

Understanding the diagnostic yield of current endoscopic biopsy for gastric neoplasm

A prospective single-center analysis based on tumor characteristics stratified by biopsy number and site

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Abstract

Although there are general guidelines on endoscopic biopsy for diagnosing gastric neoplasms, they are predominantly based on outdated literature obtained with fiberscopes without analyses specific to tumor characteristics.

This study aims to comprehensively characterize the contemporary endoscopic biopsy by determining the diagnostic yield across different lesion morphologies and histological stages, especially exploring how the number and site of biopsy may influence the overall yield.

Biopsy samples from suspected gastric neoplasms were collected prospectively from May 2011 to August 2014 in a tertiary care medical center. A standardized methodology was used to obtain a total of 6 specimens from 2 defined sites per lesion. Rate of positive diagnosis based on the biopsy number and site was assessed for specific gastric lesion morphologies and histological stages.

A total of 1080 biopsies from 180 pathologically diagnosed neoplastic lesions in 176 patients were obtained during the study. For depressed/ulcerative and polypoid lesions, the yield was already >99% by the fourth biopsy without further gain from additional biopsies. Lower overall yield was observed for infiltrative lesions (57.1% from 4 biopsies). The site of biopsy did not influence the diagnostic yield except for with infiltrative lesions in which biopsies from thickened mucosal folds were of higher yield than erosive regions.

Obtaining 4 specimens may be sufficient for accurate diagnosis of a depressed/ulcerative or polypoid gastric lesion regardless of its histological stage. For infiltrative lesions, at least 5 to 6 biopsies per lesion with more representative sampling from thickened mucosal folds may be preferable.

Abbreviations: AGC = advanced gastric cancer, EGC = early gastric cancer.

Keywords: biopsy, diagnostic yield, endoscopy, gastric neoplasm, sensitivity

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1. Introduction

Gastric cancer remains a major health issue as the fifth most common malignancy and the third cause of cancer-related mortality worldwide.^[1] The timeliness and accuracy of diagnosing gastric cancer is particularly crucial as the 5-year survival rate of early gastric cancer (EGC) exceeds 90%, whereas the 5-year survival rate of advanced gastric cancer (AGC) is approximately 30%.^[2] Video endoscopy and endoscopic biopsy are currently the investigative tools of choice for diagnosis of gastric cancer.^[3,4] There have been studies in the past on the diagnostic yield of endoscopic biopsies of gastric cancers along with suggestions on the optimal number and site of biopsies, but the overall characterization of the conventional endoscopic biopsy as a tool for diagnosing gastric cancer is general by in large and based on outdated studies that have predominantly used fiberscopes.^[3–7] In fact, video endoscopes that are currently being used in most endoscopy units have higher resolution and wider visual fields than fiberscopes, allowing sampling to be more precise than before. Tremendous improvements in the relevant fields, for example, biopsy forceps and histological methods, have facilitated obtaining an adequate amount of tissue at a desired site and remarkable progress in the pathological diagnosis of neoplastic diseases. Thus, the sensitivity, that is, the capability of a test to correctly rule out nonmalignancy, of endoscopic biopsy for diagnosing gastric neoplasms in the current clinical setting remains unknown. As with any clinical intervention,

understanding the characteristics of the contemporary endoscopic biopsy such as the necessary number or favored site of biopsy for any given lesion would empower the clinician to optimize its application, thereby avoiding unnecessary use, reducing health-care costs, and minimizing complications. Therefore, in this study, we sought to thoroughly characterize the diagnostic yield of current conventional endoscopy by specifically obtaining the rate of correct sampling for the different endoscopic morphologies (depressed/ulcerative, polypoid, and infiltrative) as well as their histological stage (dysplasia, EGC, and AGC), and then stratifying the analysis by the number and site of the biopsies.

2. Materials and methods

2.1. Study population and endoscopic procedure

From May 2011 to August 2014, biopsy samples from endoscopically suspected neoplastic gastric lesions during endoscopy at the Dongguk University Ilsan Hospital were collected prospectively. After a fast for at least 8 hours, upper endoscopy was performed in the digestive tract endoscopic operation room at Dongguk University Ilsan Hospital. The procedure was performed by 6 gastroenterologists with gastroenterology and endoscopy specialty board certification and >5 years of endoscopy experience. Specimens were obtained with forward-viewing standard gastroscopes (GIF-H260, Olympus Medical Systems, Tokyo, Japan) and video endoscopy systems (EVIS LUCERA CLV 260, Olympus Medical System). Six specimens were taken serially from a lesion using standard biopsy forceps (FB-25K-1, Olympus Medical System, Tokyo, Japan). The endoscopic findings were described by updated Paris classification or Borrmann type according to morphological features.^[8,9] The overall endoscopic morphology of a lesion was also classified into 3 major types: depressed/ulcerative, polypoid, or infiltrative. To minimize inadvertent sampling bias, biopsy methodology was adapted from current guidelines and was standardized across all endoscopists for each lesion morphology.^[10] For a depressed/ulcerative lesion, specimens #1 to 4 were obtained from the inner rim of the lesion, and #5 to 6 were from the slough/base. Whenever a mucosal island was observed, the fifth specimen was taken from the island. For a polypoid lesion, specimens #1 to 4 were gathered from the protruding surface, and #5 to 6 were from the inner margin adjacent to normal mucosa. For an infiltrative lesion, the specimens #1 to 3 were obtained from erosions or focal ulcerations of the lesion, and #4 to 6 were taken from thickened folds. The endoscopic findings, that is, location, size, macroscopic classification, and shape, were described immediately after the examination by endoscopists.

2.2. Pathologic diagnosis

Each sample was immediately fixed in 10% formalin solution in separate vials. A code number was assigned to each vial to identify the serial order, which was blinded to the pathologist. Hematoxylin and eosin-stained tissue sections of the biopsy tissues were microscopically examined by 3 gastrointestinal pathologists. Pathologic results were reported as positive when a lesion turned out to have one of the following neoplastic findings: adenocarcinoma, high-grade dysplasia, and low-grade dysplasia.^[11] This study was conducted in accordance with the Helsinki Declaration and approved by the Institutional Review Board of Dongguk University Ilsan Hospital (No. 2011-16). Informed consent was waived by the Board and patients' anonymity was preserved.

2.3. Statistical analysis

The categorical variables were compared using the χ^2 test with Yates correction or Fisher exact test, as applicable. Mean values were expressed as means \pm standard errors (SE). Cumulative diagnostic sensitivity was calculated as true positives divided by sum of true positives and false negatives among pathologically positive lesions. The nonparametric Cochran and McNemar tests were used to analyze the cumulative diagnostic yields according to the sampling order. Differences were considered statistically significant when *P* values were <0.05. Data were analyzed using SPSS 20.0 for Windows (SPSS Inc, Chicago, IL).

3. Results

3.1. General patient demographics and number of cases used for analysis

There were a total of 325 patients suspected for gastric neoplasms during the study period. The mean patient age was 68.0 ± 1.0 years, and the male-to-female ratio was 108:68 (Table 1). There were a total of 334 suspected lesions from this cohort that were biopsied, and 154 of them were pathologically diagnosed as benign. Because our aim was to identify the rate of correct sampling, that is, the rate of positive diagnosis from truly neoplastic lesions, pathologically benign lesions were excluded

Table 1
Patient demographics and tumor characteristics in the cohort.

Variable	Patients (N = 176) Lesions (N = 180)
Mean age, y	68.0 \pm 1.0
Male:female	108:68
Size, mm	28.6 \pm 1.0
Classification by shape, no. (%)	
Depressed or ulcerative	145 (80.6)
Polypoid	21 (11.7)
Infiltrative	14 (7.8)
Classification by depth, no. (%)	
Advanced gastric cancer*	
Type I	4 (2.2)
Type II	16 (8.9)
Type III	57 (31.7)
Type IV	14 (7.8)
Early gastric cancer [†]	
Type I	1 (0.6)
Type IIa	7 (3.9)
Type IIb	13 (7.2)
Type IIc	40 (22.2)
Type III	1 (0.6)
Dysplasia	27 (15.0)
Histopathological characteristics	
Adenocarcinoma, tubular [‡]	114 (63.3)
Well differentiated	32 (17.8)
Moderately differentiated	49 (27.2)
Poorly differentiated	33 (18.3)
Adenocarcinoma, mucinous [‡]	2 (1.1)
Signet ring cell carcinoma [‡]	25 (13.9)
High-grade dysplasia	13 (7.2)
Low-grade dysplasia	25 (13.9)

* Borrmann Classification.

[†] Updated Paris classification.

[‡] Histopathology was classified in accordance with WHO classification (4th edition). Data represent means \pm standard error mean or N (%).

from the analysis. Thus, final analysis for diagnostic yield was performed with 180 lesions (1080 biopsies) from 176 patients.

3.2. Gross morphologic and histopathologic characteristics of gastric neoplasms in the cohort

The mean size of the lesions was 28.6 ± 1.0 mm (range 3–50) and the most common site location was the anterior wall of the antrum (Figure S1, <http://links.lww.com/MD/B144>). When classified by the overall shape, depressed/ulcerative type (n = 145, 80.6%) was the most common, followed by polypoid (n = 21, 11.7%) and infiltrative types (n = 14, 7.8%). By depth, Borrmann type III (n = 57, 31.7%) among AGC and type IIc (n = 40, 22.2%) among EGC were the most common, respectively. Histopathologic examinations revealed that tubular adenocarcinoma was the most frequent (n = 114, 63.3%), followed by signet ring cell carcinoma (n = 25, 13.9%), low-grade dysplasia (n = 25, 13.9%), and high-grade dysplasia (n = 13, 7.2%) (Table 1).

3.3. Diagnostic yield of current conventional endoscopic biopsy stratified by endoscopic morphology and histological tumor stage

Out of 1080 specimens obtained from 180 truly neoplastic lesions, positive results were obtained in 800 specimens (74.1%). When stratified by endoscopic appearance, the overall positive rates per biopsy sample were 74.5% (649/870), 86.5% (109/126), and 51.2% (43/84) for the depressed/ulcerative, polypoid, and infiltrative types, respectively (Table 2). The infiltrative type had the lowest positive rate per biopsy of all types (P < 0.01). When stratified by histological tumor stage only, the overall positive rates per biopsy sample were 74.3% (406/546), 69.6% (259/372), and 83.3% (135/162) for AGC, EGC, and dysplastic lesions, respectively (P < 0.01; Table 2).

Importantly, because not all samples can be obtained from the same region of a lesion, we then performed subgroup analyses to determine whether the biopsy site was a significant factor in the overall diagnostic yield for each morphological type and histological stage as shown in Table 3. Among the 870 biopsies obtained from 145 depressed/ulcerative lesions, the diagnostic yield of sampling from the inner rim was 74.7% (433/580), nearly equal to that from the base, 74.5% (140/192), with no significant difference overall and at any of the histological stages. Similarly, the diagnostic yields did not significantly differ between the 2 different biopsy sites, area of protrusion (72/84, 85.7%),

Table 3
Positive rate of biopsies with regards to the biopsy site classified by endoscopic morphology and histological stage.

Endoscopic morphology classified by histological stage	Biopsy site 1	Biopsy site 2	P-value
Depressed/ulcerative	Inner rim	Slough	
Total (N=870)	433/580 (74.7%)	216/290 (74.5%)	0.96
AGC (N=426)	221/284 (77.8%)	112/142 (78.9%)	0.80
EGC (N=354)	165/236 (69.9%)	79/119 (66.9%)	0.57
Dysplasia (N=90)	47/60 (78.3%)	25/30 (83.3%)	0.58
Polypoid	Protrusion	Adjacent margin	
Total (N=126)	72/84 (85.7%)	37/42 (88.1%)	0.71
AGC (N=36)	20/24 (83.3%)	11/12 (91.7%)	0.49
EGC (N=18)	11/12 (91.7%)	4/6 (66.7%)	0.18
Dysplasia (N=72)	41/48 (85.42%)	22/24 (91.7%)	0.45
Infiltrative	Erosions	Thickened folds	
Total/AGC (N=84)*	13/42 (31.0%)	28/42 (66.7%)	0.001

AGC=advanced gastric carcinoma, EGC=early gastric carcinoma.
* All infiltrative cases are AGC.

and adjacent margins (37/42, 88.1%). In contrast, among 84 biopsies obtained from infiltrative gastric cancers, biopsies from thickened folds (28/42, 66.7%) were of significantly higher yield than those from erosions (13/42, 31%; P = 0.001).

To further characterize the diagnostic yield of current conventional endoscopic biopsy, we then assessed the cumulative sensitivity based on the number of serial biopsies. Figure 1 shows the cumulative diagnostic yield according to the order with which specimens were taken. Overall, cumulative sensitivity reached >95% with a fourth biopsy and was increased further to 100% with a fifth biopsy. When stratified by gross morphology, the cumulative diagnostic sensitivity for the depressed/ulcer type from specimens #1 to 4 was 144/145 (99.3%) and that from specimens #1 to 5 reached 145/145 (100%). Thus, for depressed/ulcerative gastric cancer lesions, adding a fourth biopsy significantly increased the rate of correct diagnosis (132/145 vs. 144/145, P < 0.01), but adding a fifth biopsy did not. For the polypoid type, the overall yield reached 100% (21/21) with 3 biopsies. For the infiltrative type, no significant increases in the cumulative sensitivity could be detected serially up to the fourth specimen (4/14 vs. 8/14, P = 0.13), but adding a fifth biopsy specimen significantly enhanced the yield (8/14 vs. 14/14, P = 0.03).

Next, we also explored whether the cumulative diagnostic sensitivity is impacted by histological tumor stage. Figure 2 shows the diagnostic yields for AGC, EGC, and dysplasia per serial biopsy. The total numbers of lesions classified into AGC, EGC, and dysplasia were 91, 62, and 27, respectively. For AGC, the yield was approximately 90% with 4 biopsies with significant increase with the addition of a fifth biopsy (P = 0.03). For EGC, the cumulative diagnostic yield increased significantly up to the fourth specimen (P < 0.01) and reached 100% (62/62). For dysplasia, the yield from having 3 specimens reached 100% (27/27).

3.4. Patient follow-up and final confirmation of cases

One hundred and thirty-six (77.3%) patients received subsequent treatment—71 patients underwent endoscopic treatment and 65 patients underwent surgical treatment—and all of these cases contained neoplastic tissues in the final specimen. Reconfirmation was not possible in the other 40 patients who did not undergo treatment because of high risk or were transferred to another hospital.

Table 2
Overall rate of positive biopsy stratified by endoscopic morphology and histological tumor stage.

Variable	No. of biopsies	No. of positive results (%)	P
Overall	1080	800	NA
Endoscopic morphology			<0.001
Depressed or ulcerative	870	649 (74.5%)	
Polypoid	126	109 (86.5%)	
Infiltrative	84	43 (51.2%)	
Histological tumor stage			0.004
AGC	546	406 (74.3%)	
EGC	372	259 (69.6%)	
Dysplasia	162	135 (83.3%)	

AGC=advanced gastric cancer, EGC=early gastric cancer.

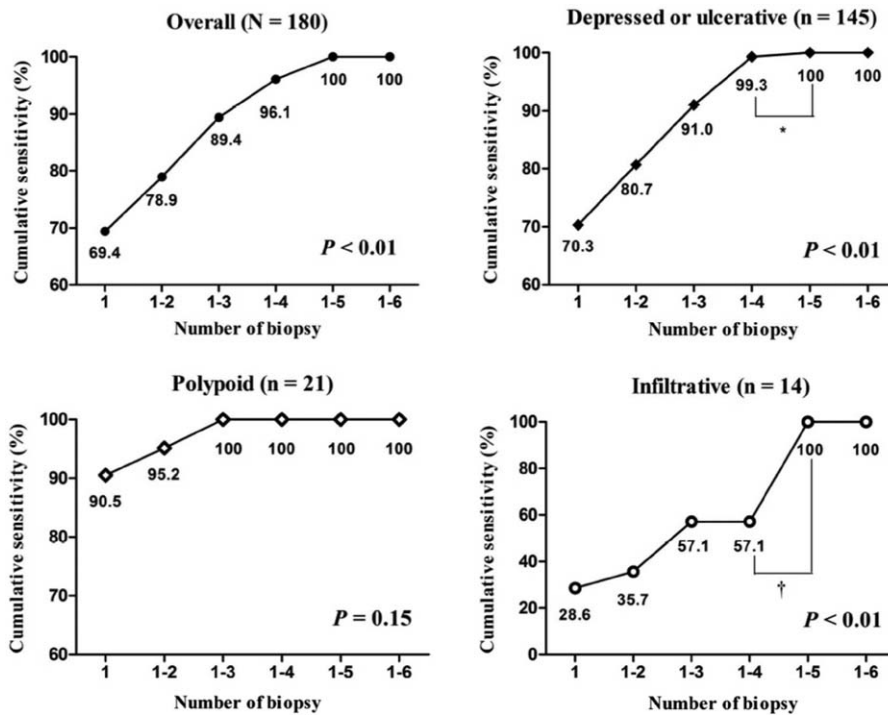


Figure 1. Cumulative diagnostic yield according to the order of serial endoscopic biopsy classified by the endoscopic morphology of a lesion. **P* > 0.10; †*P* = 0.03.

4. Discussion

Detailed characterization of any diagnostic test is crucial to its optimal application. Many studies have explored the properties of scope-guided biopsy of gastric cancers in the past, but most of

the findings are from >2 decades ago and would seemingly have been outdated because of the remarkable improvements seen in endoscopic, optical, and histological technology.^{15,12,13} Although another group has looked at the diagnostic yield of

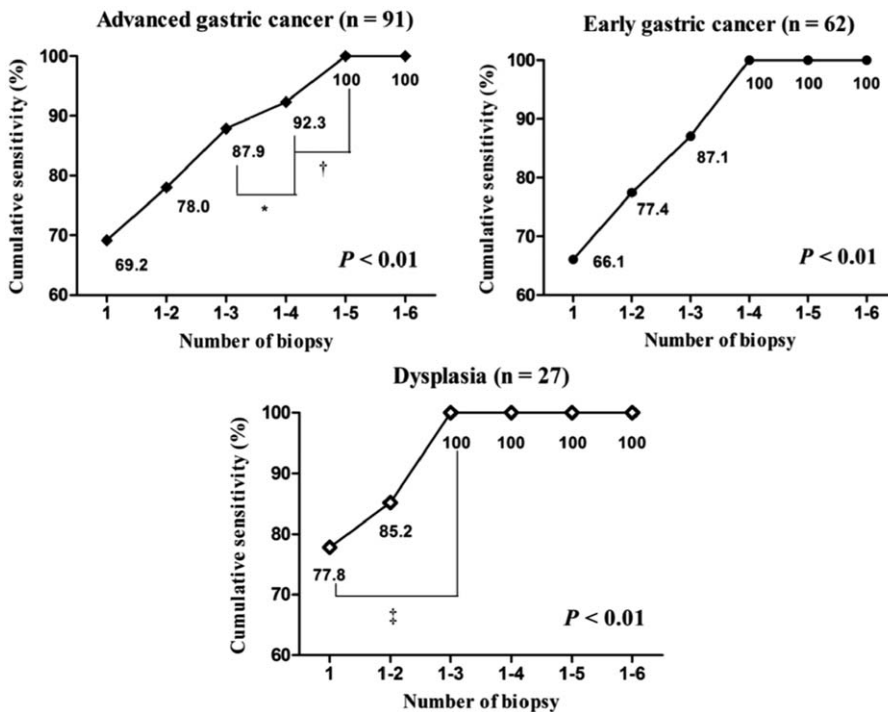


Figure 2. Cumulative diagnostic yield according to the order of serial endoscopic biopsy classified by the histological stage of a lesion. **P* = 0.13; †*P* = 0.03; ‡*P* = 0.03.

endoscopic biopsy of AGCs using contemporary tools,^[14] we are the first to present a comprehensive approach by looking at the diagnostic yield across major types of endoscopic morphology and histological stages tumor, while stratifying the analysis by the biopsy site as well as examining the cumulative yields according to number of serial biopsies.

In our analysis of the number of biopsies associated with correct diagnosis, we have found that the overall rate of correct neoplastic diagnosis increased above >95% by the fourth biopsy with further increase to 100% (no false-negative result among neoplastic lesions) by the fifth biopsy. Interestingly, when the rate was stratified by endoscopic morphology, the diagnostic yield for either polypoid or depressed/ulcerative type lesions did not significantly benefit from adding a fifth biopsy, whereas having at least 5 biopsies was critical for the correct diagnosis of infiltrative type lesions. Thus, our study uniquely has characterized that based on the current conventional endoscopic biopsy technique, the previous suggestions recommending at least 6 to 10 biopsies no longer applies broadly.^[15] Specifically, our findings suggest that in current conventional endoscopy, obtaining 4 biopsies per lesion is sufficient for >99% correct diagnostic yield for the depressed/ulcerative or polypoid type lesions, whereas at least 5 to 6 biopsies per lesion would be necessary to ensure optimal yield for infiltrative type lesions. This is because of the morphology of the infiltrative lesions and predominantly submucosal invasion of these tumors because of which distinguishing neoplastic regions from the normal mucosa becomes more difficult, also relatable to a previous report of higher frequency of nondiagnostic biopsy from infiltrative types.^[16–18] When stratified by histological tumor stage, data also suggested that 4 to 5 biopsies per lesion may be sufficient. Overall, dysplasia appeared to be more easily detected with significance in comparison to EGC or AGC, and with cumulative yield analysis, AGC appeared to have the highest false-negative rate. These findings are consistent to previous reports, in which earlier-stage lesions were detected more readily.^[4,5] Tatsuta et al^[4] elaborated that in AGCs, cancer tissues would be covered by normal mucosa in which case biopsy samples may be too superficial. Furthermore, in advanced ulcerative lesions, necrotic tissues appeared more prevalent (personal observations) and may affect the yield per sample. An additional factor to consider with interpretation of our data is that the AGC group contains all infiltrative type cases, for which the diagnostic challenge likely stems from the intrinsic tumor morphology and not necessarily the histological stage.

We also asked whether the biopsy site was an important factor for determining the diagnostic yield by looking at 2 different sites per endoscopic morphology. Interestingly, the biopsy site did not influence the overall yield for depressed/ulcerative or polypoid types, but for infiltrative type lesions, our data suggested that sampling thickened folds lead to fewer false-positive results than sampling erosive areas. With regards to depressed/ulcerative lesions, some studies have suggested that samples should be obtained from the rim of an ulcer avoiding the crater, which mainly has exudative materials and lacks tissue structures.^[19,20] In contrast, Hatfield et al noted that normal mucosa may be heaped up over the neoplastic tissue at the inner rim of depressed/ulcerative lesions.^[13] Regardless, marked improvements in endoscopic devices facilitating accessibility and exact targeting may have contributed to permitting the site of biopsy in these types of lesions to be less critical. However, accurate diagnosis of infiltrative type lesions remains elusive with conventional

endoscopic biopsy even with contemporary technology. In fact, to our knowledge, there have not been studies analyzing the optimal biopsy site for infiltrative gastric cancers in the context of current standard endoscopy. Although our observation is novel and data-driven, it is unclear as to why thickened folds were the sites of higher diagnostic yield than erosive areas in our cohort.

When assessing the optimal number of biopsies per lesion, diagnostic yields may certainly increase with higher numbers, but there are several disadvantages associated with excessive sampling. As the number of patients who take antiplatelet or anticoagulant agents for the prevention or treatment of cardiocerebrovascular diseases is ever increasing, acquiring an excessive number of biopsies might lead to higher risk of significant bleeding unnecessarily. Furthermore, oozing from the previous biopsy sites makes further sampling inappropriate because of obscured endoscopic field and repeated sampling within the same lesion to be of less diagnostic value. Not only does higher number of biopsies add to the overall procedural burden, for example, procedure duration and potential patient morbidity, it also leads to higher pathologist workload and medical costs. Acquiring as few as 4 samples per lesion is also in line with the observation made by Yalamurthi et al^[21] from their study of missed endoscopic diagnosis of gastric cancer in which 77% of missed diagnosis was associated with obtaining <4 biopsy samples per lesion. Thus, obtaining as few as 4 for polypoid or depressed/ulcerative types would potentially minimize the negative aspects related to the procedure.

There were a few limitations in this study. First, given the heterogeneity in the study population with respect to tumor characteristics, separate subgroup analyses had to be performed to identify significant associations. Second, confirmation of the positive cases from 176 patients by definitive pathology was not possible in some patients (40/176, 22.7%); our study aims at reducing false-negative diagnoses without data that look at false-positive diagnoses, but it should also be noted that false-positive rate is generally rare in gastric cancer cases.^[12,22] Lastly, specialized endoscopic techniques that reduce the adequate number of biopsies by more accurate targeting such as endoscopic ultrasound, jumbo forceps, and magnifying narrow band image were not used.^[23–25] Further studies incorporating these methods would be valuable.

Taken together, this study employed a prospective, comprehensive methodology to provide an updated characterization of the current conventional endoscopy in the context of diagnosing gastric cancers. It confirmed previous reports showing relatively higher false-negative rates with infiltrative type lesions among types of endoscopic morphology and AGCs among histological tumor stages. Importantly, unprecedented comparisons using serial sampling and analyzing 2 different biopsy sites per lesion type suggested that in the current age, even as few as 4 biopsies may be of sufficient diagnostic yield in cases of depressed/ulcerative or polypoid type lesions and that the particular site of biopsy may not influence the overall diagnostic yield in these lesion types. On the contrary, infiltrative types still require at least 5 to 6 biopsies per suspected region to have yield above 95% with thickened folds to be a potentially favored site over erosive areas for optimal yield.

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