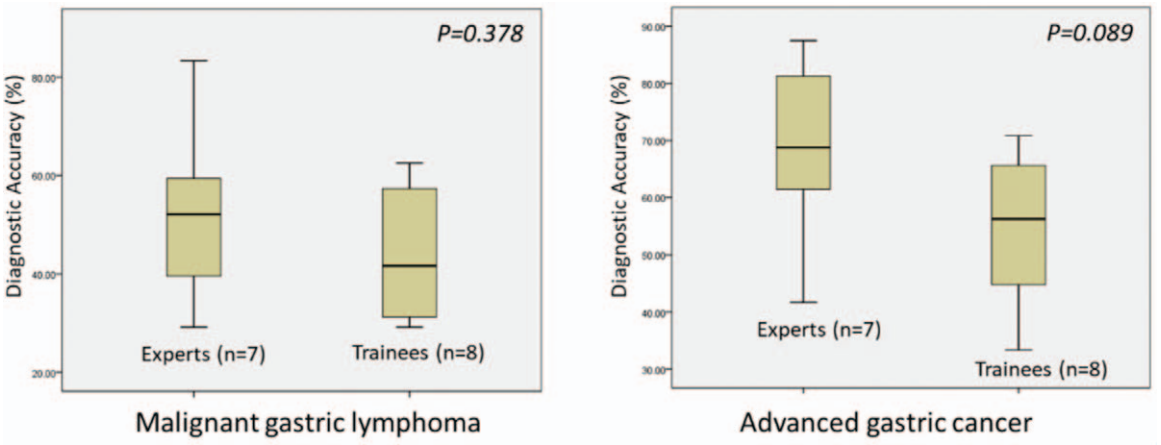

Figure 5. Accuracy of diagnosis according to malignant gastric lymphoma or advanced gastric cancer.

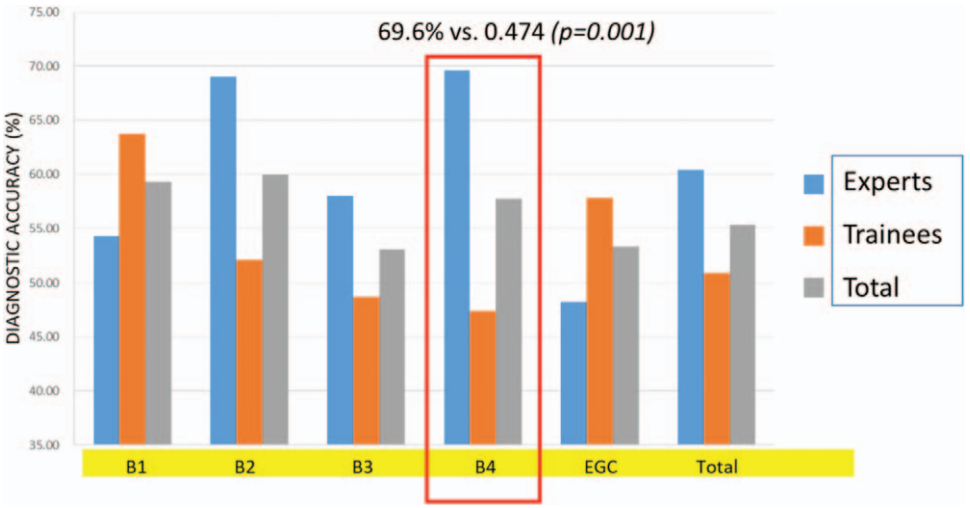

Figure 6. Diagnostic accuracy according to endoscopic classification (B1: Borrmann type 1, B2: Borrmann type 2, B3: Borrmann type 3, B4: Borrmann type 4, EGC: early gastric cancer).

3.4. Inter-observer agreement of final diagnosis and endoscopic classification groups

Inter-observer agreement of final diagnosis and endoscopic classification groups was shown in the Table 1. Overall, only slight to fair inter-rater agreement was found by all endoscopists with Fleiss kappa of 0.082 to 0.271. In addition, the kappa value in the expert group (Fleiss kappa, 0.134–0.387) was higher than that of the trainee group (Fleiss kappa, 0.098–0.261) in all cases, final diagnosis, and endoscopic classification groups, except for the EGC like type lesion.

3.5. Cases with a low diagnostic rate

The overall accuracy of the diagnosis of Borrmann type 3 was low (Fig. 7). In some cases of this type, the diagnostic accuracy was less than 20%; Cases in this type had Borrmann type 3-like diffuse large B-cell lymphoma (DLBCL) and AGC in the antrum and body of the stomach.

Of the 2 DLBCL, 1 had ulcerative lesions with irregular borders in the antrum, which is often seen in advanced gastric cancer. The second case showed a subepithelial tumor-like mass shape, resulting in a low rate of diagnosis because most endoscopists saw GISTs rather than lymphomas.

Of the 2 cases diagnosed as AGC, the first showed an ulcero-infiltrative lesion in the antrum with an uneven, reflexed, glass-like ulcer base. Owing to these characteristics, many endoscopists considered diseases occurring mainly in the submucosa as lymphoma rather than adenocarcinoma. The second case also had an ulcero-infiltrative lesion with an inwardly curled border, resulting in a low rate of diagnosis, with many endoscopists misdiagnosing it as lymphoma.

4. Discussion

This study was designed to understand whether endoscopic examination findings could distinguish between MGL and AGC. In general, gastric lymphomas are diverse and difficult to diagnose on endoscopy. However, there are no studies about the degree of difficulty in diagnosis and objectively distinguishing these cases from gastric cancer. Therefore, this study aimed to quantify the degree of difficulty in distinguishing between AGC and MGL. The rate of endoscopic diagnosis for AGC was higher

Table 1

Inter-observer agreement on final diagnosis and endoscopic classification.

	Fleiss kappa statistic (95% CI)		
Category	**All endoscopists (n = 15)**	**Experts (n = 7)**	**Trainees (n = 8)**
According to final diagnosis			
All cases (=96)	0.174 (0.173–0.174)	0.262 (0.261–0.263)	0.166 (0.165–0.166)
MGL cases (n = 48)	0.134 (0.133–0.134)	0.185 (0.184–0.186)	0.157 (0.156–0.158)
AGC cases (n = 48)	0.082 (0.082–0.083)	0.134 (0.132–0.136)	0.098 (0.097–0.099)
According to endoscopic classification			
Borrmann type 1 (n = 10)	0.271 (0.269–0.272)	0.387 (0.384–0.389)	0.242 (0.240–0.244)
Borrmann type 2 (n = 6)	0.261 (0.259–0.263)	0.384 (0.380–0.388)	0.160 (0.157–0.163)
Borrmann type 3 (n = 48)	0.123 (0.122–0.124)	0.206 (0.205–0.208)	0.122 (0.121–0.123)
Borrmann type 4 (n = 24)	0.139 (0.139–0.140)	0.242 (0.240–0.245)	0.136 (0.135–0.138)
EGC like type (n = 8)	0.228 (0.227–0.229)	0.200 (0.198–0.203)	0.261 (0.258–0.263)

Kappa less than 0 indicated poor agreement, 0.01 to 0.20 indicated slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1.00 near perfect agreement.

AGC = advanced gastric cancer, CI = confidence interval, EGC = early gastric cancer, MGL = malignant gastric lymphoma.

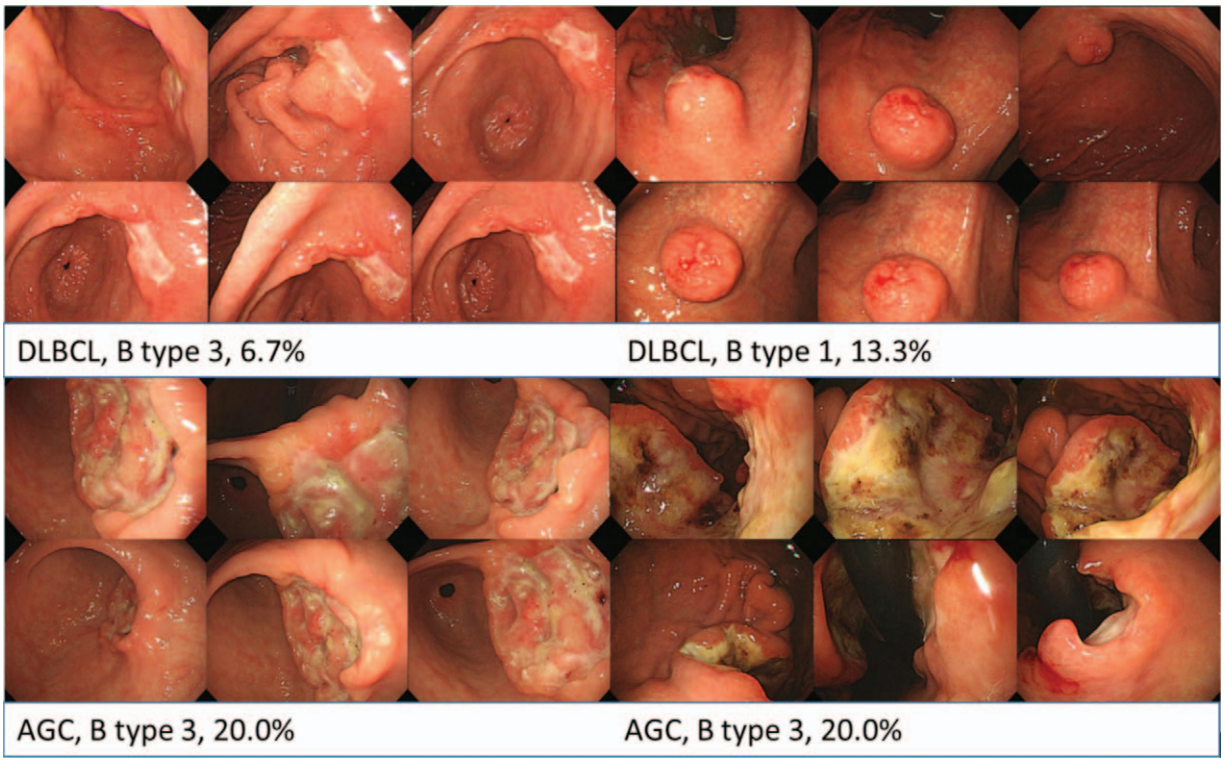

Figure 7. Endoscopic findings of 4 cases with a lower accuracy rate (≤20%) in both groups. (DLBCL: diffuse large B-cell lymphoma, B type: Borrmann type, AGC: advanced gastric cancer).

than that for MGL. This difference is because the prevalence of AGC is much higher than that of MGL, especially in Asia.[1] In addition, there are typical technical methods for classification of AGC into the Borrmann types, which makes it easier to diagnose.[2]

Previous studies suggested many endoscopic or gross pathological classification of malignant lymphomas. In the study by Isomoto et al, endoscopic findings of gastric lymphoma were divided into superficial spreading type, mass forming type, and diffuse infiltrating type. In particular, this study attempted to identify other features of gastric cancer through magnified and narrow band images and determined mucosal aggregation of interstitial cellular elements to be a feature observed in lymphoma.[10] However, this method of classification requires complete observation of the stomach for 3 minutes, which is difficult to implement in screening endoscopy. In one study, observation longer than 3 minutes, but less than 4 minutes, had a higher diagnostic rate for gastric neoplasia.[11] A longer observation time with magnified endoscopy can increase the accuracy of diagnosis or discovery of lesions; however, in clinical situations the entire stomach needs to be examined in a relatively limited time, and the first impression of an endoscopist is crucial in making a diagnosis and for performing biopsy.

In another study by Zeggai et al, the macroscopic features of malignancies were classified into lesions such as ulcers, infiltrates, and polypoids. Of these, the ulcer type was the most common.[12] According to a study conducted by Cui et al, endoscopic findings were divided into 2 groups—suspected and unsuspected gastric lymphomas—mainly in ulcerative, polypoid, granulo-nodular, and infiltrative forms. Among these groups, the ulcerative forms were identified and subdivided into single, multiple, and diffuse ulcerative forms. The infiltrative form was the most common type that was endoscopically misdiagnosed as gastric lymphoma, and turned out to be inflammation or carcinoma (52.6%).[5]

In this study, we determined the differential diagnosis of AGC to be most important for clinical diagnosis. Therefore, we matched the most common Borrmann type terms: fungating, ulceration, infiltration, mass forming, and erosive, with our Borrmann type classification of AGC. We also matched similar morphology for gastric lymphoma as described in the literature. Based on these criteria, we reviewed the endoscopic findings of cases and reclassified them by Borrmann type. Subsequently, using a simple 15-second test, we examined the difference in diagnostic accuracy according to the endoscopists' experience. Diagnostic accuracy tended to depend on the experience of the endoscopist. However, when MGL was divided by the Borrmann type, which is a classification of AGC, the difference in diagnostic accuracy was not different between the groups, according to the endoscopic classification. In a previous study, the infiltrative type was significantly higher in the group diagnosed with non-lymphoma. Similarly, this study also showed the largest difference of 69.6% and 47.7% for Borrmann type 4, based on the finding of an infiltrative lesion. This is probably because Borrmann type 4 cases differ from other gastric cancers in pathophysiological mechanism and rate of progression.[13]

The diagnostic accuracy of the expert group was measured higher than that of the trainee group, but the inter-observer agreement was not high in both groups. These findings show that although the disease can be more accurately diagnosed according to the experience of an endoscopists, it is still difficult to distinguish between MGL and AGC, and biopsy is important for final diagnosis. However, it is necessary to continuously try

endoscopic differential diagnosis because the endoscopic doctor's impression is helpful in the process of biopsy, additional staining, and diagnosis by the pathologist.

This study has several limitations. First, 2 expert endoscopists distinguished the endoscopic classification of MGL matching AGC, and selection bias might have occurred. Second, only cases with endoscopic findings of AGC and MGL were evaluated, which could have limitations because of the exclusion of EGC and low-grade lymphoma, such as mucosa-associated lymphoid tissue lymphoma. Third, when evaluating the test, if the options included only AGC and MGL, there was a possibility of choosing 1 without a clear impression. Therefore, we included additional options (GIST, metastatic cancer, and none of the above). While this might have made the test objective, these limitations could also lead to confusion. Nevertheless, the purpose of this study was to objectively determine the effectiveness of diagnosing MGL and AGC by endoscopic examination, based on the experience of the endoscopist. Differences in individual endoscopic skills and knowledge among the participating endoscopists confirmed the importance of the endoscopist's experience.

In conclusion, although experts had a higher rate of endoscopic diagnostic accuracy, differentiating between MGL and AGC based on endoscopic findings was difficult, especially for beginners. MGL should always be considered in the differential diagnoses, even if the malignancy is determined as AGC (especially Borrmann type 4) on endoscopy. In addition, even among a group of experts, the diagnostic accuracy was about 60%. Thus, actively considering MGL in the differential diagnosis could be helpful in improving the clinical diagnostic accuracy.

Author contributions

Conceptualization: Kyoungwon Jung, Moo In Park.
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Supervision: Moo In Park.
Writing – original draft: Kyoungwon Jung, Il Hyeong Choe.
Writing – review & editing: Moo In Park, Seun Ja Park, Won Moon, Sung Eun Kim, Jae Hyun Kim, Kwang Il Seo.

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