Long-Term Outcome of Gastric Mild-Moderate Dysplasia: A Real-World Clinical Experience

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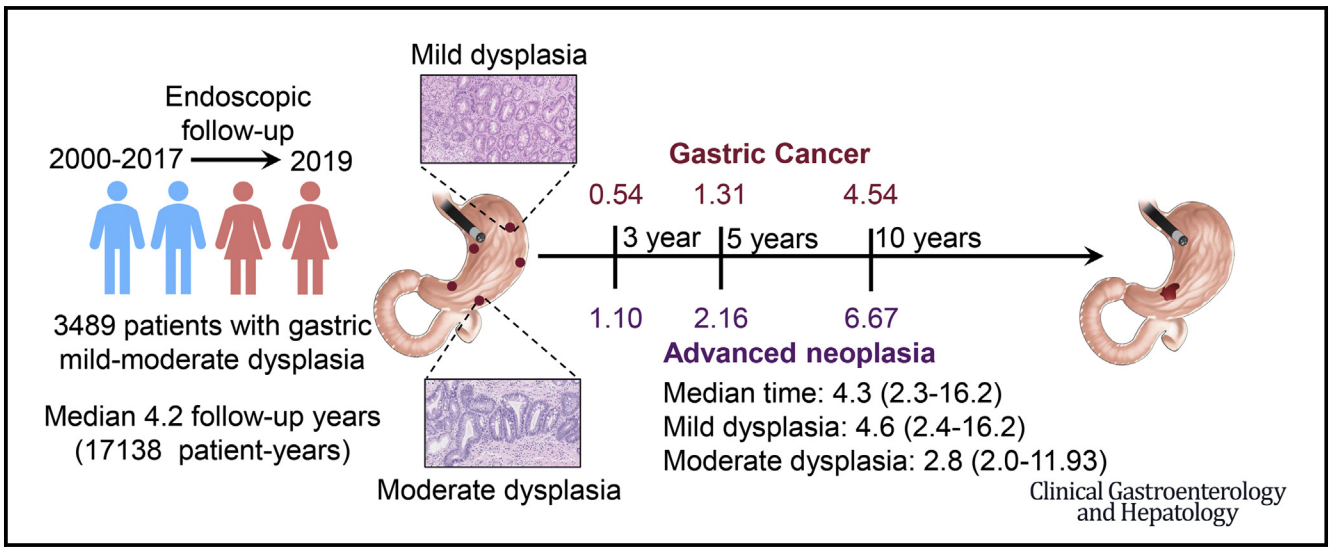

BACKGROUND & AIMS: The natural course of gastric mild-moderate dysplasia in a country with high incidence of gastric cancer (GC) is relatively unknown. We aimed to determine the long-term cumulative incidence of and risk factors for advanced neoplasia in patients with gastric dysplasia.

METHODS: This was a single-center observational study including all consecutive patients diagnosed with gastric mild-moderate dysplasia between 2000 and 2017. Follow-up data were collected until December 2019. We determined the cumulative incidence of advanced neoplasia and identified risk factors with Cox regression.

RESULTS: A total of 3489 consecutive participants were followed for a median of 4.19 years from initial mild-moderate dysplasia diagnosis. The median surveillance interval between index endoscopy and next follow-up endoscopy was 1.08 years, and more than half of patients had at least 3 surveillance gastroscopies. During the study period, the majority of participants did not show disease progression, either with dysplasia not detected (51.4%) or with persistent dysplasia (46.1%). There were 88 (2.9%) patients (5.13 per 1000 patient-years) who progressed to advanced neoplasia within a median of 4.3 years. The annual incidence of advanced neoplasia and GC were 0.43% and 0.26%, respectively, within 5 years of mild-moderate dysplasia diagnosis. Increasing age, male sex, moderate dysplasia, dysplasia detected in fundus or cardia at index endoscopy, and persistent *Helicobacter pylori* infection during follow-up were independent risk factors for developing advanced neoplasia.

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Abbreviations used in this paper: CI, confidence interval; GC, gastric cancer; HGD, high-grade dysplasia; H.pylori, Helicobacter pylori; IM, intestinal metaplasia; IQR, interquartile range; LGD, low-grade dysplasia.

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CONCLUSIONS: **Even in a country with high incidence of GC, the majority of patients with gastric mild-moderate dysplasia did not experience disease progression in the long term. Intensified surveillance during the first 5 years after mild-moderate dysplasia detection is suggested.**

Keywords: Gastric Dysplasia; Intraepithelial Neoplasia; Gastric Cancer; Risk Factors.

See editorial on page 1226.

Gastric cancer (GC) is one of the most common malignant tumors worldwide and remains a major health threat in the Asia-Pacific region, although its overall incidence has been declining in recent years.[1] Intestinal-type gastric adenocarcinoma represents the final outcome of the progression from nonatrophic gastritis to atrophic gastritis, then intestinal metaplasia (IM), and finally dysplasia and GC. This cascade is known as the Correa model.[2] Thus, endoscopic surveillance and treatment of precancerous lesions is advocated in at-risk patients before GC develops.[3]

Gastric dysplasia, also known as intraepithelial neoplasia, is a precancerous lesion and the penultimate step in gastric carcinogenesis.[4] Unlike gastric atrophy or IM, a risk assessment tool predicting the progression risk of dysplasia is not available because of its unclear natural history. Current available evidence suggests that most mild-moderate dysplasia (3-tier classification system) or low-grade dysplasia (LGD) (2-tier system) will apparently regress or persist in the long run, while there is also an increased risk of progression to cancer (from 0% to 40%) (Supplementary Table 1). In the case of severe or high-grade dysplasia (HGD), 50%–60% of patients will progress to GC within a short time,[5] and it is usually detected concomitantly with cancerous lesions; therefore, immediate endoscopic therapy is recommended in current guidelines.[3] However, it should be noted that most of these data originate from Western countries where the differences in environmental and genetic factors as well as *Helicobacter pylori (H.pylori)* prevalence should be taken into account. Limited follow-up duration and small sample sizes also result in wide variation in the reported incidence of GC among these patients. In addition, only one study with a relatively small sample size (n = 546) has been done in a Chinese population,[6] and thus there is a need for large studies with long-term follow-up to better quantify GC risk in those with gastric dysplastic lesions.

To address this need, we analyzed data collected from a large tertiary hospital in China, with the aims of describing the natural history of gastric mild-moderate dysplasia and identifying potential risk factors for progression. The findings may provide a basis for decisions regarding gastric dysplasia surveillance practice.

Materials and Methods

Study Design and Participants

We conducted a single-center observational study including all consecutive patients with histologically confirmed gastric mild-moderate dysplasia between January 2000 and December 2017 in the Gastroenterology Department of Peking University Third Hospital, a tertiary referral center in China. Follow-up data were collected until December 2019. The institutional review board of Peking University Third Hospital approved this study with waiver of consent (reference number 424-01).

Inclusion and Exclusion Criteria

Individuals ≥18 years of age with a first diagnosis of mild-moderate dysplasia in the period of 2000–2017 were considered eligible for this study. Subjects were required to have ≥12 months' follow-up time and ≥1 endoscopic and histological follow-up after the index endoscopy. Patients were excluded (1) if they had a diagnosis of either gastric or esophageal malignancy prior to or simultaneously with the index endoscopy, (2) if esophageal malignancy or gastrointestinal endocrine tumor was detected during follow-up, (3) if they had history of endoscopic or surgical gastric resection, and (4) if their first diagnosis of dysplasia was incidental in gastric polyps.

Biopsy Protocol

For all patients that underwent gastroscopy for the first time in our center, biopsies were taken adhering to the local protocol,[7] with random biopsies from the antrum (lesser curvature at 2–3 cm from the pylorus) and corpus (lesser curvature at 4 cm proximal to the incisura) and multiple targeted biopsies from all endoscopically abnormal areas. If patients were diagnosed with gastric dysplasia, a repeat endoscopy was recommended in 3–6 months for moderate dysplasia and in 1 year for mild dysplasia; for those with severe dysplasia, an immediate endoscopic examination was repeated and intervention was performed when necessary. For patients undergoing subsequent surveillance endoscopy, random biopsies in the antrum and corpus, repeated biopsies at the apparently same location as previously noted, and targeted biopsies for newly visible lesions were taken.

Histological Diagnosis of Gastritis, Dysplasia and H. pylori Infection

The biopsy specimens were assessed by gastrointestinal pathologists and graded (none, mild, moderate,

and severe) for the presence of inflammation, atrophic gastritis, and IM in accordance with the updated Sydney classification system.[8] Dysplasia was diagnosed in line with the 3-tier system (mild, moderate, and severe) (Supplementary Figure 1).[9] *H. pylori* status was determined by histology with Warthin-Starry staining. More detailed information on histological diagnosis criteria is available in the Supplementary material/Methods. We assessed interobserver agreement using a representative biopsy set of 100 randomly selected cases that were evaluated by 2 senior pathologists. The kappa values were 0.71 (95% confidence interval [CI], 0.58–0.84) for grading dysplasia, 0.82 (95% CI, 0.70–0.95) for atrophy diagnosis, and 0.86 (95% CI, 0.74–0.97) for IM diagnosis.

Data Collection

The baseline data of each eligible subjects were collected from the medical records, and the pathological reports of each case were reviewed manually by 3 investigators (H.L., S.X., and Y.X.). The process of data retrieval is detailed in the Supplementary Materials/Methods. The collected data included (1) age and sex; (2) the date and total numbers of gastroscopies with biopsies (including the index endoscopy); (3) the histopathological diagnosis of dysplasia and background gastric mucosa, as well as *H. pylori* status; and (4) information on pathological diagnosis of neoplasia and interventions for those developed advanced neoplasia.

Study Endpoint

The study endpoint was defined as development of advanced neoplasia (severe dysplasia or GC) during surveillance up to December 31, 2019. If participants did not develop advanced neoplasia, the censoring date was the time of their last surveillance endoscopy before December 31, 2019.

Statistical Analysis

Continuous variables were presented as mean ± SD or median (interquartile range [IQR]). Categorical variables were reported as count and percentage. The cumulative incidence of advanced neoplasia was estimated with the Kaplan-Meier method. A Cox proportional hazards model was then used to determine independent risk factors for progression to advanced neoplasia. Risk factors with a P value <.2 in univariate analysis, and previously reported risk factors in the literature, were included in a multivariable model. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). All statistical tests were 2-tailed, and P value <.05 was considered to be statistically significant.

What You Need to Know

Background

Gastric dysplasia carries a potential risk of malignant transformation. The natural history and progression risk of gastric mild-moderate dysplasia are not well defined.

Findings

In a country with high gastric cancer incidence, the development of advanced neoplasia (severe dysplasia and gastric cancer) was not common (incidence rate: 5.13 per 1000 person-years). Median time to advanced neoplasia development was 4.3 years after detection of mild-moderate dysplasia. Increasing age, male sex, moderate dysplasia, dysplasia detected in fundus or cardia, and persistent *Helicobacter pylori* infection were associated with advanced neoplasia development.

Implications for patient care

Intensified surveillance during the first 5 years after gastric mild-moderate dysplasia diagnosis is suggested.

Results

Study Population

Screening 112,320 consecutive outpatients with matching information in our pathological databank, we identified 11,360 patients who were diagnosed with gastric mild-moderate dysplasia between January 1, 2000, and December 31, 2017. After application of eligibility criteria, 3489 patients were included in the analysis (Figure 1). Baseline characteristics were similar between those included, and those with index endoscopy only or surveillance endoscopy >1 year but with follow-up <1 year (n = 7558), except that male sex and *H. pylori* infection at index endoscopy were more prevalent in those excluded (Supplementary Table 2).

The demographic and clinical characteristics of the study population are summarized in Table 1. For all follow-up subjects, the ratio of male to female was 0.89:1, and the mean age at cohort entry was 61.5 ± 11.6 years. At the initial endoscopic biopsy, 93.2% of patients were diagnosed with mild dysplasia and 6.8% were diagnosed with moderate dysplasia. The most common location for dysplasia was the antrum in 48.6% (n = 1697). Histopathology of the background mucosa regarding the distribution of atrophy and IM was available for 1969 patients, and it was noted that dysplasia commonly arose in the setting of atrophy and IM. At index endoscopy, 735 (21.1%) patients had active *H. pylori* infection.

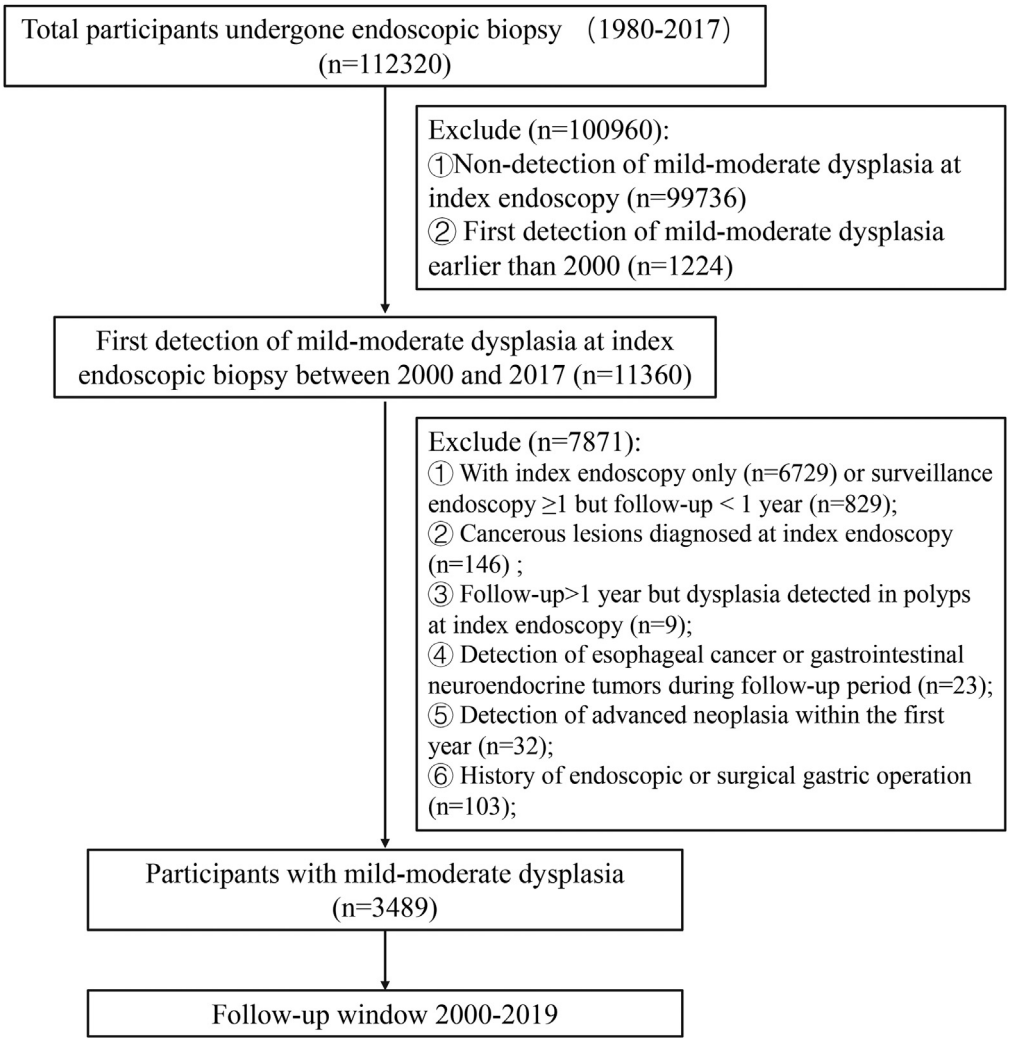

Figure 1. Flow diagram of patient recruitment.

Follow-Up and Endoscopic Surveillance

For the entire cohort, median follow-up was 4.19 (IQR, 2.33–19.31) years after index endoscopy, contributing a total of 17,138 patient-years (Table 2). After the initial diagnosis, 55% of patients received at least 3 surveillance endoscopies with biopsies, and the proportion of patients with more than 3 surveillance endoscopies was higher for those with moderate dysplasia (Table 2). We observed that follow-up durations increased in parallel with the increase in the number of follow-up endoscopy (Supplementary Table 3), indicating that the increased number of surveillance endoscopy was not due to repeat examinations within a short time. Another important datapoint was the time interval between the index endoscopy and next surveillance endoscopy. For all follow-up subjects, the median interval was 1.08 (IQR, 0.72–13.71) years (Table 2). The median interval for patients with moderate dysplasia (0.53 [IQR, 0.27–10.21] years) was shorter than that of those with mild dysplasia (1.10 [IQR, 0.79–13.71] years).

Evolution of Dysplastic Lesions

During follow-up, 3401 (97.5%) patients did not show lesion progression, with dysplasia not detected in 51.4%, or persistence in 46.1%. Progression to advanced neoplasia was observed in only 88 (2.5%) patients (incidence rate, 5.13 per 1000 patient-years), with 34 developing severe dysplasia (incidence rate, 1.98 per 1000 patient-years) and 54 developing GC (incidence rate, 3.15 per 1000 patient-years) after the first year of index endoscopy (Table 2). Evolution of mild-moderate dysplasia is described in Table 3. Moderate dysplasia had a higher rate of progression than mild dysplasia (7.6% vs 2.2%). Subgroup analyses showed that different follow-up durations (<3 years, 3–6 years, 6–9 years, 9–15 years, and ≥15 years) did not impact the outcome of mild-moderate dysplasia (Supplementary Figure 2*A*), while those enrolled earlier (2000–2008) had a higher rate of progression than those included after 2008 (4.8% vs 1.9%) (Supplementary Figure 2*B*). Among patients who developed advanced neoplasia, a wide range in time from initial diagnosis to advanced lesion development

Table 1. Baseline Characteristics of 3489 Included Patients With Mild-Moderate Dysplasia

Variable	Study Population (N = 3489)	Mild Dysplasia (n = 3252)	Moderate Dysplasia (n = 237)
Sex			
Male	1639 (47.0)	1501 (46.2)	138 (58.2)
Age, y			
Mean ± SD	61.5±11.6	61.4±11.6	63.2±11.6
Median (IQR)	62.0 (54.0–70.0)	62.0 (54.0–70.0)	64.0 (55.5–72.0)
Dysplasia Location			
Antrum	1697 (48.6)	1617 (49.7)	80 (33.8)
Incisura	761 (21.8)	726 (22.3)	35 (14.8)
Corpus	224 (6.4)	213 (6.5)	11 (4.6)
Fundus	6 (0.2)	5 (0.2)	1 (0.4)
Cardia	24 (0.7)	21 (0.6)	3 (1.3)
Multifocal site	777 (22.3)	670 (20.6)	107 (45.1)
Histology of background mucosa			
Distribution of atrophy			
None	132 (3.8)	125 (3.8)	7 (3.0)
Antrum-restricted	1242 (35.6)	1163 (35.8)	79 (33.3)
Corpus-restricted	49 (1.4)	48 (1.5)	1 (0.4)
Extensive	546 (15.6)	504 (15.5)	42 (17.7)
NA	1520 (43.6)	1409 (43.4)	108 (45.6)
Distribution of IM			
None	33 (0.9)	32 (1.0)	1 (0.4)
Antrum-restricted	1168 (33.5)	1099 (33.8)	69 (29.1)
Corpus-restricted	15 (0.4)	15 (0.5)	0 (0.0)
Extensive	753 (21.6)	694 (21.3)	59 (24.9)
NA	1520 (43.6)	1412 (43.4)	108 (45.6)
***H. pylori* status**			
Negative	2754 (78.9)	2554 (78.5)	200 (84.4)
Positive	735 (21.1)	698 (21.5)	37 (15.6)
Period of initial diagnosis			
2000–2008	744 (21.3)	712 (21.9)	32 (13.5)
2009–2017	2745 (78.7)	2540 (78.1)	205 (86.5)

Values are n (%), unless otherwise indicated.
H. pylori, *Helicobacter pylori*; IM, intestinal metaplasia; IQR, interquartile range; NA, not available; SD, standard deviation.

(median 4.31 [IQR, 2.29–16.16] years) was noted, and those with moderate dysplasia progressed to advanced neoplasia within a shorter time (median 2.79 years). Additionally, it was notable that 4 patients (2 progressed to GC, 2 developed severe dysplasia) occurred after 1 year but <1.5 years after index endoscopy. We also noted that there were 32 patients (13 mild dysplasia, 19 moderate dysplasia) diagnosed with advanced neoplasia (13 severe dysplasia, 19 cancer) within the first year after index endoscopy (median 3 [IQR, 1.91–7.43] months) (Figure 1). For *H. pylori* status, the infection rate declined to 4.3%, while 2.1% of patients were not infected at initial diagnosis.

Clinical Characteristics and Outcome of Patients Developed Advanced Neoplasia

Characteristics of those with advanced neoplasia at index endoscopy and last follow-up are shown in Supplementary Table 4. Mean age at the time of diagnosis of advanced neoplasia was 70.3 ± 9.7 years, 62 (70.5%) were male, and 15% of patients had current infection with *H. pylori*. Median time interval between endoscopies until advanced neoplasia diagnosis was shorter among those with severe dysplasia (12.1 [IQR, 3.6–19.4] months), although the mean number of surveillance endoscopies was similar between those who progressed to severe dysplasia (4.4 ± 3.6) and GC (3.3 ± 2.1). Regarding the outcome of these patients, 23.5% of patients diagnosed with severe dysplasia underwent follow-up and 70.6% of patients received endoscopic resection. Of the 54 patients with GC, 24 (44.4%) individuals diagnosed as early GC underwent endoscopic resection, and 37% received surgical therapy.

Rate of Progression to Advanced Neoplasia by Kaplan-Meier Analysis

Using the Kaplan-Meier method, we estimated progression rate as a function of follow-up time. The

Table 2. Follow-Up of Patients With Gastric Mild-Moderate Dysplasia

Variable	Study Population (N = 3489)	Mild Dysplasia (n = 3252)	Moderate Dysplasia (n = 237)
Follow-up duration, y			
Median (IQR)	4.19 (2.33–19.31)	4.24 (2.33–19.31)	3.60 (2.35–16.91)
Minimum–maximum	1.00–19.31	1.00–19.31	1.09–16.91
Accumulated person-years	17,138.37	16,116.62	1021.75
Time intervals to first surveillance endoscopy, y	1.08 (0.72–13.71)	1.10 (0.79–13.71)	0.53 (0.27–10.21)
Times of surveillance endoscopy			
1	768 (22.0)	745 (22.9)	23 (9.7)
2	791 (22.7)	743 (22.8)	48 (20.3)
3	589 (16.9)	544 (16.7)	45 (19.0)
4	402 (11.5)	357 (11.0)	45 (19.0)
5	283 (8.1)	260 (8.0)	23 (9.7)
>5	656 (18.8)	603 (18.5)	53 (22.4)
Progression			
Advanced neoplasia	88 (2.5)	70 (2.2)	18 (7.6)
GC	54 (1.5)	41 (1.3)	13 (5.5)
Time to diagnosis of advanced neoplasia, y			
Median (IQR)	4.31 (2.29–16.16)	4.56 (2.44–16.16)	2.79 (2.03–11.93)
Minimum–maximum	1.10–16.16	1.10–16.16	1.33–11.93
Incidence rate, per 1000 person-years			
Advanced neoplasia	5.13	4.34	17.62
GC	3.15	2.54	12.72
Final *H. pylori* status			
Negative	3338 (95.7)	3111 (95.7)	226 (95.4)
Positive	151 (4.3)	140 (4.3)	11 (4.6)
Changes in *H. pylori* status			
Negative-negative	2681 (76.8)	2489 (76.5)	192 (81.0)
Positive-negative	657 (18.8)	623 (19.2)	34 (14.3)
Negative-positive	73 (2.1)	65 (2.0)	8 (3.4)
Positive-positive	78 (2.2)	75 (2.3)	3 (1.3)

Values are n (%) or median (IQR), unless otherwise indicated.
GC, gastric cancer; H. pylori, *Helicobacter pylori*; IQR, interquartile range.

cumulative incidence of lesion progression at 3, 5, and 10 years after initial mild-moderate dysplasia diagnosis was 1.10 (95% CI, 0.77–1.57), 2.16 (95% CI, 1.63–2.86), and 6.67 (95% CI, 5.05–8.79), respectively (Figure 2*A*). For GC development only, the cumulative incidence was 0.54 (95% CI, 0.33–0.90), 1.31 (95% CI, 0.90–1.90), and 4.54 (95% CI, 3.17–6.48) at 3, 5, and 10 years, respectively (Figure 2*B*). In terms of clinical characteristics (Supplementary Figure 3), the cumulative incidence of advanced neoplasia was significantly higher for the older

Table 3. Evolution of Gastric Mild-Moderate Dysplasia Over Follow-Up Periods

	Follow-Up End					
Index Endoscopy	No Detected	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	GC	Total
Mild dysplasia	1688 (51.9)	1340 (41.2)	154 (4.7)	29 (0.9)	41 (1.3)	3252 (93.2)
Moderate dysplasia	105 (44.3)	87 (36.7)	27 (11.4)	5 (2.1)	13 (5.5)	237 (6.8)
Total	1793 (51.4)	1427 (40.9)	181 (5.2)	34 (1.0)	54 (1.5)	3489

Values are n (%).
GC gastric cancer.

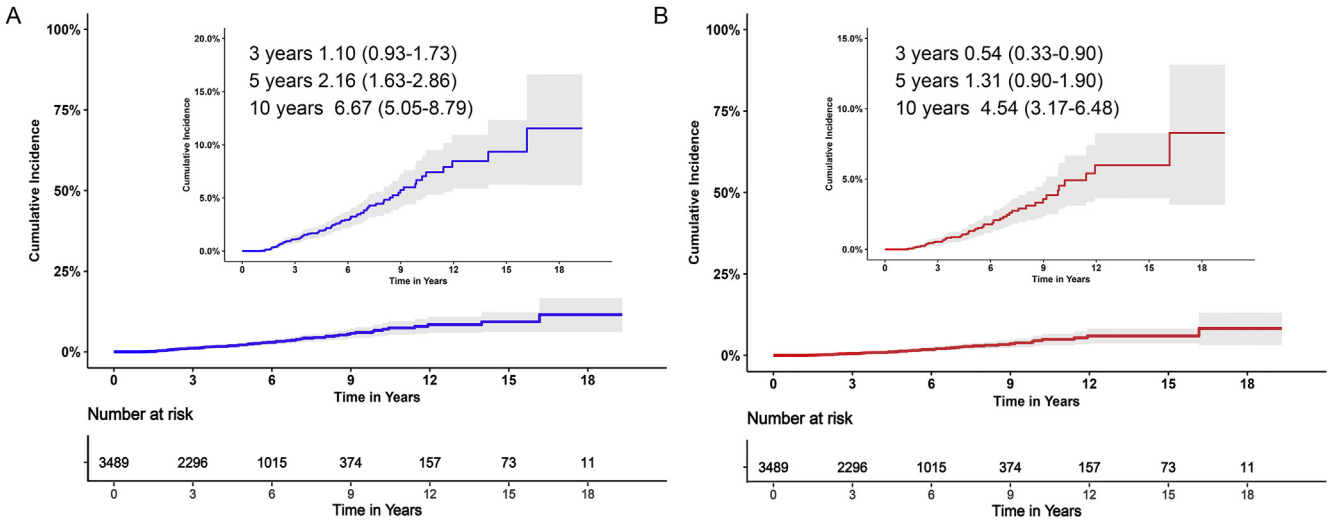

Figure 2. Kaplan-Meier plots showing cumulative incidence of developing advanced neoplasia or GC only after detection of gastric mild-moderate dysplasia. (*A*) Cumulative incidence of advanced neoplasia. (*B*) Cumulative incidence of GC only.

age group (≥65 years of age) ($P = .001$), for male sex ($P < .001$), for moderate dysplasia ($P < .001$), for dysplasia in the fundus or cardia ($P < .001$), for corpus or extensive IM ($P = .007$) at initial endoscopy, and for persistent *H. pylori* infection ($P < .001$) during the surveillance period.

Risk Factors Associated With Lesion Progression

To further assess the independent risk factors for lesion progression, univariate and multivariate analyses were performed using Cox regression (Table 4). Univariate analyses showed that age, male sex, moderate dysplasia, location of dysplasia at initial diagnosis, and persistent *H. pylori* infection during follow-up were associated with lesion progression. Adjusted multivariate analyses demonstrated that increasing age, male sex, moderate dysplasia, dysplasia detected in fundus or cardia, and active *H. pylori* infection at initial diagnosis and persistent *H. pylori* infection during follow-up were independently associated with progression risk. Background status of gastric mucosa and time period at initial diagnosis were not associated with neoplastic progression. The analysis was repeated using only GC as the outcome, and similar results were identified except for active *H. pylori* infection at initial diagnosis (Table 4).

Discussion

Dysplasia represents the penultimate stage in the cascade of intestinal-type gastric adenocarcinoma.[2] Detection of dysplasia is therefore critical to identify those at risk for GC. In line with previous research,[4] our data showed that gastric dysplasia can be found anywhere in the stomach, but the antrum was the most common site. Diffuse mucosal changes (atrophy and IM) were often the background for dysplasia development but not universally.[10] Thus, the multifocal distribution further emphasizes the significance of comprehensive and systematic endoscopy with biopsies in the presence of atrophy or IM, in order to detect dysplasia and even synchronous cancer.

The overall risk of malignancy for mild-moderate dysplasia or LGD varies across studies over different follow-up durations, as summarized in Supplementary Table 1. In the present study, we found that even in a country with high gastric cancer incidence, the majority of patients with mild-moderate dysplasia maintained a stable disease state, and the overall incidences of advanced neoplasia and GC were 5.13 and 3.15 per 1000 person-years, respectively. A nationwide research conducted in the Netherlands revealed that the annual incidence of GC was 0.6% for mild-moderate dysplasia within 5 years after diagnosis.[11] Another large follow-up study from Sweden also indicated that dysplasia (including LGD and HGD) increased the risk of GC with an incidence of 2.6 per 1000 person-years.[12] A recent systematic review and meta-analysis reported a pooled incidence rate of GC following LGD (including mild-moderate dysplasia) of 11.25 (95% CI, 3.91–21.22) per 1000 person-years.[13] On the other hand, our data also showed that 32 patients progressed to advanced neoplasia during a median of 3 months after index endoscopy, and 4 cases had lesion progression between 1 and 1.5 years. These observations suggest a missed or synchronous cancer at the time of index endoscopy, and the significance of early surveillance endoscopy after dysplasia detection.

We should point out that sampling error was a concern in defining histologic changes in both our studies and previous research. Detection of dysplasia, especially mild dysplasia and some moderately dysplastic lesions, is often incidental, while taking random biopsies. Even in the context of extensive biopsies, sampling errors cannot be

Table 4. Risk Factors for Progression and Gastric Cancer Incidence in Univariate and Multivariate Cox Regression Analysis

	Advanced Neoplasia (n = 88)			GC (n = 54)		
Variables	Univariable HR (95% CI)	Multivariable HR (95% CI)[a]	Multivariable HR (95% CI)[b]	Univariable HR (95% CI)	Multivariable HR (95% CI)[a]	Multivariable HR (95% CI)[b]
Age	1.04 (1.02–1.06)	1.04 (1.02-1.07)	1.04 (1.01-1.07)	1.04 (1.01–1.08)	1.06 (1.02–1.10)	1.05 (1.02–1.09)
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	2.77 (1.76–4.39)	2.72 (1.53-4.83)	2.75 (1.55-4.88)	3.04 (1.67–5.51)	3.03 (1.44–6.38)	3.14 (1.49–6.61)
Degree of dysplasia						
Mild	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	4.36 (2.59–7.34)	4.62 (2.34-9.10)	4.73 (2.36-9.48)	5.52 (2.95–10.34)	5.86 (2.61–13.15)	6.28 (2.71–14.53)
Location of dysplasia						
Antrum	Ref	Ref	Ref	Ref	Ref	Ref
Incisura	2.09 (1.16–3.75)	1.23 (0.59-2.57)	1.15 (0.55-2.40)	1.72 (0.82–3.61)	1.05 (0.43–2.54)	0.95 (0.39–2.30)
Corpus	1.83 (0.74–4.51)	0.75 (0.16-3.47)	0.72 (0.15-3.39)	1.77 (0.59–5.33)	NA	NA
Fundus/cardia	2.96 (0.53–29.43)	15.15 (1.72-133.60)	12.56 (1.23-128.24)	6.15 (0.81–46.73)	26.03 (2.71–249.95)	20.81 (1.70–255.54)
Multifocal	3.89 (2.28–6.62)	1.65 (0.80-3.42)	1.45 (0.69-3.03)	3.40 (1.75–6.61)	1.43 (0.59–3.46)	1.17 (0.47–2.90)
Background gastric mucosa						
Distribution of atrophy						
None	Ref	Ref	Ref	Ref	Ref	Ref
Antrum	1.66 (0.40–6.94)	1.97 (0.37-10.53)	3.07 (0.58-16.26)	1.10 (0.26–4.74)	1.28 (0.22–7.43)	2.29 (0.39–13.39)
Corpus/extensive	2.47 (0.58–10.49)	1.45 (0.26-8.27)	2.52 (0.46-13.98)	1.46 (0.33–6.46)	1.33 (0.20–9.02)	2.90 (0.45–18.63)
Distribution of IM						
None	Ref	Ref	Ref	Ref	Ref	Ref
Antrum	0.71 (0.10–5.27)	0.37 (0.04-4.03)	0.49 (0.04-5.68)	0.57 (0.08–4.29)	0.41 (0.04–4.86)	0.60 (0.04–8.37)
Corpus/extensive	1.61 (0.22–11.85)	0.92 (0.08-10.44)	1.10 (0.09-13.17)	0.88 (0.12–6.62)	0.62 (0.05–8.35)	0.75 (0.05–11.54)
***H. pylori* status at index endoscopy**						
Negative	Ref	Ref	—	Ref	Ref	—
Positive	1.52 (0.97–2.39)	2.06 (1.17-3.59)	—	1.30 (0.72–2.36)	1.45 (0.68–3.09)	—
Changes in *H. pylori* status						
Negative-negative	Ref	—	Ref	Ref	—	Ref
Positive-negative	1.36 (0.81–2.28)	—	1.81 (0.97-3.38)	1.07 (0.53–2.18)	—	1.03 (0.41–2.60)
Negative-positive	6.95 (3.15–15.31)	—	7.02 (2.61-18.84)	9.93 (4.15–23.77)	—	9.75 (3.09–30.78)
Positive-positive	7.02 (3.19–15.45)	—	10.10 (3.72-27.40)	8.24 (3.21–21.16)	—	13.03 (4.10–41.38)
Period of initial diagnosis						
2000–2008	Ref	Ref	Ref	Ref	Ref	Ref
2009–2017	1.022 (0.63–1.66)	1.26 (0.65-2.46)	1.28 (0.66-2.48)	1.31 (0.69–2.49)	1.21 (0.52–2.79)	1.23 (0.53–2.87)

CI, confidence interval; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; IM, intestinal metaplasia; NA, not available; Ref, reference.

[a]Adjusted for age, sex, degree of dysplasia, location of dysplasia, distribution of atrophy, distribution of IM, *H. pylori* status at index endoscopy, and period of initial diagnosis.

[b]Adjusted for age, sex, degree of dysplasia, location of dysplasia, distribution of atrophy, distribution of IM, changes in *H. pylori* status, and period of initial diagnosis.

ruled out entirely. This remains a structural limitation of studies involving endoscopic follow-up of gastric precancerous conditions or lesions. Additionally, the possibility of small foci of dysplasia being removed at the initial biopsy cannot be entirely ruled out. In view of this, we cannot make definite conclusions whether a given area of dysplasia actually regressed. For future studies with well-defined populations, targeted biopsies and high-resolution endoscopy might better define the natural history (regression, persistence or progression) of specific gastric neoplastic lesions.

Regarding surveillance strategy, the current consensus recommends surveillance endoscopy in 1 year after the initial diagnosis.[3] According to our experience, periodic follow-up at 1-year intervals is sufficient for mild dysplasia and treatment is usually not necessary. On the other hand, a 3- to 6-month interval can be considered in patients with moderate dysplasia due to the higher risk of progression. In this context, it may be appropriate to consider annual surveillance endoscopy for all patients with LGD in 2-tier system. Additionally, the short time interval between endoscopies until severe dysplasia detection re-emphasizes the importance of regular endoscopic follow-up. Given our finding that the majority of cases with advanced neoplasia developed within 5 years, intensified surveillance during the first 5 years after detection of mild-moderate dysplasia might be necessary. However, this should be further assessed by future prospective studies.

As mentioned previously, only a small proportion of patients eventually developed advanced neoplasia, and therefore strict surveillance may not be appropriate for all individuals, and should be aimed at those at higher risk. We identified male sex and increasing age as important independent risk factors for overall progression of mild-moderate dysplasia. These findings are in line with a previous report from Western populations.[11] Regarding mucosal atrophy or IM, there were insufficient data to determine the risk of progression to advanced neoplasia, though earlier research had identified that the grade of coexisting atrophic gastritis was a risk factor for mild dysplasia progression.[14] Unlike a previous study that considered mild-moderate dysplasia as a single category in Cox regression analysis,[11] stratified analysis (mild dysplasia vs moderate dysplasia) by Kaplan-Meier or Cox regression model in our study demonstrated that patients with moderate dysplasia tended to progress within a short time period. Therefore, combining mild dysplasia and moderate dysplasia into a single LGD category in 2-tier classification might not be well justified.[15] Regarding the effect of *H. pylori* infection on dysplasia progression, our data demonstrated that it does seem important, although previous research had found that *H. pylori* infection in dysplastic stomach was not a determining factor.[14] Nevertheless, it needs to be emphasized that *H. pylori* eradication does significantly reduce GC development and prevent metachronous neoplasia after endoscopic resection of gastric neoplasms.[16,17] Thus, patients with gastric dysplasia can benefit from *H. pylori* eradication, with the goal to decrease the probability of lesion progression.

There are some important strengths to our study. To the best of our knowledge, this is the largest real-world observational study to date among patients with gastric mild-moderate dysplasia in a country with high incidence of GC. Moreover, individual chart reviews were performed to verify the pathologic diagnosis of dysplasia, resulting in a lower risk of misclassification than that of claims-based data.[11] The generalizability of our findings in populations at high risk for GC may help clinicians formulate appropriate surveillance strategies.

Our study also has several limitations. First, bias might be inevitable given the retrospective design. Selection bias may exist due to the lower proportion of male patients and *H. pylori* infection at index endoscopy, although the stochastic dropout during endoscopic surveillance in routine practice was inevitable. In addition, the patients followed in this study underwent endoscopy for various reasons, including evaluation of abdominal discomfort and surveillance of previously diagnosed premalignant conditions in other medical centers. Thus, the observed rates of progression might not accurately estimate risk for all patients. Second, it is well known that environmental risk factors (smoking, alcohol use, etc.) and genetic factors are contributing factors to GC development, but this information was not available in our database. Similarly, lack of complete information on *H. pylori* treatment restricted our ability to directly assess whether eradication had an impact on progression, though changes in *H. pylori* status might be a reflection of therapy. Finally, all patients included in our study received endoscopic examinations using standard white light endoscopy, which might be inferior to newer technologies (such as magnification endoscopy, narrow band imaging, etc.) for dysplasia detection. While sampling error is an issue that affects studies including ours, it does also occur in real-world practice.

Taken together, this study demonstrates that the incidence of GC in gastric mild-moderate dysplasia is low, but some individuals are at increased risk. More frequent endoscopic surveillance might be considered for those with risk factors, including older age, male sex, presence of moderate dysplasia, and persistent *H. pylori* infection during the first 5 years after an index endoscopy. Future prospective studies will be needed to determine the optimal and cost-effective surveillance intervals based on risk stratification. It also remains to be seen whether follow-up can be discontinued for patients with no dysplasia detected during surveillance.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.10.032.

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Conflicts of Interest
The authors disclose no conflicts.

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Supplementary Material

Methods

Histological Diagnosis of Atrophy, Intestinal Metaplasia, and Dysplasia

Atrophic gastritis was assessed on the basis of the loss of glandular structures, including nonmetaplastic loss of glands, intestinal metaplasia (IM), and pseudopyloric metaplasia. For IM confined to the area of the gastric pit was not considered as atrophy. If the specimen did not include the muscularis mucosa, one could refer to mucosal gland size, density, and interstitial response to infer whether atrophy was present. IM was diagnosed with the appearance of metaplastic intestinal gland in the mucosa, which could be recognized morphologically by the presence of goblet cells, absorptive cells, and cells resembling colonocytes. Histologic subtyping of IM was not determined routinely. Baseline and the last follow-up biopsy sets from individuals with 3 biopsy specimens (1 from the antral mucosa [lesser curvature], 1 from the oxyntic mucosa [lesser curvature], and 1 from the incisura angularis) were analyzed for the topographical distribution of atrophy or IM. The anatomical distribution of atrophy or IM was classified as none (no atrophy/IM in both the antrum and the corpus), antrum-restricted (denoting atrophy/IM restricted to antrum and/or incisura), or corpus or extensive (denoting atrophy/IM restricted to corpus or had atrophy/IM in both antrum and corpus).[1,2]

Dysplasia diagnosis was made on the basis of both disorganized mucosal architecture and abnormalities in cytology and differentiation but lacking any infiltrating features.[3,4] In line with the recommendation from our local gastroenterology society,[5–7] a 3-tier system (mild, moderate, and severe) of gastric dysplasia has been adopted in our center since 1980 up to now. Mild dysplasia was diagnosed with mild irregularity of mucosal architecture with back-to-back gland formation and nuclear stratification with slightly increased nuclear-cytoplasmic ratio (Supplementary Figure 1*A*). Moderate dysplasia was diagnosed when there was slight architectural irregularity with tubules lined by basophilic cells with thin, elongated nuclei confined to the lower part of the cells. Nuclear atypia was moderate, and there was reduction of secretory products and back-to-back gland formation (Supplementary Figure 1*B*). Severe dysplasia showed disorganized mucosal architecture with irregularly shaped tubules with diffuse budding and branching of the crypts and possible papillary growth. Cells have marked basophilia and hyperchromatic pseudostratified nuclei, and most of the nuclei reached the upper half of the cells. Meanwhile, cellular and nuclear polarity was lost (Supplementary Figure 1*C*). In a lesion containing varying degrees of dysplasia, the most severe grade was recorded. Location of dysplasia was documented as antrum, incisura, corpus, fundus, and cardia. If dysplasia was founded in more than 1 site, the case was considered as multifocal lesions. For cases with multifocal dysplasia, the most advanced grade was documented among all dysplastic lesions.

Query of Histopathology Database

All histopathology reports in our center have been kept in an electronic database since 1980. Each report could be tracked to an individual with a unique ID, allowing follow-up on an individual basis with the matched ID. Every record in the database contained patient's demography (name, sex, age), histopathology information (diagnosis names, representative images and original report given by the gastrointestinal pathologist who made the diagnosis), and endoscopic report (endoscopic appearance and endoscopic diagnosis given by endoscopist). For this present analysis, we queried the database using search terms "stomach" within predetermined time frame (1980–2019), all records of an individual underwent gastroscope with biopsies during this period were extracted and exported. Then, SAS software (version 9.4; SAS Institute, Cary, NC) was applied to arrange the records and screen out all patients first diagnosed with mild and moderate dysplasia but not with severe dysplasia between January 2000 and December 2017 via the diagnosis name. Index endoscopy referred to the endoscopy with biopsies in which histologic finding of mild-moderate gastric dysplasia was first determined. Intervention for those detected with advanced neoplasia was ascertained through linkage with medical system if the individual received operation in our center.

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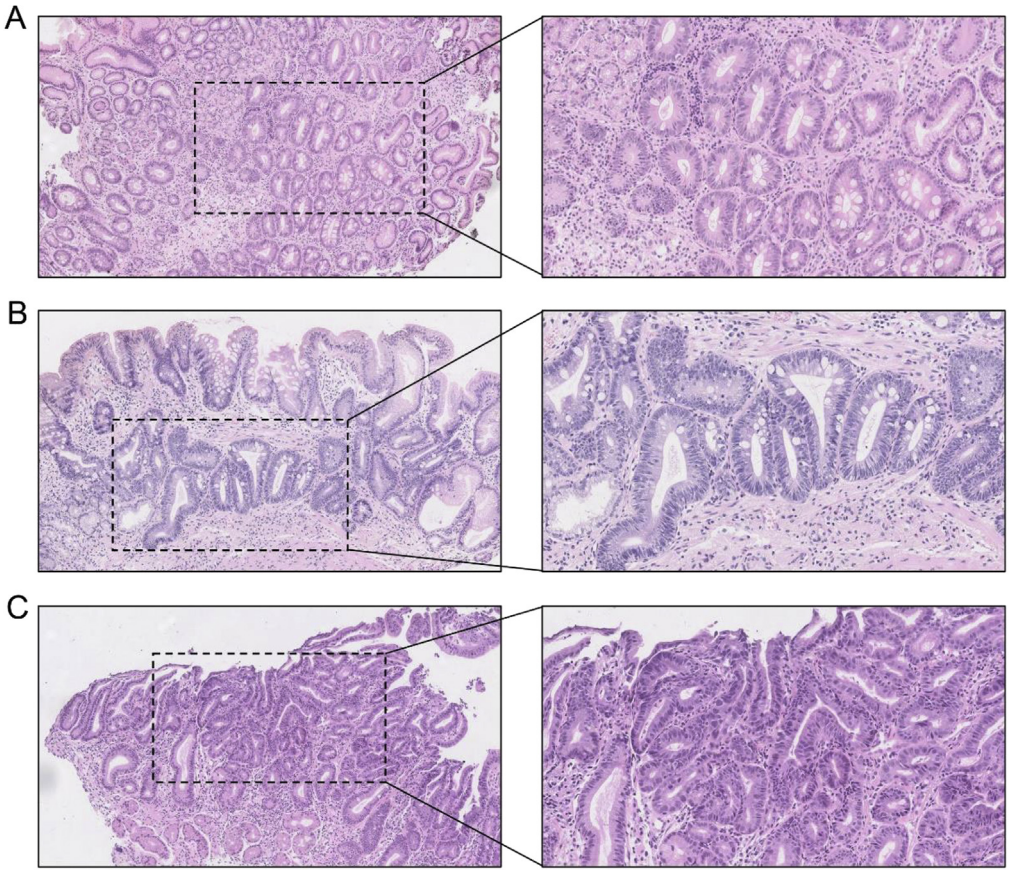
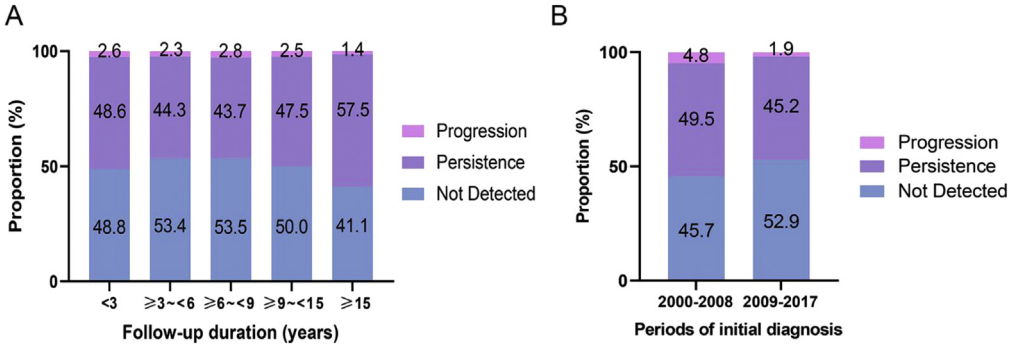
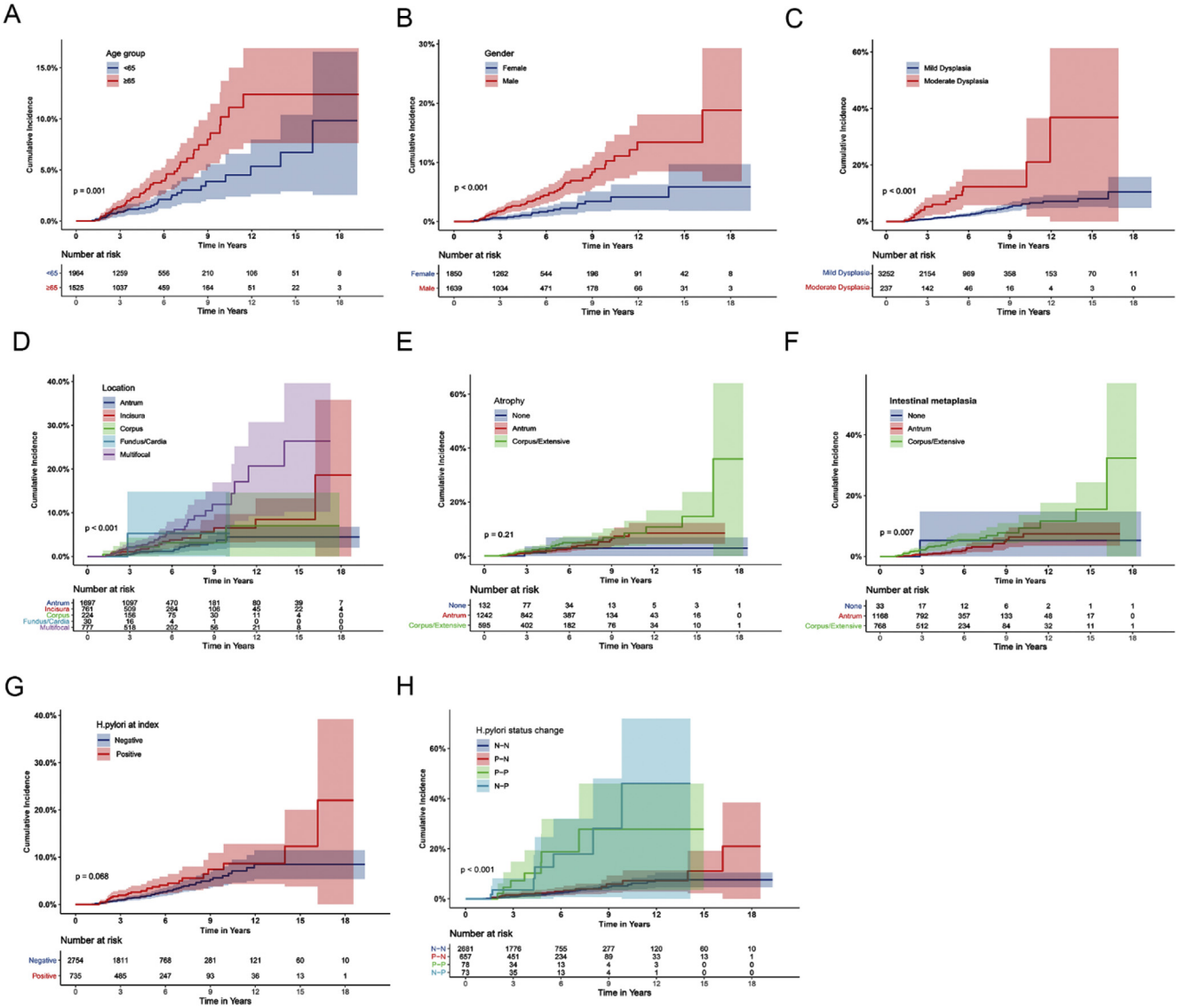


Supplementary Figure 1. Three-tier classification of gastric dysplasia. (*A*) Mild dysplasia. Mild irregularity of mucosal architecture with back-to-back gland formation and nuclear stratification with slightly increased nuclear-cytoplasmic ratio. (*B*) Moderate dysplasia. Slight architectural irregularity with tubules lined by basophilic cells with thin, elongated nuclei confined to the lower part of the cells. Nuclear atypia was moderate, and there was reduction of secretory products and back-to-back gland formation. (*C*) Severe dysplasia. Disorganized mucosal architecture with irregularly shaped tubules with diffuse budding and branching of the crypts and possible papillary growth. Cells have marked basophilia and hyperchromatic pseudostratified nuclei, and most of the nuclei reach the upper half of the cells. Cellular and nuclear polarity was lost. Magnification: left $\times$100, right $\times$200.



Supplementary Figure 2. Outcomes of mild-moderate dysplasia with regard to follow-up durations and periods of dysplasia detection. (*A*) Outcomes vs follow-up durations. The outcome of dysplasia was similar regarding different follow-up durations ($<$3 years [n = 1193], $\geq$3 to $<$6 years [n = 1281], $\geq$6 to $<$9 years [n = 744], $\geq$9 to $<$15 years [n = 198], $\geq$15 years [n = 73]) (P = .187, tested by chi-square test). (*B*) Outcomes vs periods of initial dysplasia detection. Those enrolled earlier (2000–2008, n = 744) had a higher rate of progression than that of included later (2009–2017, n = 2745) ($P < .001$, tested by chi-square test).



Supplementary Figure 3. Kaplan-Meier cumulative incidence for advanced neoplasia stratified by different individual factors. (*A*) Older patients (≥65 years of age) are associated with a higher risk of disease progression. (*B*) Compared with female patients, male patients with mild-moderate dysplasia are more likely to develop advanced neoplasia. (*C*) The risk of advanced neoplasia is significantly higher in moderate versus mild dysplasia. (*D*) Cumulative incidence of advanced neoplasia regarding the different location of mild-moderate dysplasia (antrum, incisura, corpus, fundus/cardia, and multifocal sites). (*E*, *F*) Patients with corpus or extensive atrophy or intestinal metaplasia in background mucosa are at higher risk of disease progression. (*G*) *Helicobacter pylori* infection at index endoscopy is not associated with advanced neoplasia development. (*H*) Persistent Helicobacter pylori *infection* after dysplasia detection increases the risk of disease progression. *P* value was calculated by log-rank test. N, negative; P, positive.

Supplementary Table 1. Summarization of Published Researches Investigating the Natural History of Gastric Mild-Moderate Dysplasia/LGD

Study	Country	Follow-Up Duration (Mean)	Patients	Outcome		
				No Detected (%)	Persistent Detection (%)	Progression (Severe Dysplasia/ HGD/GC) (%)
Farini R, 1983[8]	Italy	NA	Mild: 20	65	30	0
Saraga EP, 1987[9]	Switzerland	3.5 y	Mild: 23 Moderate: 41	NA	NA	1.6
Coma del Corral MJ, 1990[10]	Spain	2.16 y	Moderate: 41	53.6	34.4	12.2
Rugge M, 1991[11]	Italy	1.57 y	Mild: 47 Moderate: 22	Mild: 66 Moderate: 30[a]	Mild: 15 Moderate: 30	Mild: 19 Moderate: 40
Di Gregorio, 1993[12]	Italy	NA	Mild: 73 Moderate: 16	Mild: 74 Moderate: 56	Mild: 19 Moderate: 56	Mild: 7 Moderate: 13
Fertitta AM, 1993[13]	Italy	1.08 y	Moderate: 21	38	28	33
Bearzi I, 1994[14]	Italy	NA	LGD: 81	49.4	18.5	32.1
Rugge M, 1995[15]	Italy	Mild: 2 y Moderate: 2.58 y	Mild:53 Moderate: 33	Mild: 35.8 Moderate: 12.1	Mild: 43.4 Moderate: 39.4	Mild: 7.5 Moderate: 33.3
Kokkola A, 1996[16]	Finland	NA	Mild: 84 Moderate: 14	NA	NA	Mild: 0 Moderate: 21.4[b]
You WC, 1999[17]	China	NA	Mild: 503	68.9	27.2	2.8[c]
Rugge M, 2003[18]	Italy	NA	LGD: 90	53.3	31.1	15.6
Yamada H, 2004[19]	Japan	6 y	LGD: 38	NA	NA	0
de Vries AC, 2008[20]	The Netherlands	2.5 y	LGD: 2968	NA	NA	9.1[c]
Raftopoulos SC, 2012[21]	Australia	NA	LGD: 5	80	20	0
den Hoed CM, 2013[22]	The Netherlands	NA	LGD: 18	100	0	0
Li D, 2016[23]	United States	24,440 person-years	LGD: 141	NA	NA	4.3[c]
den Hollander, 2019[24]	The Netherlands	4.75 y	LGD: 23	96	4	0

GC, gastric cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NA, not available.
[a]No dysplasia or detection of mild dysplasia.
[b]Only for severe dysplasia.
[c]Only for gastric cancer.

Supplementary Table 2. Baseline Characteristics Between the 3489 Included Patients and 7558 Excluded Patients

Variable	Included Patients (n = 3489)	Excluded Patients (n = 7558)
Sex		
Male	1639 (47.0)	3952 (52.3)
Female	1850 (53.0)	3606 (47.7)
Age at index endoscopy, y		
Mean ± SD	61.5 ± 11.61	59.7 ± 13.0
Median (IQR)	62.0 (54–70)	61.0 (52–69)
Degree of dysplasia		
Mild	3252 (93.2)	7060 (93.4)
Moderate	237 (6.8)	498 (6.6)
Dysplasia location		
Antrum	1697 (48.6)	3537 (46.8)
Incisura	761 (21.8)	1715 (22.7)
Corpus	224 (6.4)	507 (6.7)
Fundus	6 (0.2)	18 (0.2)
Cardia	24 (0.7)	42 (0.6)
Multifocal site	777 (22.3)	1739 (23.0)
***H. pylori* status at index**		
Negative	2754 (78.9)	5550 (73.4)
Positive	735 (21.1)	2008 (26.6)

Values are n (%), unless otherwise indicated.
H. pylori, *Helicobacter pylori*; IQR, interquartile range.

Supplementary Table 3. Follow-Up Durations Regarding the Different Number of Surveillance Endoscopy

The Number of Surveillance Endoscopy	Follow-Up Durations		
	Mild Dysplasia	Moderate Dysplasia	Total Cohort
1	1.70 (1.23–13.71)	2.20 (1.34–10.21)	1.71 (1.24–13.71)
2	3.03 (2.15–16.74)	2.28 (1.66–11.25)	2.96 (2.13–16.74)
3	4.25 (3.08–15.05)	3.08 (2.28–11.66)	4.14 (3.02–15.05)
4	5.23 (4.14–16.12)	3.87 (2.91–8.40)	5.12 (3.97–16.12)
5	6.04 (4.97–16.57)	4.58 (3.72–8.31)	5.92 (4.83–16.57)
> 5	8.27 (6.66–19.31)	6.21 (5.27–16.91)	8.17 (6.49–19.31)

Values are median (interquartile range).

Supplementary Table 4. Characteristics of 88 Patients With Advanced Neoplasia

	Severe Dysplasia (n = 34)	Gastric Cancer (n = 54)
Sex		
Male	23 (67.6)	39 (72.2)
Age, y		
At entry	65.2 ± 11.00	65.6 ± 8.41
At progression	69.4 ± 11.26	70.9 ± 8.63
Dysplasia at index endoscopy		
Degree		
Mild	28 (82.4)	41 (75.9)
Moderate	6 (17.6)	13 (24.1)
Location		
Antrum	7 (20.6)	15 (27.8)
Incisura	10 (29.4)	13 (24.1)
Corpus	1 (2.9)	4 (7.4)
Fundus	0 (0.0)	0 (0.0)
Cardia	0 (0.0)	1 (1.9)
Multifocal sites	16 (47.1)	21 (38.9)
Histology of background mucosa at index endoscopy		
Distribution of atrophy		
None	0 (0.0)	2 (3.7)
Antrum-limited	11 (32.4)	21 (38.9)
Corpus-limited	1 (2.9)	1 (1.9)
Extensive	9 (26.5)	13 (24.1)
NA	13 (38.2)	17 (31.5)
Distribution of IM		
None	0 (0.0)	1 (1.9)
Antrum-limited	5 (14.7)	18 (33.3)
Corpus-limited	0 (0.0)	0 (0.0)
Extensive	16 (47.1)	18 (33.3)
NA	13 (38.2)	17 (31.5)
***H. pylori* status**		
At index		
Negative	22 (64.7)	40 (74.1)
Positive	12 (35.3)	14 (25.9)
At last follow-up		
Negative	31 (91.2)	44 (81.5)
Positive	3 (8.8)	10 (18.5)
Histological type of gastric cancer		
Intramucosal carcinoma	—	3 (5.6)
Tubular adenocarcinoma	—	34 (63.0)
Papillary adenocarcinoma	—	6 (11.1)
Mucinous adenocarcinoma	—	4 (7.4)
Signet-ring carcinoma	—	2 (3.7)
Poor differentiation carcinoma	—	2 (3.7)
Undetermined histology	—	3 (5.6)
The number of surveillance endoscopy	4.4 ± 3.6	3.3 ± 2.1
Intervals between endoscopies until advanced neoplasia, months	12.0 (3.6–19.4)	21.4 (12.1–53.0)
Intervention		
Follow-up	8 (23.5)	—
Endoscopic resection	24 (70.6)	24 (44.4)
Surgery	0 (0.0)	20 (37.0)
Chemical therapy	0 (0.0)	1 (1.9)
NA	2 (5.9)	9 (16.7)

Values are n (%), mean ± SD, or median (interquartile range).
H. pylori, *Helicobacter pylori*; IM, intestinal metaplasia; NA, not available.