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# Effect of histologic differences between biopsy and final resection on treatment outcomes in early gastric cancer

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## Abstract

**Background and study aims** Biopsy-based histologic diagnosis is important in determining the treatment strategy for early gastric cancer (EGC). However, there are few studies on how histologic discrepancy may affect patients' treatment outcomes. We aimed to investigate the impact of histopathologic differences between biopsy and final specimens from endoscopic resection (ER) or gastrectomy on treatment outcomes in patients with EGC. We also examined the predictive factors of histologic discrepancy.

**Patients and methods** We analyzed the data of 1851 patients with EGC treated with ER or gastrectomy. We compared the histology between biopsies and final resected specimens from ER or gastrectomy. We also examined changes in treatment outcomes according to histologic differences.

**Results** Histologic discrepancy was observed in 11.9% of patients in the ER group and 10.7% of those in the gastrectomy group. In patients treated with ER who showed histologic discrepancy, 80.9% showed differentiated-type EGC (D-EGC) on biopsy but undifferentiated-type-EGC (UD-EGC) after ER, of which 78.9% were non-curative resection. In patients treated with gastrectomy who showed histologic discrepancy, 39% showed UD-EGC on biopsy but showed D-EGC after gastrectomy. A total of these patients had absolute and expanded indications for ER. Moderately differentiated and poorly differentiated adenocarcinoma on biopsy were predictive factors of histologic discrepancy in UD-EGC and D-EGC on final resection, respectively.

**Conclusions** About 10% of patients showed histologic discrepancy between biopsy and final resection with ER or gastrectomy. Histologic discrepancy can affect treatment outcomes, such as non-curative resection in ER or missing the opportunity for ER in gastrectomy.

**Keywords** Early gastric cancer · Histology · Biopsy · Endoscopic submucosal dissection · Gastrectomy

Gastric cancer is the fifth most common cancer in the world and the third most commonly associated with cancer-related mortality [1]. Although the incidence is decreasing, stomach cancer still has the second highest cancer incidence in Korea, and it is associated with the third highest cancer mortality in Korea [2, 3]. According to the national cancer screening program for gastric cancer from 1999, the proportion of patients with early gastric cancer (EGC) among those with gastric cancer has been steadily increasing in Korea [4]. Recently, endoscopic resection (ER), rather than gastrectomy, has been receiving worldwide attention as treatment for EGC because it can preserve the stomach and thus can improve patients' quality of life, as compared with radical gastrectomy. The Japanese expanded criteria for ER proposed by Gotoda et al. have been used worldwide for deciding whether to perform

Yonsoo Kim and Hong Jin Yoon have contributed equally to this work.

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ER or gastrectomy for EGC [5, 6]. The expanded criteria for ER include: (1) differentiated-type intramucosal cancer without ulcer findings; (2) differentiated-type intramucosal cancer no larger than 3 cm in diameter, with ulcer findings; (3) differentiated-type minute invasive submucosal cancer no larger than 3 cm in diameter; and (4) undifferentiated-type intramucosal cancer no larger than 2 cm in diameter, without ulcer findings [6]. Prior to gastrectomy for EGC, endoscopic findings, especially the results of biopsy, are important in choosing whether to perform ER or gastrectomy. In addition, when diagnosed with undifferentiated-type EGC, only patients with an intramucosal tumor less than 2 cm in size without ulceration are classified according to the expanded ER criteria. Therefore, the preoperative histologic type is very important for determining the treatment direction.

However, the histologic type of the initial biopsy does not always match that of the final specimen from ER or gastrectomy. Biopsy is taken from the surface of the lesion and there may be errors made in sampling; [7] therefore, histologic diagnosis based on biopsy is limited. Several studies have been conducted to investigate histologic discrepancy, but most of these have been limited to ER. In this study, we analyzed the frequency of histologic discrepancy, including in ER and gastrectomy, and the effect of treatment on patient outcomes.

## Patients and methods

### Study participants

We analyzed data of 1851 patients with EGC from January 2009 to December 2016 who were treated with ER or gastrectomy. Of these, 1343 patients were treated with ER and 508 patients underwent gastrectomy. Among patients with EGC, ER was performed in those who met the Japanese criteria, including the expanded indications. All ER was performed by gastroenterologist. In patients who underwent esophagogastroduodenoscopy (EGD) outside the hospital, we reviewed biopsy pathology slides to confirm the histology of lesions.

Of the 1343 patients who underwent ER, we excluded those who met any of the following criteria: (1) endoscopic biopsy result with dysplasia, (2) external hospital slides could not be obtained or reviewed, (3) ER after gastrectomy. Therefore, a total of 395 patients were finally included in the ER group.

Of the 508 patients who underwent gastrectomy, we excluded those who met any of the following criteria: (1) endoscopic biopsy result diagnosed as high-grade dysplasia, (2) endoscopic biopsy result diagnosed as adenocarcinoma but with indistinguishable degree of differentiation, (3) external hospital slides could not be obtained or reviewed, (4) inaccurate submucosal invasion depth. Thus, a total of 384 patients were finally included in the gastrectomy group.

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (IRB No.3-2019-0109).

### Categorization of participants

We compared the pathology of initial biopsies and final resected specimens between the ER and gastrectomy groups. In a comparison between the two groups, patients were classified according to histologic discrepancy. That is, if the pathology of the initial biopsy and final resected specimen were consistently differentiated-type (D-EGC) (including well differentiated (AWD) and moderately differentiated adenocarcinoma (AMD)) or undifferentiated-type (UD-EGC) (including poorly differentiated adenocarcinoma (APD) and signet ring cell carcinoma (SRC)), the patient was categorized as having no histologic discrepancy. If the pathology of the initial biopsy was differentiated-type and that of the final specimen was undifferentiated-type or vice versa, the patient was categorized as having histologic discrepancy. Histologic discrepancy consisted of a change from D-EGC on biopsy to UD-EGC on final resection or from UD-EGC on biopsy to D-EGC on final resection.

Clinicopathologic characteristics were analyzed between patients with histologic discrepancy and those with no histologic discrepancy. In addition, we analyzed the immediate outcomes of ER, such as curative resection (CR), according to histologic discrepancy in the ER group. Lesions meeting the indications for ER among patients in the gastrectomy group were analyzed according to histologic discrepancy.

### Statistical analysis

We used IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) for the statistical analysis. We used *t* tests to analyze sequential data, and the Chi squared test was used to compare discontinuous data between the two groups. Univariate and multivariate logistic regression analyzes were conducted to determine the significant factors affecting histologic discrepancy. Statistical significance was defined as $p < 0.05$.

## Results

### Comparison according to histologic discrepancy

Patients in the ER group had significantly older age, smaller sized tumor, and more frequent mucosal cancer than those in the gastrectomy group. Significantly greater ulceration was observed in the gastrectomy group than in the ER group (Supplementary Table 1).

When we classified all lesions according to histologic discrepancy, including those among patients in the ER and gastrectomy groups, 88 lesions (11.3%) showed histologic discrepancy. AMD on biopsy was more frequently observed in lesions with histologic discrepancy whereas AMD and SRC on biopsy were more frequently observed in lesions without histologic discrepancy. After final resection, APD, lymphovascular invasion (LVI), and submucosal invasion were significantly more frequent in lesions with histologic discrepancy (Table 1).

In the ER group, lesions with histologic discrepancy showed larger size, more frequent AMD on biopsy, and more frequent APD in the final resected specimen. In addition, lesions with histologic discrepancy had a higher rate of non-curative resection after ER. Lesions with histologic discrepancy showed more frequent LVI and perineural invasion (PNI) after ER (Supplementary Table 2).

Among patients who underwent gastrectomy, histologic discrepancy was significantly more frequent in male patients. Lesions with histologic discrepancy also involved more frequent AMD on biopsy and more frequent APD

**Table 1** Clinicopathologic characteristics according to histologic discrepancy in patients treated with endoscopic resection and gastrectomy

| | Without histologic discrepancy ($n=691$) | With histologic discrepancy ($n=88$) | $p$ value |
|---|---|---|---|
| Age (years, mean ± SD) | 60.85 ± 12.31 | 58.99 ± 12.35 | 0.182 |
| Tumor size (mm, mean ± SD) | 24.25 ± 16.48 | 29.8 8 ± 20.44 | **0.003** |
| Tumor size ($n$, %) | | | **0.048** |
| ≤ 20 mm | 360 (52.1) | 36 (40.8) | |
| > 20 mm | 331 (47.9) | 52 (59.1) | |
| Sex (male, $n$, %) | 444 (64.3) | 66 (75.0) | **0.046** |
| Location ($n$, %) | | | 0.553 |
| Upper | 55 (8.0) | 10 (11.4) | |
| Mid | 275 (39.8) | 34 (38.6) | |
| Lower | 361 (52.2) | 44 (50.0) | |
| Gross type ($n$, %) | | | 0.238 |
| Elevated | 119 (17.2) | 21 (23.9) | |
| Flat | 241 (34.9) | 25 (28.4) | |
| Depressed | 331 (47.9) | 42 (47.7) | |
| Ulceration ($n$, %) | 46 (6.7) | 10 (11.4) | 0.107 |
| Histology on biopsy ($n$, %) | | | **< 0.001** |
| AWD | 223 (32.3) | 6 (6.8) | |
| AMD | 185 (26.8) | 57 (64.8) | |
| APD | 135 (19.5) | 21 (23.9) | |
| SRC | 148 (21.4) | 4 (4.5) | |
| Histology on final resection ($n$, %) | | | **< 0.001** |
| AWD | 160 (23.1) | 1 (1.1) | |
| AMD | 248 (35.9) | 24 (27.3) | |
| APD | 120 (17.4) | 60 (68.2) | |
| SRC | 163 (23.6) | 3 (3.4) | |
| Depth of invasion ($n$, %) | | | **0.004** |
| Mucosa | 461 (66.7) | 45 (51.1) | |
| Submucosa | 230 (33.3) | 43 (48.9) | |
| Treatment ($n$, %) | | | 0.59 |
| ER | 348 (50.4) | 47 (53.4) | |
| Gastrectomy | 343 (49.6) | 41 (46.6) | |
| Lymphovascular invasion ($n$, %) | 60 (8.7) | 19 (21.6) | **< 0.001** |
| Perineural invasion ($n$, %) | 7 (1.0) | 3 (3.4) | 0.060 |

Histologic discrepancy (bold) was determined by comparing the pathology between initial biopsy and final resected specimen

*ER* endoscopic resection, *AWD* adenocarcinoma well differentiated, *AMD* adenocarcinoma moderately differentiated, *APD* adenocarcinoma poorly differentiated, *SRC* signet ring cell carcinoma, *SD* standard deviation

in the final resected specimen. However, the proportion of AMD in the final pathology was also higher for lesions with histologic discrepancy than for those without histologic discrepancy, which differed from the ER group. After surgical resection, LVI and submucosal invasion were more frequently observed in lesions with histologic discrepancy (Supplementary Table 3).

#### Treatment outcomes of participants with histologic discrepancy

In the ER group, 11.9% of patients had histologic discrepancy; this proportion was 10.7% of patients in the gastrectomy group (Table 2). Among patients who had histologic discrepancy in the ER group, 80.9% had D-EGC on biopsy and UD-EGC after ER. In this group, 78.9% showed non-curative resection after ER. Among patients with histologic discrepancy, 19.1% had UD-EGC on biopsy and D-EGC after ER. Most patients in this group showed CR by ER.

Among patients who underwent gastrectomy and had histologic discrepancy, 61.0% had D-EGC on biopsy and UD-EGC after gastrectomy. Most (80.0%) lesions in these patients were beyond the indication for ER. Among patients treated surgically who had histologic discrepancy, 39% had UD-EGC on biopsy and D-EGC after gastrectomy. Half of these lesions were within ER indications, including absolute and expanded indications (Table 2). Figure 1 summarizes the treatment outcomes according to histologic discrepancy among patients with EGC.

### Clinicopathologic characteristics associated with histologic discrepancy

#### Lesions with differentiated-type histology on biopsy

We analyzed the data of all patients in the ER and gastrectomy groups. Among patients with D-EGC on biopsy, 63 were diagnosed with UD-EGC after resection. When compared according to histologic discrepancy, lesions with histologic discrepancy were significantly associated with younger age, larger size, ulceration, AMD on biopsy, APD after resection, submucosal invasion, LVI, and PNI. However, according to multivariate analysis, AMD on biopsy and LVI were significantly associated with histologic discrepancy (Table 3).

#### Lesions with undifferentiated-type histology on biopsy

In the analysis of patients in the ER and gastrectomy groups, 25 patients were diagnosed with D-EGC after resection among those with UD-EGC on biopsy. When compared according to histologic discrepancy, lesions with histologic discrepancy were significantly associated with male sex, lower location, APD on biopsy, and AMD after resection. However, according to multivariate analysis, male sex, and APD on biopsy were significantly associated with histologic discrepancy (Table 4).

## Discussion

The inconsistency of histologic differentiation between biopsy and final resection specimens, including from ER or gastrectomy in EGC, affects the treatment outcomes. Therefore, it is important to clarify the frequency of discordance and the factors affecting such discrepancy. In this study, we analyzed the frequency of histologic discrepancies and associated factors as well as the treatment outcomes of patients with discordant histologic findings.

The histologic discrepancy in EGC between biopsy and final resection findings is reported to be 2.3–11.9% [7–9]. According to our study results, the rate of histologic discrepancy was about 10% in both the ER and gastrectomy groups. The rate of histologic discrepancy was 13.4% in patients with differentiated-type EGC on initial biopsy, and 8.1% in patients with undifferentiated-type EGC on biopsy.

**Table 2** Summary of histologic discrepancy between the ER and gastrectomy groups

| | ER | | Gastrectomy | |
|---|---|---|---|---|
| Histologic discrepancy (*n*, %) | 47/395 (11.9) | | 41/384 (10.7) | |
| *D to UD (*n*, %) | 38/47 (80.9) | | 25/41 (61.0) | |
| | CR | 8 (21.1) | Within expanded ER Ix | 5 (20.0) |
| | Non-CR | 30 (78.9) | Beyond ER Ix | 20 (80.0) |
| **UD to D (*n*, %) | 9/47 (19.1) | | 16/41 (39.0) | |
| | CR | 7 (77.8) | Within absolute ER Ix | 3 (18.8) |
| | | | Within expanded ER Ix | 5 (31.2) |
| | Non-CR | 2 (22.2) | Beyond ER Ix | 8 (50.0) |

*ER* endoscopic resection, *CR* curative resection, *Non-CR* non-curative resection, *Ix* indication

*D to UD: Differentiated-type EGC on biopsy and undifferentiated-type EGC on final resection

**UD to D: Undifferentiated-type EGC on biopsy and differentiated-type EGC on final pathology

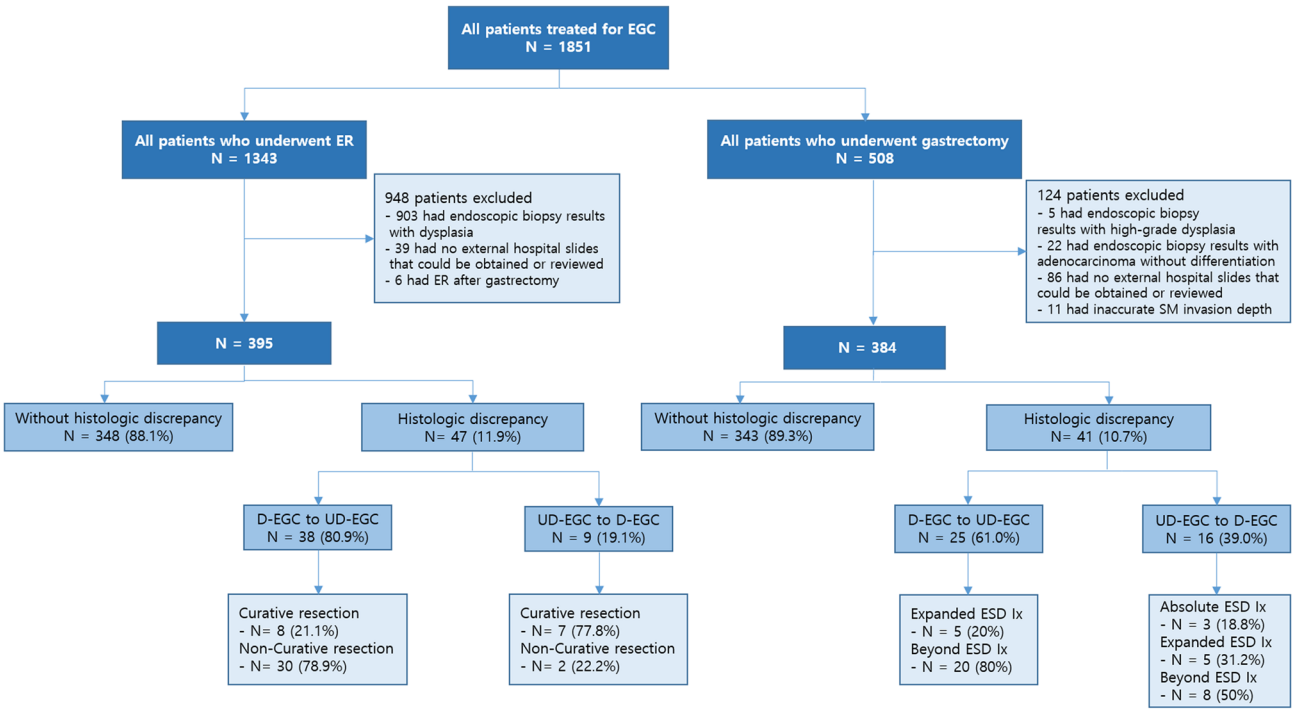


**Fig. 1** Treatment outcomes according to histologic discrepancy in endoscopic resection and gastrectomy

Inconsistencies between biopsy and final pathologic results after ER or gastrectomy are not only due to the nature of the tumor but also owing to the limitations of biopsy itself [10]. First, specimens collected in biopsy may be damaged owing to technical factors; therefore, the duct formation of cancer cells may not be clearly seen, which may lead to misdiagnosis of APD [7]. In addition, the histological heterogeneity of gastric cancer is important. That is, two or more histologic types are commonly observed in the same tumor [11]. Histologic heterogeneity is considered to be an important tumor factor that contributes to inconsistent histologic differentiation of a pathologic diagnosis before and after a procedure. When adenocarcinomas are mixed with more than two types of histology, classification is made according to that of the largest area of cancer cells; [12] this principle also applies to the Japanese classification [6, 13]. However, histological heterogeneity is difficult to predict before treatment because there are currently no clear criteria regarding factors that can be seen in general endoscopic findings, and de-differentiation is usually observed in areas where tumors invade the submucosa [10].

One study identified independent predictive factors for diagnosis of atypical glands, low-grade dysplasia, high-grade dysplasia, or D-EGC in forceps biopsy but a pathology diagnosis of UD-EGC after ER; these predictive factors were age $\leq 60$ years, female sex, body location, flat or depressed type, and $> 2$ cm in size [14]. However, the above study was limited because only patients with ER were included. In addition, gastrectomy was the primary treatment option for UD-EGC at the institution in that study. According to the results of the present study, which included all patients who underwent ER and gastrectomy, only detection of AMD and APD on biopsy were predictors of a likely change in pathology after the final resection. In other words, image-enhanced endoscopy (IEE), such as narrow band image with magnifying endoscopy or confocal endoscopy will be helpful in targeting biopsy.

Other studies investigating histologic discrepancy mostly involved adenoma on biopsy, but ER pathology was analyzed in EGC [15, 16]. The advantage of our study is that only histologically confirmed patients with carcinoma were included. This is a very important point because ER is considered the first priority for adenoma, but this differs for EGC.

One of the strengths of our study was the analysis of treatment outcomes in patients with histologic discrepancy. Among patients treated with ER, non-CR accounted for 78.9% of patients who showed histologic discrepancy, with differentiated-type EGC on initial biopsy. In one study on histologic discrepancy in ER, 4.4% of 596 EGCs were diagnosed after ER, from differentiated to undifferentiated-type, and the complete resection rate was significantly lower, similar to our study [8]. Compared with D-EGC, UD-EGC has a high rate of incomplete resection when ER is performed, ranging from 15% to as high as 45% [17–19]. UD-EGC shows a tendency toward intramucosal spread over

**Table 3** Clinicopathologic characteristics associated with histologic discrepancy among lesions with differentiated-type histology on biopsy

| | Without histologic discrepancy ($n=408$) | With histologic discrepancy ($n=63$) | $p$ value | Multivariate analysis | |
|---|---|---|---|---|---|
| | | | | OR (95% Cl) | $p$ value |
| Age (years, mean ± SD) | 65.17 ± 9.91 | 60.14 ± 12.29 | **0.003** | | |
| Tumor size (mm, mean ± SD) | 22.73 ± 16.13 | 30.97 ± 18.35 | **< 0.001** | | |
| Tumor size ($n$, %) | | | **0.004** | | |
| ≤ 20 mm | 228 (55.9) | 23 (36.5) | | | |
| > 20 mm | 180 (44.1) | 40 (63.5) | | | |
| Sex ($n$, %) | | | 0.946 | | |
| Male | 306 (75) | 47 (74.6) | | | |
| Female | 102 (25) | 16 (25.4) | | | |
| Location ($n$, %) | | | 0.101 | | |
| Upper | 45 (11.0) | 9 (14.3) | | | |
| Mid | 142 (34.8) | 29 (46.0) | | | |
| Lower | 221 (54.2) | 25 (39.7) | | | |
| Gross type ($n$, %) | | | 0.304 | | |
| Elevated | 90 (22.1) | 16 (25.4) | | | |
| Flat | 144 (35.3) | 16 (25.4) | | | |
| Depressed | 174 (42.6) | 31 (49.2) | | | |
| Ulceration ($n$, %) | | | **0.003** | | **0.05** |
| No | 389 (93.3) | 52 (83.7) | | Ref | |
| Yes | 19 (4.7) | 9 (14.3) | | 2.518 (0.999–6.342) | |
| Histology on biopsy ($n$, %) | | | **< 0.001** | | **< 0.001** |
| AWD | 223 (54.7) | 6 (9.5) | | Ref | |
| AMD | 185 (45.3) | 57 (90.5) | | 10.765 (4.498–25.764) | |
| Histology on final resection ($n$, %) | | | **< 0.001** | | |
| AWD | 160 (39.2) | 0 (0.0) | | | |
| AMD | 248 (60.8) | 0 (0.0) | | | |
| APD | 0 (0.0) | 60 (95.2) | | | |
| SRC | 0 (0.0) | 3 (4.8) | | | |
| Depth of invasion ($n$, %) | | | **0.016** | | |
| Mucosa | 265 (65) | 31 (49.2) | | | |
| Submucosa | 143 (35) | 32 (50.8) | | | |
| Treatment ($n$, %) | | | 0.428 | | |
| ER | 267 (65.4) | 38 (60.3) | | | |
| Operation | 141 (34.6) | 25 (39.7) | | | |
| Lymphovascular invasion ($n$, %) | | | **< 0.001** | | **0.008** |
| Yes | 37 (9.1) | 16 (25.4) | | Ref | |
| No | 371 (90.9) | 47 (74.6) | | 0.318 (0.136–0.744) | |
| Perineural invasion ($n$, %) | | | **0.021** | | |
| Yes | 4 (1.0) | 3 (4.8) | | | |
| No | 404 (99.0) | 60 (95.2) | | | |

Histologic discrepancy (bold) was determined by comparing the pathology between initial biopsy and final resected specimen

*ER* endoscopic resection, *AWD* adenocarcinoma well differentiated, *AMD* adenocarcinoma moderate differentiated, *APD* adenocarcinoma poorly differentiated, *SRC* signet ring cell carcinoma, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation

a gradient of the gross margin; on endoscopy, the actual tumor size is often ambiguous and larger than the assumed size of the lesion [20, 21]. In this way, UD-EGC is likely to involve the resection margin in the case of ER. Although the CR rate of UD-EGC (including APD) is low, but long-term outcomes are good if CR is achieved [17, 22, 23]. Therefore, evaluation to improve CR is important and careful approach is needed in UD-EGC. The complete resection rate can be increased if the predicting factors for UD-EGC are known in cases with histologic discrepancy.

**Table 4** Clinicopathologic characteristics associated with histologic discrepancy among lesions with undifferentiated-type histology on biopsy

| | Without histologic discrepancy ($n=283$) | With histologic discrepancy ($n=25$) | $p$ value | Multivariate analysis OR (95% Cl) | $p$ value |
|---|---|---|---|---|---|
| Age (years, mean ± SD) | 54.62 ± 12.77 | 56.08 ± 12.25 | 0.583 | | |
| Tumor size (mm, mean ± SD) | 26.43 ± 16.74 | 27.12 ± 25.17 | 0.85 | | |
| Tumor size ($n$, %) | | | 0.607 | | |
| ≤ 20 mm | 132 (46.6) | 13 (52.0) | | | |
| > 20 mm | 151 (53.4) | 12 (48.0) | | | |
| Sex ($n$, %) | | | **0.009** | | **0.048** |
| Male | 138 (48.8) | 19 (76.0) | | Ref | |
| Female | 145 (51.2) | 6 (34.0) | | 0.374 (0.141–0.990) | |
| Location ($n$, %) | | | **0.032** | | |
| Upper | 10 (3.5) | 1 (4.0) | | | |
| Mid | 133 (47.0) | 5 (20.0) | | | |
| Lower | 140 (49.5) | 19 (76.0) | | | |
| Gross type ($n$, %) | | | 0.279 | | |
| Elevated | 29 (10.2) | 5 (20.0) | | | |
| Flat | 97 (34.3) | 9 (36.0) | | | |
| Depressed | 157 (55.5) | 11 (44.0) | | | |
| Ulceration ($n$, %) | | | 0.356 | | |
| No | 256 (90.5) | 24 (96.0) | | | |
| Yes | 27 (9.5) | 1 (4.0) | | | |
| Histology on biopsy ($n$, %) | | | **0.001** | | **0.005** |
| APD | 135 (47.7) | 21 (84.0) | | Ref | |
| SRC | 148 (52.3) | 4 (16.0) | | 0.204 (0.067–0.621) | |
| Histology on final resection ($n$, %) | | | **< 0.001** | | |
| AWD | 0 (0.0) | 1 (4.0) | | | |
| AMD | 0 (0.0) | 24 (96.0) | | | |
| APD | 120 (42.4) | 0 (0.0) | | | |
| SRC | 163 (57.6) | 0 (0.0) | | | |
| Depth of invasion (n, %) | | | 0.172 | | |
| Mucosa | 196 (69.3) | 14 (56.0) | | | |
| Submucosa | 87 (30.7) | 11 (44.0) | | | |
| Treatment ($n$, %) | | | 0.437 | | |
| ER | 81 (28.6) | 9 (36.0) | | | |
| Operation | 202 (71.4) | 16 (64.0) | | | |
| Lymphovascular invasion ($n$, %) | | | 0.504 | | |
| Yes | 23 (8.1) | 3 (12.0) | | | |
| No | 260 (91.9) | 22 (88.0) | | | |
| Perineural invasion ($n$, %) | | | 0.605 | | |
| Yes | 3 (1.1) | 0 (0.0) | | | |
| No | 280 (98.9) | 25 (100.0) | | | |

Histologic discrepancy (bold) was determined by comparing the pathology between initial biopsy and final resected specimen

*ER* endoscopic resection, *AWD* adenocarcinoma well differentiated, *AMD* adenocarcinoma moderate differentiated, *APD* adenocarcinoma poorly differentiated, *SRC* signet ring cell carcinoma, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation

In the gastrectomy group, 20% of the patients among those who had differentiated-type EGC on initial biopsy and histologic discrepancy were eligible for ER. In patients with undifferentiated-type EGC on initial biopsy and histologic discrepancy, 50% of patients were included in the indication of ER. Therefore, among patients with histologic discrepancy in the gastrectomy group, about 40% of them were included in the indication for ER. This means that the opportunity was missed to preserve the stomach in patients who could be treated with ER, which

would improve their quality of life. Therefore, these results support the importance of reducing histologic discrepancy.

The limitations of our study are as follows. First, selection bias may be present in this single-center retrospective study. Second, the lack of consistency about biopsy is present, such as number of biopsies, technique of endoscopist and location of biopsies. The number of biopsies was not included in the study because the number of initial biopsies was not confirmed, including among patients who received the pathology slide after undergoing biopsy at another hospital. Third, endoscopy with biopsy was performed by a number of different physicians in this study. In addition, different endoscopic forceps were used to perform biopsies among the included patients. Despite these limitations, this study is useful because we included patients who underwent ER as well as gastrectomy, and we investigated the treatment progress of patients.

There are a variety of options for reducing histologic discrepancy, to better guide the patient's treatment direction. If the predictive factors for histologic discrepancy in UD-EGC are known, we can consider circumferential mapping biopsy before ER or wide marking during ER. [14, 24, 25] If a patient has a predictive factor for histologic discrepancy in D-EGC, there may be several options, such as rebiopsy or ER before gastrectomy.

In addition to these procedural aspects, determining the ideal number of biopsies to reduce histological discrepancies or performing a prospective investigation, as in the case of AMD and APD, to determine whether re-examination is necessary could help in choosing the patient's treatment, which could have an impact on the treatment progress. However, according to a previous mapping study, the biopsy site was more important than the number of biopsies in reducing histologic discrepancy. That study reported that a zone of transition from differentiated to undifferentiated-type histology was usually found; therefore, it may be helpful to perform biopsies at several peripheral sites of the lesion for an exact histological diagnosis in EGC [26]. In addition, targeted biopsy using IEE may be helpful, to decrease histologic discrepancy.

In conclusion, about 10% of patients diagnosed with EGC showed histologic discrepancy between biopsy and the final resection, including ER and gastrectomy. Histologic discrepancy can affect treatment outcomes: e.g., non-curative resection in ER versus missing the opportunity for ER in patients who undergo gastrectomy. If the initial biopsy reveals AMD or APD, there is a possibility of histologic discrepancy. Therefore, improving pathologic accuracy is critical in providing patients with the best treatment option.

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## References

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L (2017) Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 3:524–548
2. Eom BW, Jung K-W, Won Y-J, Yang H, Kim Y-W (2018) Trends in gastric cancer incidence according to the clinicopathological characteristics in Korea, 1999-2014. Cancer Res Treat 50:1343
3. Jung K-W, Won Y-J, Oh C-M, Kong H-J, Lee DH, Lee KH (2017) Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014. Cancer Res Treat 49:292
4. Choi IJ (2009) Gastric cancer screening and diagnosis. Korean J Gastroenterol 54:67–76
5. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y (2000) Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 3:219–225
6. Association JGC (2011) Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 14:113–123
7. Takao M, Kakushima N, Takizawa K, Tanaka M, Yamaguchi Y, Matsubayashi H, Kusafuka K, Ono H (2012) Discrepancies in histologic diagnoses of early gastric cancer between biopsy and endoscopic mucosal resection specimens. Gastric Cancer 15:91–96
8. Shim CN, Kim H, Kim DW, Chung HS, Park JC, Lee H, Shin SK, Lee SK, Lee YC (2014) Clinicopathologic factors and outcomes of histologic discrepancy between differentiated and undifferentiated types after endoscopic resection of early gastric cancer. Surg Endosc 28:2097–2105
9. Lee I-S, Park Y-S, Lee JH, Park JY, Kim H-S, Kim B-S, Yook J-H, Oh S-T, Kim B-S (2013) Pathologic discordance of differentiation between endoscopic biopsy and postoperative specimen in mucosal gastric adenocarcinomas. Ann Surg Oncol 20:4231–4237
10. Joo M, Kim K-M (2014) Histologic discrepancy between gastric biopsy and resection specimen in the era of endoscopic treatment for early gastric cancer. Korean J Gastroenterol 64:256–259
11. Bosman FT, Carneiro F, Hruban RH, Theise ND (2010) WHO classification of tumours of the digestive system. World Health Organization, Geneva
12. Kim WH, Park CK, Kim YB, Kim YW, Kim HG, Bae HI, Song KS, Chang HK, Chang HJ, Chae YS (2005) A standardized pathology report for gastric cancer. Korean J Pathol 39:106–113
13. Association JGC (2011) Japanese classification of gastric carcinoma: 3rd english edition. Gastric Cancer 14:101–112
14. Min B-H, Kang KJ, Lee JH, Kim ER, Min YW, Rhee P-L, Kim JJ, Rhee JC, Kim K-M (2014) Endoscopic resection for undifferentiated early gastric cancer: focusing on histologic discrepancies between forceps biopsy-based and endoscopic resection specimen-based diagnosis. Dig Dis Sci 59:2536–2543
15. Kim JH, Kim YJ, An J, Lee JJ, Cho JH, Kim KO, Chung J-W, Kwon KA, Park DK, Kim JH (2014) Endoscopic features

suggesting gastric cancer in biopsy-proven gastric adenoma with high-grade neoplasia. World J Gastroenterol 20:12233
16. Park JS, Hong SJ, Han JP, Kang MS, Kim HK, Kwak JJ, Ko BM, Cho JY, Lee JS, Lee MS (2013) Early-stage gastric cancers represented as dysplasia in a previous forceps biopsy: the importance of clinical management. Dig Liver Dis 45:170–175
17. Okada K, Fujisaki J, Yoshida T, Ishikawa H, Suganuma T, Kasuga A, Omae M, Kubota M, Ishiyama A, Hirasawa T (2012) Long-term outcomes of endoscopic submucosal dissection for undifferentiated-type early gastric cancer. Endoscopy 44:122–127
18. Kang HY, Kim SG, Kim JS, Jung HC, Song IS (2010) Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Surg Endosc 24:509–516
19. Kim J-H, Lee YC, Kim H, Song KH, Lee SK, Cheon JH, Kim H, Hyung WJ, Noh SH, Kim CB (2009) Endoscopic resection for undifferentiated early gastric cancer. Gastrointest Endosc 69:e1–e9
20. Ninomiya Y, Yanagisawa A, Kato Y, Tomimatsu H (2000) Unrecognizable intramucosal spread of diffuse-type mucosal gastric carcinomas of less than 20 mm in size. Endoscopy 32:604–608
21. Katsube T, Konnno S, Hamaguchi K, Shimakawa T, Naritaka Y, Ogawa K, Aiba M (2005) The efficacy of endoscopic mucosal resection in the diagnosis and treatment of group III gastric lesions. Anticancer Res 25:3513–3516
22. Kim J-H, Kim YH, Jung DH, Jeon HH, Lee YC, Lee H, Lee SK, Park JC, Shin SK, Youn YH (2014) Follow-up outcomes of endoscopic resection for early gastric cancer with undifferentiated histology. Surg Endosc 28:2627–2633
23. Hahn KY, Park CH, Lee YK, Chung H, Park JC, Shin SK, Lee YC, Kim H-I, Cheong J-H, Hyung WJ (2018) Comparative study between endoscopic submucosal dissection and surgery in patients with early gastric cancer. Surg Endosc 32:73–86
24. Yao K, Anagnostopoulos G, Ragunath K (2009) Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy 41:462–467
25. Bok GH, Jeon SR, Cho JY, Cho J-H, Lee WC, Jin SY, Choi IH, Kim HG, Lee TH, Park EJ (2013) The accuracy of probe-based confocal endomicroscopy versus conventional endoscopic biopsies for the diagnosis of superficial gastric neoplasia (with videos). Gastrointest Endosc 77:899–908
26. Lee JH, Kim J-H, Rhee K, Huh CW, Lee YC, Yoon SO, Youn YH, Park H, Lee SI (2013) Undifferentiated early gastric cancer diagnosed as differentiated histology based on forceps biopsy. Pathol Res Pract 209:314–318