



Article

Assessment of the Accuracy and Clinical Impact of the Preoperative Histopathology of Resected Early Gastric Cancers

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Abstract

Background/Objectives: Superficial gastric neoplasms, including dysplasia and early adenocarcinoma, are increasingly managed by endoscopic submucosal dissection (ESD). Preoperative assessment relies on endoscopic forceps biopsy (EFB), despite its limited ability to predict final histology. The diagnostic value of repeat biopsy, the influence of the endoscopy setting where biopsies were taken, and the clinical relevance of histologic discrepancies remain incompletely defined. **Methods:** We conducted a retrospective, single-center study of 270 superficial gastric lesions resected by ESD between 2015 and 2024. Histologic concordance between EFB and ESD was evaluated, including comparisons between initial and repeated biopsies, and between community- and hospital-based settings. Multivariable models identified predictors of histologic discrepancy and assessed the impact of underestimation on curative resection. The association between biopsy repetition and submucosal fibrosis was also explored. **Results:** Histologic concordance between EFB and ESD was 54.1%, with underestimation in 41.1% and severe underestimation in 8.9%. Repeat biopsy improved concordance from 39.3% to 60.7% ($p = 0.007$) and increased adenocarcinoma sensitivity from 12.5% to 56.3%, without increasing submucosal fibrosis. Hospital-based biopsies outperformed community-based ones across all diagnostic metrics. In multivariable analysis, older age and larger lesion size were independent predictors of discrepancy. Histologic underestimation was independently associated with a lower likelihood of curative resection ($OR = 0.148$; $p = 0.003$), although only six lesions ultimately exceeded formal ESD criteria due to undetected high-risk features. **Conclusions:** EFB frequently underestimates histological severity in superficial gastric neoplasia. Repeat biopsy and centralized evaluation significantly improve diagnostic accuracy without increasing procedural risk. However, the role of biopsy lies primarily in excluding high-risk features rather than providing definitive staging. In this context, ESD serves not only as curative therapy but also as a key diagnostic step for accurate staging and treatment planning.

Keywords: stomach neoplasms/pathology; stomach neoplasms/diagnosis; Endoscopic Mucosal Resection; biopsy; endoscopic/methods; reproducibility of results



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1. Introduction

Superficial gastric neoplasms, encompassing gastric dysplasia and early adenocarcinoma, represent progressive stages within the gastric carcinogenesis cascade [1].

Endoscopic submucosal dissection (ESD) has become the preferred treatment for these lesions, offering outcomes comparable to surgical gastrectomy in cases where the risk of lymph node metastasis is presumed to be below 1% [2]. By enabling en-bloc resection and comprehensive histopathologic assessment, ESD allows for precise staging, evaluation of resection curability, and preservation of future surgical options when necessary [3].

The indication for ESD relies primarily on the exclusion of features suggestive of deep submucosal invasion, based on detailed endoscopic assessment, taking into consideration lesion size, depth of invasion, and lesion ulceration, using high-resolution imaging and chromoendoscopy, complemented by histologic characterization through endoscopic forceps biopsy (EFB) [4,5].

Despite its role, EFB has well-documented limitations in accurately predicting the final histopathologic diagnosis, largely due to sampling errors and tumor heterogeneity [6,7]. Over the past decade, numerous studies have evaluated the diagnostic concordance between EFB and ESD specimens, reporting widely variable agreement rates—from 23.7% to over 80%—depending on lesion characteristics, biopsy number, and study population [8–15]. Discrepancies most often involve upgrading from low-grade dysplasia to high-grade dysplasia or invasive carcinoma, particularly in lesions ≥ 2 cm, with features such as depression, ulceration, nodularity, or surface redness [8,9,16–25].

While these discrepancies have been associated with higher rates of non-curative resection and adverse pathology, their direct impact on therapeutic decision-making remains unclear [26–29]. Moreover, the potential benefit of biopsy repetition, the relative performance of hospital-based versus community-based endoscopists, and the association between repeated biopsy and submucosal fibrosis have been only partially explored and with inconsistent results [11,30–33].

In this context, we aimed to assess the diagnostic accuracy of the initial and the repeated EFB in predicting final ESD histology, compare concordance rates between community and expert endoscopists, and evaluate whether biopsy repetition is associated with submucosal fibrosis. Additionally, we examined the clinical impact of histologic discrepancies, particularly their association with non-curative resections and the risk of inappropriate treatment.

2. Results

From a total of 286 lesions assessed for eligibility between January 2015 and December 2024, 16 were excluded due to non-epithelial histology ($n = 6$), piecemeal resection ($n = 6$), or incomplete resection ($n = 4$). The final study cohort comprised 270 lesions from 214 patients, which were included in the subsequent analyses.

2.1. Diagnostic and Sampling Pathways

Figure 1 summarizes the diagnostic and sampling pathways. Most patients were referred following community-based EFBs, with approximately one-third undergoing repeat biopsy by a hospital-based endoscopist before ESD. In contrast, patients diagnosed within the hospital directly proceeded to ESD. These subgroups formed the basis for subsequent concordance and diagnostic performance analyses.

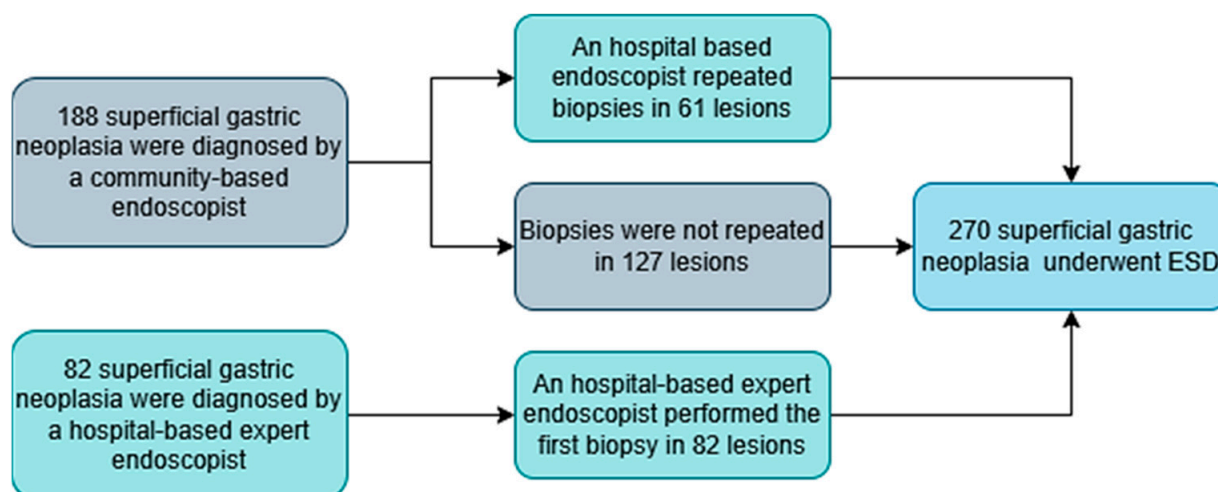


Figure 1. Diagnostic pathways prior to ESD.

2.2. Patient and Lesion Characteristics

Baseline patient and lesion characteristics are summarized in Table 1. Most lesions were in the lower third of the stomach (antrum/incisura) and exhibited flat or slightly elevated morphology (IIa/IIb, Paris Classification). On the initial biopsy, 94% of lesions were classified as dysplastic, either low-grade or high-grade, while adenocarcinoma was identified in fewer than 6%. Final histology confirmed dysplasia in most cases; however, adenocarcinoma—either intramucosal or with superficial submucosal invasion—was identified in approximately one-quarter of lesions. All biopsy samples of adenocarcinomas reported differentiated histology, and undifferentiated carcinoma was uncommon in ESD specimens (0.7%, $n = 2$). Submucosal fibrosis and ulceration were observed in 7.8% and 13.7% of lesions, respectively.

2.3. Histological Concordance and Misclassification Patterns

The first endoscopic biopsy (EFB), regardless of setting, showed limited overall concordance with final ESD histology (54.1%), with only fair agreement beyond chance ($\kappa = 0.25$). Weighted Kappa (linear = 0.32; quadratic = 0.39) indicated that most discrepancies involved adjacent categories (e.g., LGD $\rightarrow$ HGD). Underestimation was common (41.1%), including 32.2% mild and 8.9% severe underestimation. Mild overestimation occurred in 4.8% of cases, likely reflecting biopsy sampling of focal higher-grade atypia or overestimation by the pathologist. Table 2 summarizes histological concordance, agreement metrics, and the misclassification patterns of endoscopic biopsies compared with final ESD specimens.

Table 1. Baseline Patient and Lesion Characteristics.

Patient Characteristics	
Age, years	70.5 $\pm$ 9.5
Male sex, n (%)	134 (62.6)
Family history of gastric cancer, n (%)	41 (19.2)
Histological Background ^{β}	
Significant ^{Δ} atrophy, n (%)	130 (66)
Significant ^{Δ} Intestinal metaplasia, n (%)	144 (70.3)
Positive <i>Helicobacter pylori</i> infection, n (%)	52 (19.3)

Table 1. Cont.

Lesion Characteristics	
Size (pathology), mm	17.5 ± 9.1
Location, <i>n</i> (%)	
- Lower-third	205 (75.9)
- Middle-third	51 (18.9)
- Upper-third	14 (5.2)
Paris Classification Ω , <i>n</i> (%)	
- 0-IIa	197 (73.0)
- 0-IIb	41 (15.2)
- 0-Is	14 (5.2)
- 0-IIc	9 (3.3)
Histology on the first EFB, <i>n</i> (%)	
- LGD	184 (68.1)
- HGD	70 (25.9)
- ADC	16 (5.9)
Histology on ESD specimen, <i>n</i> (%)	
- LGD	113 (49.1)
- HGD	90 (33.3)
- IMC	47 (17.4)
- SMC (SM1 <i>n</i> = 4, SM2 <i>n</i> = 10, SM3 <i>n</i> = 6)	20 (7.4)
Differentiated * histology on EFB, <i>n</i> (%)	270 (100)
Undifferentiated * histology on ESD, <i>n</i> (%)	2 (0.7)
Ulceration, <i>n</i> (%)	37 (13.7)
Fibrosis, <i>n</i> (%)	21 (7.8)

EFB—Endoscopic Forceps Biopsy; ESD—Endoscopic Submucosal Dissection; HGD—High Grade Dysplasia; IMC—Intramucosal Cancer; LGD—Low Grade Dysplasia; SMC—Submucosal Cancer. β —Staging of pre-neoplastic lesions was missing in some lesions Δ —“Significant” was defined as moderate to severe atrophy/metaplasia according to the histopathology report. Ω —Paris Classification was defined according to the predominant subtype; *—Differentiated and undifferentiated histology were classified according to the Japanese Gastric Cancer Classification (15th edition), based on the predominant histologic component as described in the Methods. Continuous variables are expressed as mean (standard deviation), unless stated otherwise.

Among lesions with both an initial and repeat biopsy, internal concordance between the two was 60.7% ($\kappa = 0.24$), with modest agreement by weighted Kappa (linear = 0.27; quadratic = 0.30). Most discrepancies represented upgrades from the first biopsy (24.6% mild, 8.2% severe underestimation), while downgrades were less frequent (6.6% mild overestimation). These findings highlight substantial variability within EFB itself and a general trend toward initial underestimation—Figure 2.

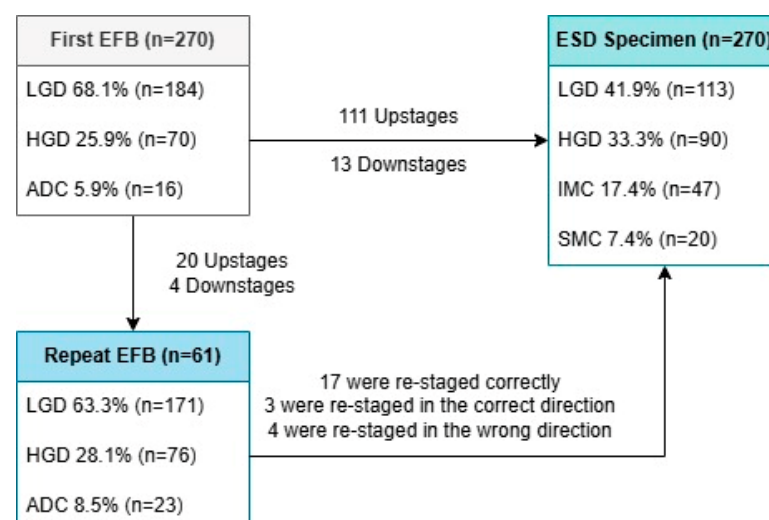


Figure 2. Concordance between initial/repeat biopsies and final ESD histology.

Table 2. Histological Concordance, Agreement Metrics, and Misclassification Patterns of Endoscopic Biopsies Compared with Final ESD Specimens.

	Overall Concordance ^Δ	LGD Concordance ^Δ	HGD Concordance ^Δ	Adenocarcinoma Concordance ^Δ	Cohen’s Kappa	Linear Kappa	Quadratic Kappa	Mild Underestimation ^Ø	Severe Underestimation ^Ø	Mild Overestimation ^Ø
First EFB and ESD	54.1% (146/270)	54.3% (100/184)	42.9% (30/70)	100% (16/16)	0.25	0.32	0.39	32.2% (87)	8.9% (24)	4.8% (13)
Repeat EFB and ESD	60.7% (37/61)	85.0% (17/20)	44.0% (11/25)	56.3% (9/16)	0.40	0.50	0.60	31.1% (19)	3.3% (2)	4.9% (3)
First EFB and Repeat EFB	60.7% (37/61)	63.8% (30/47)	50.0% (6/12)	50.0% (1/2)	0.24	0.27	0.30	24.6% (15)	8.2% (5)	6.6% (4)
Community EFB and ESD	51.6% (97/188)	89.7% (70/78)	27.3% (18/66)	20.6% (9/44)	0.21	0.28	0.36	35.1% (66)	9.0% (17)	4.3% (8)
Hospital EFB and ESD	60.1% (86/143)	85.5% (47/55)	46.9% (23/49)	41% (16/39)	0.38	0.45	0.53	28.0% (40)	6.3% (9)	5.6% (8)

EFB—Endoscopic Forceps Biopsy; ESD—Endoscopic Submucosal Dissection; HGD—High Grade Dysplasia; LGD—Low Grade Dysplasia. Values are presented as % (*n*) unless otherwise specified. All Cohen’s kappa values and weighted kappa statistics were statistically significant (*p* < 0.05). ^Δ—Concordance represents the proportion of cases in which the EFB matched the final histological classification by ESD. For example, an adenocarcinoma concordance of 100% (16/16) indicates that all lesions classified as adenocarcinoma on biopsy were confirmed as adenocarcinoma in the ESD specimen. It is important to note that this reflects a positive predictive value rather than sensitivity: there may be additional adenocarcinomas not identified by EFB, which would be captured in sensitivity analyses (see Table 3). ^Ø—Underestimation refers to biopsy undercalling lesion severity relative to ESD (e.g., diagnosing LGD when final pathology is HGD or adenocarcinoma). Overestimation refers to overcalling severity (e.g., biopsy indicates HGD, but final histology shows LGD). Mild was defined as a one-step downgrade/upgrade in lesion severity (LGD misclassified as HGD, or HGD as adenocarcinoma), while severe referred to a two-step upgrade/downgrade (LGD directly misclassified as adenocarcinoma). Mild underestimation = LGD → HGD or HGD → adenocarcinoma. Severe underestimation = LGD → adenocarcinoma. Mild overestimation = adenocarcinoma → HGD or HGD → LGD. Severe overestimation was not observed in this study.

Table 3. Diagnostic Performance of Endoscopic Biopsy Strategies Compared with Final Histology from ESD.

Biopsy Strategy (vs. ESD)		Sensitivity	Specificity	Positive LR	Negative LR	OR [95% CI]
LGD	First EFB	88.5%	46.5%	1.65	0.25	6.69 [3.46–12.90]
	Repeat EFB	85.0%	61.0%	2.18	0.25	8.85 [2.23–35.14]
	Community EFB	89.7%	40.9%	1.52	0.25	6.06 [2.66–13.81]
	Hospital EFB	85.5%	60.2%	2.15	0.24	8.90 [3.76–21.07]
HGD	First EFB	33.3%	77.8%	1.50	0.86	NS
	Repeat EFB	44.0%	77.8%	1.98	0.72	NS
	Community EFB	27.3%	78.7%	1.28	0.92	NS
	Hospital EFB	46.9%	76.6%	2.00	0.69	2.90 [1.39–6.05]
ADC	First EFB	23.9%	100%	∞	0.76	RR Δ 1.31 [1.15–1.50]
	Repeat EFB	56.3%			0.44	RR Δ 2.29 [1.31–3.98]
	Community EFB	20.5%			0.80	RR Δ 6.00 [1.08–1.46]
	Hospital EFB	41.0%			0.59	RR Δ 1.70 [1.31–2.20]

ADC—Adenocarcinoma. CI—Confidence Interval; EFB—Endoscopic Forceps Biopsy; ESD—Endoscopic Submucosal Dissection. HGD—High Grade Dysplasia; LGD—Low Grade Dysplasia; LR—Likelihood Ratio; NS—Not Significant ($p > 0.05$); OR—Odds ratio; RR—Relative Risk. This table includes all cases in the dataset, regardless of biopsy setting or repetition, and serves as a descriptive summary. Formal statistical comparisons were conducted separately using per-patient models. Because all lesions classified as adenocarcinoma on biopsy were confirmed on ESD (absence of false positives), specificity was 100%, and LR+ and OR were infinite for all strategies. AUC metrics were not included, as each biopsy strategy represents a fixed diagnostic classification rather than a continuous scoring system amenable to ROC curve analysis. Δ —Instead of OR, RRs were reported to reflect the relative probability of absence of adenocarcinoma on final histology between patients with negative vs. positive biopsy result.

2.4. Diagnostic Performance Summary

Diagnostic performance metrics across all biopsy strategies are summarized in Table 3. These results are based on the full dataset, including cases with repeated and dual-setting biopsies, and are intended to provide a descriptive overview of diagnostic behavior across strategies. Sensitivity for LGD remained consistently high (85–89%), though specificity was modest (46–61%). For HGD and adenocarcinoma, sensitivity varied more substantially depending on the biopsy strategy. Sensitivity for adenocarcinoma increased from 23.9% with the first biopsy to 56.3% with repeat biopsy and was higher in hospital-based compared to community-based settings (41.0% vs. 20.6%), while specificity remained 100% across all strategies. Odds ratios for correct LGD classification were significantly higher with repeat (OR = 8.85, 95% CI: 2.23–35.14) and hospital-based biopsies (OR = 8.90, 95% CI: 3.76–21.07), supporting the improved diagnostic yield of these approaches. Although statistically significant, the wide confidence intervals suggest imprecision, likely reflecting limited sample size for repeated biopsy cases. Given the exploratory nature of these comparisons, no correction for multiple testing was applied.

2.5. Repeat Biopsy Improves Diagnostic Agreement

Among the 61 lesions with repeated biopsies, concordance with final ESD histology improved from 39.3% to 60.7% (McNemar's test, $p = 0.007$). Cohen's kappa improved significantly from 0.078 (first biopsy) to 0.400 (repeat biopsy), indicating a shift from poor to moderate agreement ($Z = 2.39$, $p = 0.017$). Classification errors decreased from 60.7% to 39.3%, with 20 cases gaining and 4 losing concordance after repetition. Severe underestimation dropped from 16.4% to 3.3%, while mild under- and overestimation remained stable. Misclassification patterns shifted significantly ($\chi^2 = 31.677$, $p < 0.001$), with a clear trend toward milder or no errors ($\chi^2 = 15.706$, $p < 0.001$).

By histological subtype, repeat biopsy was associated with improved diagnostic sensitivity, particularly for adenocarcinoma, suggesting a potential benefit in cases with high suspicion (sensitivity: 12.5% $\rightarrow$ 56.3%, $p = 0.039$), while maintaining perfect specificity. For LGD, sensitivity remained high (85%), but specificity increased substantially (26.8% $\rightarrow$ 60.9%), improving LR+ and OR significantly (OR = 8.85, $p < 0.001$). For HGD, sensitivity improved (20.0% $\rightarrow$ 44.0%, $p = 0.070$), with a corresponding OR increase (1.04 $\rightarrow$ 2.75,

$p = 0.094$). Given the exploratory nature of these multiple comparisons, no correction for multiple testing was applied. Accordingly, p -values should be interpreted with caution.

2.6. Comparison by Setting

To compare the diagnostic performance of community versus hospital-based biopsies, two complementary analytic approaches were used as previously described, using a refined per-lesion dataset where each patient was assigned to either group.

In the strict per-lesion model, each patient was assigned to a single biopsy group based on the first available EFB, regardless of setting. In this analysis, hospital-based biopsies showed numerically higher concordance across all histological categories. Sensitivity for HGD was significantly greater in the hospital group (50.0% vs. 27.3%, $p = 0.044$; OR = 3.14, 95% CI: 1.16–8.55), and for adenocarcinoma, it was also higher (30.4% vs. 20.5%), though the difference was not statistically significant. Specificity was 100% in both groups. However, no significant differences were observed in overall concordance, kappa values, or misclassification patterns.

The second approach—the hospital-priority model—simulated real-world clinical practice by prioritizing the hospital-based expert biopsy whenever both were available. In this model, patients with dual EFBs were assigned to the hospital group, and community biopsies were excluded from analysis. Using this method, diagnostic performance was further improved: concordance for HGD and adenocarcinoma reached 46.9% and 41.0%, respectively, compared to 10.2% and 5.5% in the community group. Statistically significant gains (Fisher exact test; univariate logistic regression) were observed in sensitivity and odds ratios for both histological categories, while overall concordance and misclassification rates remained comparable. No correction for multiple comparisons was applied in this exploratory analysis; p -values should be interpreted with caution. Baseline lesion characteristics were similar between groups across most categories, with statistically significant differences in sex, H. Pylori and significant metaplasia in the strict per-lesion model and in H. Pylori, significant atrophy and metaplasia in the hospital priority model (Supplementary Table S1).

2.7. Predictors of Histologic Discrepancy

We assessed potential predictors of histological discrepancy using univariate and multivariate analyses (Table 4). In univariate comparisons, older age, larger lesion size, and the presence of ulceration were significantly associated with diagnostic discordance ($p < 0.05$). No significant associations were observed for sex, H. pylori status, lesion location, year of ESD, time between biopsy and ESD or background mucosal features such as atrophy, metaplasia, or fibrosis.

To account for clinically relevant factors potentially contributing to sampling error—even in the absence of statistically significant univariate associations—we included age, lesion size, ulceration, Paris classification, and lesion location in the multivariate logistic regression model. In this adjusted analysis, older age (OR = 1.05, 95% CI: 1.02–1.08, $p = 0.004$) and larger lesion size (OR = 1.06, 95% CI: 1.02–1.09, $p = 0.001$) were independently associated with a higher risk of histologic discrepancy. Ulceration and Paris classification demonstrated borderline associations ($p = 0.080$ and $p = 0.058$, respectively), whereas lesion location was not independently associated with discordance ($p = 0.830$). In post hoc comparisons, lesions located in the fundus and corpus were independently associated with discrepancy ($p = 0.007$ and $p = 0.039$, respectively).

Table 4. Predictors of Histologic Discrepancy between Initial Biopsy and ESD.

Variable	Concordant (n = 146)	Discordant (n = 124)	Univariate <i>p</i> -Value	Multivariate OR (95% CI)	Multivariate <i>p</i> -Value
Age (years)	69.2 ± 9.4	72.9 ± 9	0.001 (<i>t</i> -test)	1.05 (1.02–1.08)	0.004
Positive Family history of Gastric Cancer	15.8%	19.8%	0.383 (Chi-square)	—	—
Sex (Male)	61.6%	60.5%	0.846 (Chi-square)	—	—
H. pylori (positive)	21.2%	16.9%	0.372 (Chi-square)	—	—
Atrophy (significant)	67.6%	64.2%	0.611 (Chi-square)	—	—
Metaplasia (significant)	67.9%	72.7%	0.452 (Chi-square)	—	—
Lesion size (mm)	15.5 ± 7.3	19.8 ± 10.3	<0.001 (<i>t</i> -test)	1.06 (1.02–1.09)	0.001
Ulceration (yes)	8.2%	20.2%	0.004 (Chi-square)	—	0.08
Paris classification	Is/IIa/IIb/IIc	Is/IIa/IIb/IIc	0.184 (Chi-square)	—	0.058
Location (upper/middle/lower)	5.5%/17.8%/76.7%	4.8%/20.2%/75.0%	0.871 (Chi-square)	—	0.83
Year of ESD	2021 (5)	2022 (4)	0.185 (Mann–Whitney U)	—	—
Fibrosis (yes)	9.6%	5.6%	0.228 (Chi-square)	—	—
Time from biopsy to ESD (months)	6.6 ± 4.84	7.9 ± 14.3	0.344 (<i>t</i> -test)	—	—

OR, odds ratio; CI, confidence interval; ESD, endoscopic submucosal dissection. *p*-value refers to two-sided significance level for each comparison (0.05). Paris classification subtypes: Is (sessile), IIa (slightly elevated), IIb (flat), IIc (depressed). Location categories: upper (upper third), middle (middle third), lower (lower third). Multivariate odds ratios are adjusted for all variables listed in the model.

2.8. Submucosal Fibrosis

Fibrosis, assessed both histologically and endoscopically during ESD, was identified in 21 lesions (7.8%). Its frequency was lower among cases with repeat biopsy compared to single-biopsy cases (3.3% vs. 9.1%), although the difference did not reach statistical significance (Fisher's exact test, $p = 0.178$). Among the lesions that underwent repeat biopsy, we assessed whether the number of biopsy fragments correlated with submucosal fibrosis. The median number of biopsy samples (med = 1, range 1–5) did not significantly differ between lesions with and without fibrosis ($p = 0.152$, Mann–Whitney U test). Likewise, in univariable logistic regression, the number of biopsy fragments was not significantly associated with the presence of fibrosis (OR per fragment = 1.12, $p = 0.350$).

2.9. Treatment Outcomes

The main therapeutic outcomes are summarized in Table 5. To assess the clinical relevance of histologic discrepancy between initial biopsy and final ESD diagnosis, we analyzed its association with curative resection. Among 270 lesions, curative resection was achieved in 91.5% of cases overall, but this rate varied significantly by discrepancy type ($\chi^2 = 17.998$, $p < 0.001$). It was highest in concordant cases (97.3%, 142/146) and lower in cases with histological underestimation (82.9%, 92/111). All overestimated cases (13/13) were curative.

Table 5. Treatment Outcomes.

Treatment Outcomes	% (n)
R0 resection	94.4% (n = 255/270)
R1 resection	3.3% (n = 9/270)
Rx resection	2.2% (n = 6/270)
Risk stratification	
Very low/eCura A	87.4% (236/270)
Low/eCura B	0.7% (2/270)
High/eCura C2	8.5% (23/270)
Local/eCura C1	3.3% (9/270)
Submitted to surgery	5.6% (15/270)
Local disease in the surgical specimen	n = 7
LMN on the surgical specimen	n = 2
LMN on the watch-and-wait strategy	n = 0
Death by gastric cancer	n = 0

LMN: lymph node metastasis. Risk stratification is defined according to ESGE and JGCA criteria. R0 resection: complete resection with negative horizontal and vertical margins; R1 resection: incomplete resection due to histologically positive margins; Rx resection: resection with indeterminate margin status.

In multivariable logistic regression adjusting for ulceration, Paris classification, differentiation, lesion size, and location, histologic underestimation remained independently associated with reduced odds of curative resection (OR = 0.148; 95% CI: 0.042–0.529; $p = 0.003$). Ulceration and non-distal location were also strong negative predictors (OR = 0.140; 95% CI: 0.043–0.449; $p = 0.001$) (OR = 0.077; 95% CI: 0.015–0.402; $p = 0.002$). Patients who underwent repeat biopsy had a numerically lower rate of curative resection (86.9% vs. 92.8%), although the difference was not statistically significant ($\chi^2 = 2.136$, $p = 0.144$).

2.10. Clinical Impact of Underestimation

Among the 111 lesions underestimated by the initial biopsy, 6 cases represented instances of potential overtreatment. Notably, lesion size was a key determinant of clinically relevant underestimation. Larger lesions not only showed higher rates of histologic discrepancy but also accounted for the majority of cases in which underestimation resulted in non-curative resection, thereby potentially altering the optimal therapeutic approach.

Two lesions initially classified as low- and high-grade dysplasia were ultimately diagnosed as undifferentiated adenocarcinomas on the ESD specimen, both estimated and confirmed to exceed 20 mm in size—thus meeting formal criteria for surgical resection according to JGCA and ESGE guidelines. An additional four ulcerated lesions, each measuring ≥ 30 mm, were also underestimated on initial biopsy (diagnosed as low- or high-grade dysplasia), but were subsequently upstaged to adenocarcinoma on final pathology, placing them outside the standard indications for curative ESD.

3. Discussion

This study highlights the diagnostic limitations of EFB in the preoperative assessment of superficial gastric neoplasms. Histological discrepancy was frequent (45.9%) and predominantly driven by underestimation (41.1%). This misclassification had measurable therapeutic consequences, particularly through its association with a lower likelihood of curative resection (78.4% vs. 94.5%).

Most discrepancies involved upgrades from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) or adenocarcinoma, including a non-negligible proportion of severe underestimation (8.9%). These patterns are consistent with prior reports, which describe histologic upgrading in 12% to over 60% of LGD cases, and adenocarcinoma rates of 11–25% in lesions initially classified as LGD [8,9,16,21,23,28], emphasizing the limitations of focal sampling in lesions with heterogeneous histologic architecture. However, the distinction between high-grade dysplasia and intramucosal carcinoma remains a topic of debate. Western pathology frameworks often require unequivocal evidence of invasion into the lamina propria to define carcinoma, whereas Japanese classifications may base the diagnosis on cytologic and architectural atypia alone, even in the absence of clear invasion. Given that both diagnoses typically warrant complete resection, some authors do not consider this transition a true discrepancy, particularly when management is unaffected. Furthermore, interobserver variability and biopsy sampling limitations may account for much of the observed discordance [34]. Cases with apparent downgrading of histologic grade merit careful correlation of endoscopic, biopsy, and procedural information. Potential mechanisms include complete removal of neoplastic tissue during forceps biopsy—especially for flat lesions—mismatch between biopsy and ESD sites, and interpretive discrepancies due to sampling artifacts. In our series, downgraded cases were rare and none showed adverse outcomes, yet these findings underscore the need for rigorous evaluation when biopsy-to-resection downgrade occurs.

Higher lesion size and older age emerged as independent predictors of histological discrepancy. These factors have been consistently associated with misclassification in

multiple studies and likely reflect greater histological complexity and malignant potential [16,19,21,25,28,33]. Lesion location, time to resection, and background mucosal changes did not show significant associations in our cohort, suggesting that intrinsic lesion characteristics may play a more prominent role than contextual or temporal factors. Although gastric location was not an independent predictor of discrepancy in our multivariable analysis, the predominance of Paris IIa lesions in the distal stomach with differentiated histology likely contributed to the concordance observed. This selection pattern may limit the generalizability of our findings to lesions with more complex morphology, upper/proximal location, or undifferentiated histology, which are known to pose even greater diagnostic challenges.

Repeat biopsy significantly improved diagnostic accuracy. The concordance rate increased from 39.3% to 60.7%, with a marked rise in sensitivity for adenocarcinoma and a fourfold reduction in severe underestimation. These results mirror those of Jeon and colleagues [30], who showed that increasing the number of samples enhances diagnostic yield. Concerns that repeated sampling might induce submucosal fibrosis and complicate resection were not confirmed in our data; fibrosis was numerically less frequent in the re-biopsied group. Similar findings from Choi support the safety of re-biopsy when clinically justified, particularly in the setting of discordant endoscopic and histologic findings [28,35].

The setting in which biopsies were performed had a marked impact on diagnostic performance. Hospital-based biopsies outperformed community-based ones across multiple parameters, even when adjusted for lesion characteristics. In both per-lesion and clinically weighted analyses, hospital-based expert biopsies showed higher sensitivity for HGD and adenocarcinoma. These findings support the referral of patients with ambiguous lesions to high-volume centers not only for therapeutic purposes but also for diagnostic reassessment. Studies by Takao, Lim, and Lee have similarly demonstrated that biopsy quality and interpretative consistency are greater in specialized settings [13,32,36].

Histologic underestimation was associated with a significantly lower rate of curative resection, even after adjusting for lesion size, ulceration, and morphology, consistent with the findings of Yeo [26]. However, in practical terms, this resulted in overtreatment in only six cases that exceeded formal ESD criteria, due to undetected undifferentiated histology or under-staging of ulcerated adenocarcinomas. This raises the question of how clinically consequential histologic discrepancies truly are.

Notably, lesion size was a key determinant of clinically relevant underestimation. Larger lesions not only showed higher rates of histologic discrepancy but also accounted for most cases where underestimation resulted in non-curative resection. This highlights the particular need for meticulous preoperative assessment in larger or morphologically complex lesions.

Although biopsy–resection discordance is frequently reported, the primary role of preoperative biopsy is to identify features that contraindicate ESD—namely undifferentiated histology and large ulcerated adenocarcinomas. Upgrading from LGD to HGD or to differentiated, non-ulcerated adenocarcinoma is relatively common but seldom alters management when resection is already indicated based on endoscopic features. Therefore, the clinical impact of histological discrepancy may be overstated, particularly when it does not cross therapeutic thresholds. Moreover, previous studies suggest that even non-curative ESD may offer acceptable oncologic outcomes in selected patients, provided that appropriate follow-up or salvage surgery is ensured [34].

Nonetheless, this study also has limitations. Because only lesions that proceeded to ESD were included, we were unable to evaluate cases in which the initial or the repeat biopsy may have led to appropriate or inappropriate exclusion from resection. Similarly, the exclusion of lesions without dysplasia or adenocarcinoma on the final histology limits inferences regarding overdiagnosis. Additionally, the lower prevalence of ulcerated,

undifferentiated-type, and malignant lesions may have attenuated the true clinical impact of histological underestimation. Furthermore, external biopsy specimens were not centrally reviewed, which may have introduced variability in histologic interpretation, limiting our ability to fully discern whether the discordance reflects overdiagnosis, sampling variation, or procedural artifacts. Nevertheless, this cohort is among the largest Western series examining histologic concordance between EFB and ESD, and is distinctive in its evaluation of operator experience, the diagnostic contribution and implications of repeat biopsy, and the broader clinical implications of misclassification beyond curative resection rates.

4. Materials and Methods

4.1. Patients and Study Design

This retrospective, single-center study was conducted using a prospectively maintained registry of ESD procedures performed at Unidade Local de Saúde Gaia Espinho, a tertiary referral center in Portugal. The study included consecutive patients diagnosed with superficial gastric neoplasms who underwent ESD between January 2015 and December 2024.

Superficial gastric neoplasms were defined and managed according to established criteria from the Japanese Gastric Cancer Association (JGCA) [4] and the European Society of Gastrointestinal Endoscopy (ESGE) [5].

All lesions were sampled by EFB before ESD, either in a community or hospital setting. Cases with incomplete clinical or pathological data, piecemeal or non-evaluable resections, and non-epithelial lesions were excluded.

4.2. Pre-ESD Evaluation

Patients with suspected gastric dysplasia or early adenocarcinoma were referred for pre-ESD evaluation by an expert advanced endoscopist. All examinations were conducted using high-definition endoscopes equipped with virtual chromoendoscopy capabilities and dye-based chromoendoscopy was used at the endoscopist's clinical discretion. Lesion size was assessed endoscopically during the evaluation; however, the reported size corresponds to the histologic measurement on the resected ESD specimen. Tumor location was classified into the lower third (antrum and incisura), middle third (corpus), and upper third (cardia/fundus/proximal corpus). Morphology was categorized according to the Paris classification [36], and the presence of ulceration was systematically recorded. Metaplasia was assessed using the EGGIM scoring system [37].

The time interval (in days) between the first diagnostic EFB and ESD was recorded, along with the number of biopsy fragments obtained during EFB. Community-based EFBs were defined as those performed in external institutions before hospital referral. Most included prior staging of precancerous conditions (atrophy and intestinal metaplasia) and lesion-targeted biopsies. Repeat biopsies targeting the most suspicious area of the lesion were performed at the discretion of an expert hospital-based endoscopist, particularly when there was discordance between initial EFB findings and endoscopic appearance, or when high-risk features such as ulceration or depressed morphology were present. Patients whose lesions were first identified and diagnosed at our center underwent biopsy exclusively by expert hospital-based endoscopists. The same applied to cases in which dysplasia had been detected by community-based endoscopists through random biopsies, without documentation of an endoscopically visible lesion. These random EFB histologies were excluded from analysis, as no defined target lesion had been identified.

4.3. ESD Procedure

ESDs were performed by three expert endoscopists under general anesthesia with orotracheal intubation. High-definition endoscopes equipped with chromoendoscopy were

used in all cases. The selection of electrosurgical knives, injection solutions, and traction techniques was individualized according to lesion characteristics and endoscopist preference. ESD followed standardized steps [38]: circumferential marking, submucosal injection, mucosal incision, and submucosal dissection. Resected specimens were stretched, pinned onto cork boards to maintain orientation, and fixed in 10% buffered formalin for histopathological evaluation. Data regarding performance measures was prospectively recorded.

4.4. Histopathology Evaluation

Slide review of external biopsy specimens was not performed systematically.

All biopsy and ESD specimens obtained at our center were evaluated by an experienced gastrointestinal pathologist. Resected specimens were entirely submitted, sectioned at 2 mm intervals and assessed for tumor size, histological type, tumor depth, macroscopic type, presence of ulcerative findings, fibrosis, and margin status (lateral and vertical). Additionally, differentiation status, including mixed histologic components, as well as lymphatic, vascular, and perineural invasion, were systematically evaluated.

Histological typing and grading followed the modified Vienna classification of epithelial neoplasia [39] and the CAP/AJCC [40] recommendations: tumors were categorized by histologic type according to WHO [41] and Lauren [42] and graded using WHO. Grading was applied only to tubular and papillary adenocarcinomas (low grade, G1–G2; high grade, G3). Mucinous adenocarcinomas were not graded. Poorly cohesive/signet-ring cell carcinomas were considered high grade (G3). In lesions with mixed histologic components, classification was based on the quantitatively predominant component, with all components recorded in order of predominance when relevant. Submucosal invasion was subclassified as superficial (SM1) if the depth was less than 500 µm from the muscularis mucosae. Lymphatic and vascular invasion were initially assessed on hematoxylin and eosin (H&E) stained sections; if findings were inconclusive, additional immunohistochemical staining was performed.

4.5. Definitions and Outcomes

Histologic concordance was defined as an identical diagnostic category—low-grade dysplasia (LGD), high-grade dysplasia (HGD), or adenocarcinoma (ADC). Concordance regarding carcinoma differentiation (well-, moderately, or poorly/undifferentiated) was assessed separately. Discrepancies were categorized as upgrading (toward higher-grade histology or poorer differentiation) or downgrading (toward lower-grade histology or better differentiation). Discrepancy classification was based on the severity and direction of misclassification between biopsy and ESD histology. Mild discrepancy was defined as a one-step upgrade or downgrade in histological severity: for example, LGD misclassified as HGD, or HGD as adenocarcinoma. Severe discrepancy was defined as a two-step misclassification, such as LGD directly misclassified as adenocarcinoma.

Underestimation referred to biopsy undercalling lesion severity (e.g., LGD → HGD or adenocarcinoma), while overestimation indicated a more severe diagnosis on biopsy than in the final ESD specimen (e.g., adenocarcinoma → HGD or HGD → LGD).

Concordance was assessed both between EFB specimens (when more than one was available) and between EFB and the final ESD specimen. In lesions with repeated biopsies, the comparison with ESD was based on the histologic result from the first biopsy. To account for non-independence in patients with multiple EFBs, analyses requiring independence (e.g., community vs. hospital) were conducted separately using both first and repeat EFB data.

To assess the impact of the endoscopy setting where the EFB was obtained, two complementary approaches were employed. The first was a strict per-lesion analysis, in which

only the first available biopsy was considered for each lesion, regardless of setting. This enabled an unbiased comparison of initial diagnostic performance between community and hospital-based biopsies. The second, a “hospital-priority model”, simulated routine clinical decision-making by prioritizing the hospital-based expert biopsy when both were available. In this model, patients with both community and hospital biopsies were classified under the hospital group, and the community biopsy was excluded. These two strategies were used to compare histological concordance with final ESD diagnosis, agreement coefficients, misclassification patterns, and diagnostic performance metrics (sensitivity, specificity, likelihood ratios, and odds ratios) across endoscopy settings.

Fibrosis was defined as the presence of dense collagen deposition within the submucosal layer of the ESD specimen, identified either histologically on hematoxylin and eosin (H&E) staining or based on the endoscopist’s impression during submucosal dissection.

Curative resection was defined according to JGCA and ESGE criteria and classified using the eCura system [4,5]. Radiological staging and surveillance followed the same guidelines. Cases of non-curative resection were discussed in a multidisciplinary team meeting, and further surgical treatment was recommended based on international guidelines, clinical judgment, and patient functional status. Follow-up data, when available, included local recurrence, lymph node metastasis, and gastric cancer-related death.

In cases where the initial biopsy appeared concordant with endoscopic findings and would not alter the planned management (e.g., proceeding to ESD was already indicated), repeat biopsy was not routinely pursued.

4.6. Statistical Analysis

Categorical variables were summarized as counts and percentages, and continuous variables as means (SD) or medians (IQR), depending on distribution.

Histological concordance between EFB and ESD specimens was assessed for each diagnostic category (LGD, HGD, adenocarcinoma), and agreement beyond chance was estimated using Cohen’s kappa, linear, and quadratic weighted kappa (with 95% CIs). Kappa values were interpreted using standard thresholds. Misclassification was categorized as mild (1-level discrepancy) or severe (2-level discrepancy). Differences in concordance and misclassification rates between groups (e.g., first vs. repeat biopsy; hospital-based expert vs. community) were compared using chi-squared or Fisher’s exact tests.

Diagnostic performance metrics—including sensitivity, specificity, likelihood ratios (LR+ and LR−), and odds ratios (ORs)—were calculated for each biopsy strategy using ESD histology as reference. Comparisons of sensitivity in paired strategies (e.g., first vs. repeat biopsy in the same lesion) used McNemar’s test; differences in kappa values were assessed using Z-tests for correlated coefficients.

Univariate and multivariate logistic regression identified independent predictors of histologic discrepancy. Clinically relevant variables or those with $p < 0.10$ were included in the multivariable model. Model calibration was assessed via the Hosmer–Lemeshow test and classification accuracy.

The impact of discrepancy on curative resection was analyzed using multivariate regression adjusted for ulceration, lesion size, location, Paris classification, differentiation and time between biopsy and ESD. Subgroup analyses explored the effect of underestimation on non-curative outcomes.

The association between biopsy repetition and submucosal fibrosis was evaluated using chi-squared and logistic regression analyses. The number of biopsy fragments was compared using the Mann–Whitney U test and modeled as a continuous predictor.

All analyses were two-tailed, with $p < 0.05$ considered significant, and were performed on a per-lesion basis using SPSS Statistics (v23.0, IBM Corp., Armonk, NY, USA) and R (v4.3.2, R Foundation for Statistical Computing, Vienna, Austria).

5. Conclusions

In summary, this study confirms that EFB frequently underestimates histological severity in superficial gastric neoplasia, with direct implications for treatment planning. Repeat biopsy—particularly when performed by experienced endoscopists—can enhance diagnostic accuracy without adding procedural risk. The setting in which biopsies are performed also significantly influences diagnostic performance, underscoring the value of centralized evaluation for both diagnosis and therapy. Still, the role of EFB should not be overstated: its primary function is not to fully stage lesions, but to identify high-risk features. In this context, ESD is not only a curative treatment but also a definitive diagnostic tool, essential for accurate staging and risk stratification. More broadly, our findings underscore the importance of seeking expert second opinion at all stages of the diagnostic and therapeutic pathway, ensuring that decisions are based on the most accurate and comprehensive assessment possible. Particular attention should be given to larger lesions, which showed higher rates of histologic discrepancy and carry a greater risk of clinically relevant underestimation, potentially leading to non-curative resection.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/gidisord7040065/s1>, Table S1: Baseline lesion characteristics.

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Abbreviations

The following abbreviations are used in this manuscript:

ADC	Adenocarcinoma
CI	Confidence Interval
eCura	ESD Curative Classification
EFB	Endoscopic Forceps Biopsy
EGGIM	Endoscopic Grading of Gastric Intestinal Metaplasia

ESGE	European Society of Gastrointestinal Endoscopy
ESD	Endoscopic Submucosal Dissection
H&E	Hematoxylin and Eosin
HGD	High Grade Dysplasia
IMC	Intramucosal Cancer
IQR	Interquartile Range
JGCA	Japanese Gastric Cancer Association
LGD	Low Grade Dysplasia
LNM	Lymph Node Metastasis
LR+	Positive Likelihood Ratio
LR−	Negative Likelihood Ratio
NS	Not Significant
OR	Odds Ratio
RR	Relative Risk
SD	Standard Deviation
SM1/SM2/SM3	Submucosal Invasion Levels 1, 2, 3
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

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