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Retrospective Study

# Does the discrepancy in histologic differentiation between a forceps biopsy and an endoscopic specimen necessitate additional surgery in early gastric cancer?

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## Abstract

### AIM

To investigate the clinicopathological variables in early gastric cancer (EGC) patients in relation to differentiation discrepancy.

### METHODS

The data of 265 specimens from 240 patients with EGC, who had undergone radical operation at Hallym University Sacred Heart Hospital from 2010 to 2015, were retrospectively analyzed. We evaluated clinical, endoscopic, and histopathological data according to histological discrepancy.

### RESULTS

Clinically significant discrepancy rate showed the difference in differentiated type (well and moderately differentiated) and undifferentiated type (poorly differentiated and signet ring cell) between endoscopic biopsies and postoperative specimens was 9.4% (25/265). There were no differences in tumor location, size, gross pattern, and number of biopsies. Specimens having histological discrepancy



showed more submucosal invasion (72.0% *vs* 49.6%,  $P = 0.033$ ) and lymph node involvement (24.0% *vs* 7.9%,  $P = 0.009$ ) than specimens having non-discrepancy. The rate of a positive epidermal growth factor receptor status was higher in specimens having discrepancy than in specimens having non-discrepancy (81.0% *vs* 55.4%,  $P = 0.035$ ).

### CONCLUSION

The discordance of histologic differentiation is associated with higher submucosal invasion and lymph node metastases in EGC. Patients having histological discrepancy may require additional surgical treatments.

**Key words:** Early gastric cancer; Histological discrepancy; Differentiation; Clinicopathological factor; Endoscopic treatment; Surgical treatment

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**Core tip:** The discordance of differentiation between forceps biopsies and endoscopically resected specimens may necessitate a radical gastrectomy and predict poor outcomes. We analyzed clinicopathological variables of early gastric cancer patients in relation to differentiation discrepancy. Clinically significant discrepancy rate between endoscopic biopsies and postoperative specimens was 9.4%. Specimens having histological discrepancy showed more submucosal invasion and lymph node metastases than specimens having non-discrepancy. Patients who have histological discrepancy detected in endoscopically resected specimens may require additional surgical treatments.

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## INTRODUCTION

Endoscopic resection is widely used to treat early gastric cancer (EGC), accompanying the development of techniques for endoscopic submucosal dissection (ESD). The *en-bloc* resection method for a large superficial lesion by using a needle knife requires the application of appropriate indications due to fear of lymph node metastasis and incomplete submucosal dissection. The standard and expanded indications for endoscopic treatment of EGC are determined based on the size, depth of invasion, ulcer, and histology of the lesion<sup>[1,2]</sup>. The histopathological type, which is divided into two types; differentiated and undifferentiated, according to the presence or absence of tubular structures, is one of the important factors for choosing ESD, and the histologic diagnosis based on a forceps biopsy is critical.

The discrepancy in histologic differentiation between a forceps biopsy and an endoscopic resection specimen necessitates further treatment such as additional radical gastrectomy in EGC patients. Previous studies showed a 1.5%-8.0% rate of histologic discrepancy between the differentiated and undifferentiated types after endoscopic treatment<sup>[3-7]</sup>. The need for additional surgery in cases of histologic discrepancy is based on the likelihood of deep submucosal invasion and lymph node metastasis<sup>[8,9]</sup>. However, little is known about whether histologic discrepancy between a pre-treatment forceps biopsy and a surgical specimen is associated with more submucosal invasion and lymph node metastasis in EGC.

The aim of the present study is to investigate the clinicopathological factors for histological discrepancy in differentiation between preoperative endoscopic biopsies and surgical specimens in EGC patients who underwent gastrectomy and lymph node dissection, and to identify the prognostic factors according to the presence or absence of histological discrepancy.

## MATERIALS AND METHODS

### Patients

We initially included the patients who underwent curative radical gastrectomy with extended lymphadenectomy for EGC at the Hallym University Sacred Heart Hospital in Anyang, South Korea, from 2010 to 2015. All patients received an esophagogastroduodenoscopy (EGD) with forceps biopsy before treatment. We excluded five patients who were found to have advanced gastric cancer with EGC, four patients who had undergone operation for recurrent cancer, and one patient in whom there was lack of data for evaluating the surgical tissues. Finally, 265 EGC specimens from 240 patients were included and retrospectively analyzed. Information on clinical characteristics, including age at operation, sex, underlying disease, pathologic, and outcome data, was collected by reviewing the patient medical records. Underlying diseases included hypertension, diabetes, and cardiovascular, cerebrovascular, and pulmonary diseases. The local ethics committee at Hallym Sacred Heart Medical Center approved the use of clinical data for this study (IRB 2016-I129).

### Endoscopic evaluation

The following endoscopic findings were reviewed by two experienced endoscopists: Tumor location, gross pattern, ulceration, erythema, fold change, easy friability, exudate, and number of biopsies. Tumor location was determined based on the Japanese Classification of Gastric Cancer as upper, middle, or lower third of the stomach<sup>[10]</sup>. The gross pattern was classified into six types: Elevated (types I and IIa), flat (type IIb), depressed (types IIc and III), mixed elevated (types IIa + IIb and IIa + IIc), mixed flat (types IIb + I, IIb + IIa, IIb + IIc, and IIb + III), and mixed depressed (types IIc + IIb, IIc + I, and III).

**Table 1 Tumor differentiation between preoperative biopsies and postoperative specimens**

After surgery		Before surgery		
		Differentiated		Undifferentiated
		WD	MD	PD
Differentiated	WD	56	12	0
	MD	24	45	2
Undifferentiated	PD	4	19	103

PD: Poorly differentiated; MD: Moderately differentiated; WD: Well differentiated.

+ II c), considering the dominant pattern. Ulceration was defined as discontinuity of gastric mucosa with a creator, which is not a superficial erosion. Fold change was defined as a change in the folds including cutting, fusion, and clubbing. Easy friability was defined as bleeding on slight touch or aeration.

### Histopathological evaluation

A gastrointestinal pathologist from our hospital evaluated and reviewed the histological slides of tissues obtained by endoscopic forceps biopsy before the operation and those of the entire resected specimens obtained by radical operation. The histologic type was determined according to the World Health Organization (WHO) classification of gastrointestinal tumors<sup>[11]</sup>. The differentiation of the tumor was determined according to the proportion of the tumor that exhibited glandular structures between differentiated (well and moderately differentiated adenocarcinoma) and undifferentiated types (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). After surgery, the following histopathological parameters were evaluated: Tumor size, tumor staging of tumor confined to mucosa (I a) or submucosal invasion (I b), lymph node metastasis, lymphatic invasion, vascular invasion, and Ki-67, p53, human epidermal growth factor 2 (HER2), and epidermal growth factor receptor (EGFR) status. Based on the hematoxylin and eosin-stained slide review, the available formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks from the 243 available specimens were subjected to immunohistochemical (IHC) staining for D2-40, Ki-67, p53, HER2 and EGFR. HER2 positivity was regarded as tumor score of  $\geq 2+$  on HER2 IHC staining.

### Outcome data

Abdominal computed tomography (CT) and EGD with a biopsy were scheduled at 6 mo after surgery to detect recurrence. After the initial evaluation, abdominal CT was performed every 6 mo and EGD was performed annually for 5 years. Recurrence and death were evaluated during the follow-up period.

### Statistical analysis

Clinical and histopathological characteristics were

compared between the discrepancy and non-discrepancy groups. Categorical variables were analyzed with the  $\chi^2$  test or Fisher's exact test, and continuous variables were compared by the Student *t*-test. The Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, United States) was used for all statistical analyses. A *P* value of  $< 0.05$  was considered statistically significant.

## RESULTS

### Comparison of the characteristics of patients and tumors between the discrepancy and non-discrepancy groups

Of the 265 specimens, 137 (51.7%) showed the same pathological results of differentiated type in both the preoperative endoscopic biopsy and the postgastrectomy specimen, and 103 (38.9%) showed undifferentiated results on both histological examinations. Of the remaining 25 specimens (9.4%), 23 showed differentiated histology on preoperative biopsy, but they showed undifferentiated histology after surgery. Conversely, two specimens having poorly differentiated histology on preoperative biopsy exhibited moderately differentiated histology in the postoperative specimen (Table 1). There was excellent agreement between preoperative and postoperative histology (kappa coefficient = 0.809,  $P < 0.001$ ). Twenty-five specimens from 24 patients were included in the discrepancy group, and 240 specimens from 216 patients were included in the non-discrepancy group.

Table 2 shows a comparison of the characteristics of patients and tumors between the discrepancy and non-discrepancy groups. The median ages of the discrepancy group and the non-discrepancy group were 58 years (range, 31-83 years) and 61 years (range, 35-90 years), respectively. Sex, underlying disease, and tumor location were not significantly different between the two groups. Depressed feature was the most common gross pattern in both discrepancy and non-discrepancy groups (40.0% vs 38.8%, respectively,  $P = 0.668$ ). With respect to endoscopic tumor characteristics, fold change was significantly higher in the discrepancy group than in the non-discrepancy group (80.0% vs 45.4%,  $P = 0.001$ ). The remaining characteristics including ulcer, erythema, easy friability, and exudate were not different between the two groups. The median number of biopsies in the two groups did not show any difference. The median follow-up duration in the discrepancy group was 41 mo (range, 2-72 mo), and the median follow-up in the non-discrepancy group was 36 mo (range, 2-76 mo) ( $P = 0.629$ ). Recurrence was detected in one patient of the discrepancy group and in two patients of the non-discrepancy group during the follow-up period without statistical significance ( $P = 0.272$ ). All three patients developed recurrence at the anastomosis site and underwent additional surgery with chemotherapy. Death occurred in four patients of the non-discrepancy

**Table 2 Clinical characteristics of 240 patients and tumor characteristics in 265 specimens *n* (%)**

Variables	Discrepancy	Non-discrepancy	<i>P</i> value
Age ( <i>n</i> = 240)			
Median, yr (range)	58 (31-83)	61 (35-90)	0.073
Sex ( <i>n</i> = 240)			
Male	17 (70.8)	147 (68.1)	0.781
Female	7 (29.2)	69 (31.9)	
Underlying disease <sup>1</sup> ( <i>n</i> = 240)			
Yes	12 (50.0)	100 (46.3)	0.730
No	12 (50.0)	116 (53.7)	
Location ( <i>n</i> = 265)			
Upper	4 (16.0)	17 (7.1)	0.776
Middle	10 (40.0)	130 (54.2)	
Lower	11 (44.0)	93 (38.8)	
Gross pattern ( <i>n</i> = 265)			
Elevated	1 (4.0)	22 (9.2)	0.668
Flat	5 (20.0)	42 (17.5)	
Depressed	10 (40.0)	93 (38.8)	
Mixed elevated	2 (8.0)	24 (10.0)	
Mixed flat	4 (16.0)	31 (12.9)	
Mixed depressed	3 (12.0)	28 (11.7)	
Ulcer ( <i>n</i> = 265)			
Positive	12 (48.0)	100 (41.7)	0.542
Negative	13 (52.0)	140 (58.3)	
Erythema ( <i>n</i> = 265)			
Positive	5 (20.0)	52 (21.7)	0.847
Negative	20 (80.0)	188 (78.3)	
Fold change ( <i>n</i> = 265)			
Positive	20 (80.0)	109 (45.4)	0.001
Negative	5 (20.0)	131 (54.9)	
Easy friability ( <i>n</i> = 265)			
Positive	9 (36.0)	84 (35.0)	0.921
Negative	16 (64.0)	156 (65.0)	
Exudate ( <i>n</i> = 265)			
Positive	5 (20.0)	36 (15.0)	0.511
Negative	20 (80.0)	204 (85.0)	
Number of biopsies ( <i>n</i> = 265)			
Median (range)	3 (2-6)	3 (1-10)	0.332
Follow-up period (mo) ( <i>n</i> = 240)			
Median (range)	41 (2-72)	36 (2-76)	0.629
Recurrences during follow-up ( <i>n</i> = 240)	1 (4.2)	2 (0.9)	0.272
Death during follow-up ( <i>n</i> = 240)	0 (0.0)	4 (1.9)	1.000

<sup>1</sup>Underlying diseases include hypertension, diabetes, and cardiovascular, cerebrovascular, and pulmonary diseases.

group during the follow-up period, but it was not EGC-related death. Two patients died of lung cancer, one patient died of infection, and the remaining one patient died of cardiomyopathy.

#### **Comparison of histopathological parameters between the discrepancy and non-discrepancy groups**

The median size of specimens in the discrepancy group was larger than that of specimens in the non-discrepancy group, but this difference was not statistically significant (3.0 cm vs 2.2 cm, *P* = 0.252). The proportion of submucosal involvement was significantly higher in the discrepancy group than in the non-discrepancy group (72.0% vs 49.6%, *P* = 0.033). In addition, the rate of positivity of lymph node metastasis was significantly higher in the discrepancy group (24.0% vs 7.9%, *P* = 0.009). The rate of lymphatic invasion was slightly higher in the discrepancy group without

statistical significance (28.0% vs 17.1%, *P* = 0.177); however, the rate of vascular invasion was similar between the two groups. The rate of positive EGFR status was significantly higher in the discrepancy group than in the non-discrepancy group (81.0% vs 55.4%, *P* = 0.035) (Table 3).

#### **Comparison of histopathological parameters between the discrepancy and non-discrepancy groups with undifferentiated postoperative histology**

We performed a subgroup analysis in patients with poorly differentiated histology of postoperative specimens. There were 23 specimens in the discrepancy group and 103 specimens in the non-discrepancy group. The median size of specimens, number of biopsies, tumor location, and gross pattern were not different between the two groups. The rates of submucosal involvement and lymph node metastasis were signi-

**Table 3** Histopathological characteristics of surgical specimens *n* (%)

Variables	Discrepancy	Non-discrepancy	<i>P</i> value
Tumor size in the specimen ( <i>n</i> = 265)			
Median, cm (range)	3.0 (0.8-5.5)	2.2 (0.4-8.5)	0.252
Tumor staging ( <i>n</i> = 265)			
I a	7 (28.0)	121 (50.4)	0.033
I b	18 (72.0)	119 (49.6)	
Nodal staging ( <i>n</i> = 265)			
Positive	6 (24.0)	19 (7.9)	0.009
Negative	19 (76.0)	221 (92.1)	
Lymphatic invasion ( <i>n</i> = 265)			
Positive	7 (28.0)	41 (17.1)	0.177
Negative	18 (72.0)	199 (82.9)	
Vascular invasion ( <i>n</i> = 265)			
Positive	2 (8.0)	17 (7.1)	0.697
Negative	23 (92.0)	223 (92.9)	
Ki-67 ( <i>n</i> = 243)			
High	20 (95.2)	186 (83.8)	0.215
Low	1 (4.8)	36 (16.2)	
p53 ( <i>n</i> = 243)			
Positive	15 (71.4)	138 (62.2)	0.401
Negative	6 (28.6)	84 (37.8)	
HER2 ( <i>n</i> = 243)			
Positive (2+ and 3+)	7 (33.3)	41 (18.5)	0.102
Negative (0 and 1+)	14 (66.7)	181 (81.5)	
EGFR ( <i>n</i> = 243)			
Positive	17 (81.0)	123 (55.4)	0.035
Negative	4 (19.0)	99 (44.6)	

HER2: Human epidermal growth factor 2; EGFR: Epidermal growth factor receptor.

ificantly higher in the discrepancy group than in the non-discrepancy group (73.9% vs 49.5%,  $P = 0.034$ , and 26.1% vs 8.7%,  $P = 0.020$ , respectively). The rate of lymphatic invasion was also significantly higher in the discrepancy group than in the non-discrepancy group (30.4% vs 11.7%,  $P = 0.023$ ). The rates of positive HER2 status and EGFR status were significantly higher in the discrepancy group than in the non-discrepancy group (36.8% vs 15.8%,  $P = 0.033$ , and 84.2% vs 51.5%,  $P = 0.011$ ) (Table 4).

## DISCUSSION

In the present study, discrepancy between an endoscopic forceps biopsy and a postgastrectomy specimen was associated with higher submucosal invasion, lymph node metastases, and positive EGFR status than non-discrepancy in EGC. In the subgroup analysis performed in undifferentiated post-surgical specimens, the discrepancy group showed a higher rate of lymphatic invasion, positive EGFR, and HER2 status, along with a higher proportion of submucosal invasion and lymph node metastases. These results suggested that discordance between an endoscopic biopsy and a surgical specimen could be a predictive factor related to poor outcome in EGC.

Currently, histologic diagnosis of gastric cancer is determined according to the WHO classification. An EGC lesion consisting of both differentiated and undifferentiated carcinomas is classified based on

the quantitatively predominant type. Histological heterogeneity presenting a mixture of differentiated and undifferentiated components is the most important factor for histological discrepancy between a preoperative biopsy and a post-procedural specimen. Cases of a mixed predominantly undifferentiated type showed higher lymph node metastases than cases of a pure undifferentiated type in EGC patients (19.0% vs 6.0%)<sup>[12]</sup>. In a study of predominantly differentiated type of EGC, the mixed type was significantly associated with large tumor size, more frequent submucosal invasion, and lymphovascular invasion compared to the pure type<sup>[13]</sup>. Therefore, EGC with a mixed histologic type affects the therapeutic outcomes and the consequent clinical course<sup>[14,15]</sup>. In our study, mixed type specimens according to the Lauren classification were more frequently found in the discrepancy group than in the non-discrepancy group (45.0% vs 11.6%,  $P < 0.001$ ). Although all specimens in the discrepancy group were not of the mixed histology type, the results showing more submucosal invasion and lymph node metastases in histological discordance between a biopsy sample and a resected specimen corresponded with those of the above studies.

The rate of discrepancy between a forceps biopsy and an endoscopically resected specimen in EGC was 2.3%-5.2%<sup>[3,5,6,16]</sup>. In a study that evaluated post-surgical specimens of mucosal gastric cancer, the discrepancy rate was 11.9%<sup>[17]</sup>, which was slightly higher than the rate of 9.4% in our study. These studies



**Table 4 Comparison of histopathological characteristics between 23 specimens having discrepancy and 103 specimens having non-discrepancy along with undifferentiated postoperative histology *n* (%)**

Variables	Discrepancy	Non-discrepancy	<i>P</i> value
Tumor size in the specimen ( <i>n</i> = 126)			
Median, cm (range)	3.0 (0.8-5.5)	2.5 (0.5-8.0)	0.343
Number of biopsies ( <i>n</i> = 126)			
Median, No. (range)	3 (2-6)	3 (1-8)	0.374
Location ( <i>n</i> = 126)			
Upper	3 (13.0)	10 (9.7)	0.481
Middle	10 (43.5)	62 (60.2)	
Lower	10 (43.5)	31 (30.1)	
Gross pattern ( <i>n</i> = 126)			
Elevated	1 (4.3)	1 (1.0)	0.615
Flat	4 (17.4)	20 (19.4)	
Depressed	9 (39.1)	51 (49.5)	
Mixed elevated	2 (8.7)	6 (5.8)	
Mixed flat	4 (17.4)	16 (15.5)	
Mixed depressed	3 (13.0)	9 (8.7)	
Tumor staging ( <i>n</i> = 126)			
I a	6 (26.1)	52 (50.5)	0.034
I b	17 (73.9)	51 (49.5)	
Nodal staging ( <i>n</i> = 126)			
Positive	6 (26.1)	9 (8.7)	0.020
Negative	17 (73.9)	94 (91.3)	
Lymphatic invasion ( <i>n</i> = 126)			
Positive	7 (30.4)	12 (11.7)	0.023
Negative	16 (69.6)	91 (88.3)	
Vascular invasion ( <i>n</i> = 126)			
Positive	2 (8.7)	2 (1.9)	0.152
Negative	21 (91.3)	101 (98.1)	
Ki-67 ( <i>n</i> =120)			
High	48 (94.7)	77 (76.2)	0.119
Low	1 (5.3)	24 (23.8)	
p53 ( <i>n</i> = 120)			
Positive	13 (68.4)	59 (58.4)	0.414
Negative	6 (31.6)	42 (41.6)	
HER2 ( <i>n</i> = 120)			
Positive (2+ and 3+)	7 (36.8)	16 (15.8)	0.033
Negative (0 and 1+)	12 (63.2)	85 (84.2)	
EGFR ( <i>n</i> = 120)			
Positive	16 (84.2)	52 (51.5)	0.011
Negative	3 (15.8)	49 (48.5)	

HER2: Human epidermal growth factor 2; EGFR: Epidermal growth factor receptor.

reported that the factors associated with histological discrepancy were lesion location in the upper or middle third of the stomach, easy friability, depressed type, and large tumor size. This indicated that the likelihood of mixed histology or misdiagnosis on biopsy could increase according to tumor location, morphology, gross pattern, or size. Our study did not show significant differences in the above factors between the groups with or without discrepancy. However, in the present study, fold change and positive EGFR status were predictable factors related to discordance. The surrounding fold change in the malignant lesion was an associated factor of invasion of the deeper layer than the confined mucosal layer<sup>[5]</sup>. The discrepancy group showed more fold change than the non-discrepancy group, resulting in more submucosal invasion. EGFR, a group of transmembrane tyrosine kinase receptors that regulate cellular proliferation, survival migration, and differentiation, was expressed in 30%-50% of

gastric cancer cases and it is known to be correlated with poor prognosis<sup>[18]</sup>. More positive EGFR status in the discrepancy group could be a factor related to poor outcomes such as submucosal invasion and lymph node metastasis. Moreover, the rate of HER2 overexpression was higher in the discrepancy group than in the non-discrepancy group in the subgroup analysis performed in specimens having an undifferentiated postoperative histology. HER2 is one of the EGFR family members and it is associated with decreased survival and clinicopathological features of tumor progression in gastric cancer<sup>[19]</sup>. Higher rate of positive HER2 and EGFR status might predict a poor prognosis, and therefore, patients showing discrepancy can be treated with monoclonal antibodies directed against these receptors.

The 5-year overall survival rates of EGC patients who underwent endoscopic resection or surgical resection were 93.6%-97.5%<sup>[20,21]</sup>. Because of high survival rates and good prognosis of EGC, recurrences were observed

in one patient of the discrepancy group and in two patients of the non-discrepancy group and disease-related deaths did not occur in both groups during the median 36-mo follow-up period.

Our study had several limitations. First, the analysis was retrospective and it was a small sized study conducted in a single center. There may be unrecognized or unmeasured biases and we could not generalize the property of discrepancy between an endoscopic biopsy and a surgical specimen based on these results. Second, HER2 overexpression was regarded as  $\geq 2+$  on IHC staining. Other studies defined HER2 overexpression as 3+ on IHC staining and positivity of fluorescence in situ hybridization in 2+ on IHC staining<sup>[22,23]</sup>.

In conclusion, the discrepancy in histologic differentiation between a forceps biopsy and a postoperative specimen was associated with submucosal invasion and lymph node metastases in EGC patients. The discordance was also associated with a more positive EGFR and HER2 status. Accordingly, patients who have histological discrepancy could be predicted to achieve a poor outcome and patients who have histological discrepancy detected in an endoscopically resected specimen might be considered to require additional surgical treatments.

## COMMENTS

### Background

Endoscopic resection is widely used for the treatment of early gastric cancer (EGC). The histologic differentiation type is one of important factor for deciding endoscopic procedure and the discordance of differentiation between a forceps biopsy and endoscopically resected specimen can need a radical gastrectomy. In addition, histologic discrepancy may a predictive factor for predicting poor outcomes. Therefore, it is needed to investigate clinicopathological variables of EGC patients in relation to differentiation discrepancy.

### Research frontiers

The discordance of histological differentiation between a forceps biopsy and an endoscopic specimen is associated with higher submucosal invasion and lymph node metastases in EGC patients.

### Innovations and breakthroughs

In previous studies, the factors associated with histological discrepancy in EGC were tumor location, morphology, gross pattern, and size. In the present study, histological discrepancy was associated with higher submucosal invasion, lymph node metastases, and positive epidermal growth factor receptor (EGFR) status. In the subgroup analysis performed in undifferentiated post-surgical specimens, the discrepancy was associated with higher lymphatic invasion, positive EGFR, and human epidermal growth factor 2 (HER2) status, along with higher submucosal invasion and lymph node metastases. These results suggested that discordance of histological differentiation could be a predictive factor related to poor outcome in EGC.

### Applications

The histological discrepancy between a forceps biopsy and an endoscopic specimen could be a predictive factor for a poor outcome. Patients who have histological discrepancy detected in an endoscopically resected specimen might be considered to require additional surgical treatments.

### Terminology

EGFR is a group of transmembrane tyrosine kinase receptors that regulate cellular proliferation, survival migration, and differentiation. HER2 is one of

the EGFR family members and it is associated with decreased survival and clinicopathological features of tumor progression in gastric cancer.

### Peer-review

The present study showed that discrepancy between an endoscopic forceps biopsy and a postgastrectomy specimen was associated with higher submucosal invasion, lymph node metastasis, and positive EGFR status than non-discrepancy in EGC. The authors concluded that discordance between an endoscopic biopsy and a surgical specimen could be a predictive factor related to poor outcome in EGC. Based on their findings, the authors suggested that patients who have histological discrepancy detected in an endoscopically resected specimen might be considered to require additional surgery.

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