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Risk stratification for progression to adenocarcinoma and high-grade dysplasia in Barrett's esophagus: a cohort study from an expert Spanish center

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Risk Stratification for Progression to Adenocarcinoma and High-grade dysplasia in Barrett's Esophagus: A Cohort Study from an Expert Spanish Center

Methods

Cohort study including all patients with confirmed BE enrolled in a structured surveillance program. Patients with basal adenocarcinoma or high-grade dysplasia were excluded. Survival analyses were used to evaluate predictors of progression.

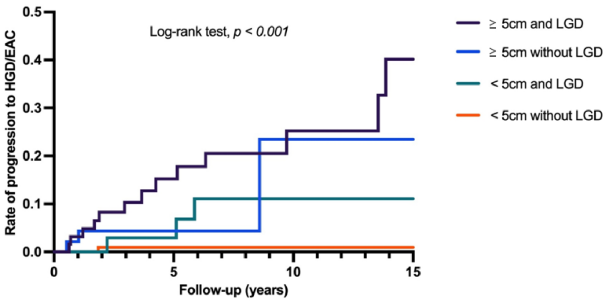
Outcomes

289 patients included, median follow-up of 5.3 years. 22 (7.6%) progressed.

Low grade dysplasia (LGD) and BE length were independently associated with progression, with additive prognostic impact.

Conclusion

Integrating LGD and BE length into risk models may improve individualized surveillance, guiding early endoscopic therapy in high-risk patients and safe de-escalation in minimal-risk groups.



Number at risk at time (years)	0	5	10	15
≥ 5cm and LGD	64	34	16	8
≥ 5cm without LGD	50	23	4	3
<5cm and LGD	44	26	16	5
<5cm without LGD	131	72	32	9

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Risk stratification for progression to adenocarcinoma and high-grade dysplasia in Barrett's esophagus: a cohort study from an expert Spanish center

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Abstract

Background and aim: Barrett's esophagus (BE) carries a risk of progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC). Identifying patients at greatest risk is crucial to optimize surveillance and guide therapy. We aimed to evaluate predictors of progression in a large cohort.

Methods: We conducted a retrospective cohort study including all adult patients with confirmed BE enrolled in a structured surveillance program at a tertiary referral Spanish center. Patients with basal HGD or EAC, or only one surveillance endoscopy were excluded. Clinical, endoscopic, and histological data were collected. The primary outcome was progression to HGD or EAC. Kaplan–Meier and Cox regression analyses were used to evaluate predictors of progression.

Results: Of 375 patients, 289 were eligible for analysis. Median age was 57 years, 73% were male, and median follow-up was 5.3 years. Hiatal hernia was present in 58%, associated with greater variability in BE measurement. 22 patients (7.6%) progressed, with an incidence of 1.44% per patient-year. Low grade dysplasia (LGD) (HR 3.9, 95% CI 1.4–11.3, p=0.012) and BE length (HR 1.2 per cm, 95% CI 1.05–1.3, p=0.032) were independently associated with progression. Kaplan–Meier analysis showed the highest risk in patients with both LGD and long segments (≈4%/year), while those without LGD and short segments had negligible risk.

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Conclusion: LGD and BE length were independent predictors of progression, with additive prognostic impact. Integrating these variables into risk models may improve individualized surveillance, guiding early endoscopic therapy in high-risk patients and safe de-escalation in minimal-risk groups.

Keywords: Barrett's esophagus. Endoscopic surveillance. Esophageal cancer.

Lay Summary

Barrett's esophagus is a condition where the normal lining of the lower esophagus is replaced by tissue similar to the intestine. This change is a consequence of long-term acid reflux and increases the chance of developing esophageal cancer, which usually has a poor prognosis if detected late. Because of this, many patients with Barrett's esophagus are offered regular endoscopies to look for early warning signs. In this study, we followed nearly 300 people with Barrett's esophagus at a specialist hospital in XX for more than five years on average. We wanted to find out which patients were most likely to develop serious changes in the esophagus, such as high-grade dysplasia (a severe precancerous change) or cancer.

We found that two factors were most important. First, patients who had low-grade dysplasia at any time during their follow-up were at much greater risk than those who never had it. Second, patients with longer Barrett's segments were also at higher risk. When these two features were present together, the risk of progression was particularly high, while people with short segments and no dysplasia had almost no risk. These results suggest that combining the presence of low-grade dysplasia and the length of Barrett's esophagus can help doctors better decide which patients need close monitoring and early treatment, and which can be safely discharge or monitored less often.

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1. Introduction

Barrett's esophagus (BE) is a premalignant condition characterized by replacement of normal squamous epithelium with intestinal-type columnar epithelium (1,2). Patients with BE are at increased risk of progression to esophageal adenocarcinoma (EAC), a malignancy with rising incidence and poor prognosis in Western countries (3,4). Surveillance programs aim to detect dysplasia and early neoplasia at a stage when endoscopic therapy can provide cure, thereby reducing disease-related mortality.

Low-grade dysplasia (LGD) is considered the earliest histological marker of neoplastic risk in BE, yet its prognostic role has been limited by interobserver variability (5,6). Expert pathology review improves reproducibility, and when confirmed, LGD carries an annual progression risk of 9–13%, compared to less than 1% when downgraded to non-dysplastic BE (7–9). In addition to dysplasia, several clinical and endoscopic features have been linked to a higher risk of progression, including male sex, longer BE segment length, obesity, and the presence of hiatal hernia (10–12). Identifying these risk factors remains crucial to optimize surveillance strategies and guide therapeutic decision-making.

According to current guidelines (6,13,14), patients with confirmed dysplasia or long-segment BE should be managed in specialized centers that meet defined criteria for case volume, procedural experience, access to surgical and oncological services, and prospective data collection. These expert centers play a pivotal role in ensuring high-quality care, optimizing treatment strategies, and generating pragmatic evidence. This study aimed to

evaluate the results of a surveillance program in a Spanish tertiary referral center, focusing on the rate of progression to high-grade dysplasia (HGD) or EAC and risk stratification.

2. Methods

2.1. Study design and population

We conducted a retrospective cohort study at Hospital Clinic of Barcelona, a tertiary referral center with expertise in BE management (15). Adult patients with BE, defined as ≥1 cm of columnar mucosa with histological intestinal metaplasia, were included between January 2000 and January 2025. Patients with HGD/EAC at index endoscopy, previous esophageal surgery, or without any surveillance endoscopy were excluded. Patients were followed until development of HGD or EAC, or until complete remission of intestinal metaplasia (CR-IM) after radiofrequency treatment.

The study protocol (HCB/2025/0723) was approved by the Institutional Review Board of Hospital Clinic of Barcelona (July 23, 2025). The study followed the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Endoscopic evaluation

All surveillance procedures were conducted within a structured BE program led by an expert team of endoscopists, gastroenterologists, surgeons, and gastrointestinal pathologists. All procedures were systematically performed by a single expert endoscopist using high-definition endoscopes equipped with virtual chromoendoscopy. At the discretion of the endoscopist, acetic acid and a transparent cap were used to optimize inspection and lesion detection.

The extent of BE was described according to the Prague classification, and visible lesions were classified using the Paris system. Biopsy sampling followed the Seattle protocol, with four-quadrant biopsies every 2 cm plus targeted biopsies of visible lesions (16). Endoscopic therapies were performed using standard techniques and guideline-based indications. Clinical evaluation and surveillance planning were coordinated by the treating gastroenterologist or primary care physician, following guideline intervals when possible.

2.3. Histopathological assessment

All biopsy and resection specimens were reviewed by GI pathologists with expertise in BE. Histological grading was performed using established criteria (17), and the highest degree of abnormality was reported for each endoscopy.

2.3. Data collection

Clinical, endoscopic, and histologic data were retrieved from a prospectively maintained institutional database and complemented by individual review of electronic medical records when necessary. Endoscopies performed outside the structured surveillance program (i.e. symptoms, endoscopic treatments for any cause) were not considered.

For patients who progressed to adenocarcinoma, tumor staging according to the TNM classification, and data regarding endoscopic and surgical treatment were collected. Data management was performed using REDCap (Research Electronic Data Capture) hosted at Hospital Clinic of Barcelona.

2.4. Definitions and outcomes

Patients were considered to have LGD at baseline if diagnosis was made at the first endoscopy at our Unit, and LGD at any time if LGD diagnosed either at baseline or during surveillance. LGD was classified as *persistent* when present in at least two consecutive endoscopies, or *non-persistent* when present in a single or non-consecutive endoscopies.

The primary outcome was progression to HGD or EAC in a patient with non-dysplastic BE or LGD at index endoscopy, and at least 6 months after the first complete endoscopic evaluation. For survival analysis, patients were censored at time of progression or latest known follow-up. Patients treated with RFA were censored at the date of CR-IM. Intra-patient variability in BE extent was defined as the difference between minimal and maximal recorded lengths (circumferential and maximal) across follow-up endoscopies.

2.5. Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQR) and categorical variables as counts and percentages. Group comparisons used Chi-square or Fisher's exact test for categorical data and Student's t-test or Mann–Whitney U test for continuous variables. Normality was tested using the Shapiro-Wilk test.

Kaplan–Meier and log-rank test survival analysis was used to estimate the cumulative risk of progression. Hazard ratios (HRs) with 95% confidence intervals (CI) were calculated using a Cox proportional hazards model that included variables significant in bivariate analysis and those considered clinically relevant. Barrett's length was analyzed as a continuous variable in the model; for descriptive and graphical purposes, it was dichotomized at 5 cm (the median value in the series) to allow comparison across strata. Calendar period (before vs. after 2018) was included to account for guidelines changes.

All statistical tests were two-sided with $p < 0.05$ considered significant. Analyses were performed using SPSS Statistics v26.0 (IBM, Armonk, NY) and GraphPad Prism v10.0 (GraphPad Software, San Diego, CA).

3. Results

3.1. Study cohort

A total of 375 patients were included. 33 (8.8%) had EAC and 19 (5.1%) had HGD at baseline and were excluded, along with 6 (1.6%) that had an EAC diagnosis within the first six months of follow-up. An additional 34 (9.1%) patients underwent only one surveillance endoscopy and were also excluded. The final analysis cohort consisted of 289 patients (77.1% of the initial cohort). Flow diagram of patient selection is shown in Figure 1.

3.2. Baseline characteristics

Study cohort demographics and follow-up characteristics are presented in Table 1. 211 (73%) were male and median age at the start of follow-up was 57 years (IQR 46.4–64.7). Hiatal hernia was present in 168 patients (58.1%), with a median axial length of 3 cm (IQR 2–4). Esophageal strictures were identified in 13 patients (4.5%), and in 7 of these cases (53.8%) it was located proximal to the upper limit of the BE segment.

Median follow-up was 5.3 years (IQR 2.5–9.3), during which patients underwent a median of 4 endoscopies (IQR 2–6). Median circumferential BE extent was 1 cm (IQR 0–5), and maximal extent was 4 cm (IQR 2–7). Patients with hiatal hernia exhibited greater variability in BE measurements: both for maximal (1.5 cm (IQR 1-3) vs. 1.0 cm (IQR 0-1), $p < 0.001$) and circumferential extent (1.0 cm (IQR 0-3) vs. 0 cm (IQR 0-1), $p < 0.001$).

At index endoscopy, 234 patients (78.9%) had non-dysplastic BE while 55 (21.1%) had LGD. During surveillance, LGD was newly detected in 53 patients (18.3%), yielding a total of 108 patients (37.4%) with LGD at any time (baseline or follow-up). In forty-two patients LGD was persistent, whereas 66 patients were classified as non-persistent LGD. RFA was performed in 21 patients with LGD, with a rate of complete eradication of intestinal metaplasia (CR-IM) of 76.2%.

3.3. Progression to HGD or EAC

During follow-up, 22 patients (7.6%) progressed to HGD (n = 13) or EAC (n = 9) yielding an incidence rate of 1.44% patients-year. Median time to progression was 4 years (IQR 1.6–8.9). Of the patients who developed EAC, staging was available in 77.7% (pT1a in 33.3%, pT1b in 33.3% and ≥pT2 in 11.1%). Endoscopic resection was performed in 6 cases (4 ESD and 2 EMR) and esophageal surgery in 4 cases, 3 of which followed a non-curative endoscopic procedure.

LGD at any time was strongly associated with a higher risk of progression compared to non-dysplastic BE (19.8% vs. 3.3%, $p < 0.001$). Progression rate did not differ significantly between patients with persistent and non-persistent LGD (22.2% vs. 18.3%, $p = 0.638$). Patient with LGD presented a median of 2 endoscopies showing LGD (IQR 1-2), with no difference between those who progressed and those who remained stable.

Patients with progression had also longer BE segments than non-progressors (median maximal length 7 cm (IQR 4.8-10) vs. 3 cm (IQR 2-6), $p < 0.001$). Progression was also more frequent among patients with hiatal hernia (10.1% vs. 4.1%, $p = 0.045$). There were no significant associations between progression and sex, calendar period (before 2018 vs. 2018 or after) or age at the start of surveillance. Variables associated with are shown in Table 2.

In the multivariable Cox model—adjusted for age, sex, presence of hiatal hernia, and calendar period— both LGD at any time (HR 3.9, 95% CI 1.4–11.3, *p = 0.012*) and BE length (HR 1.2 per cm, 95% CI 1.05-1.3, *p = 0.032*) were independently associated with progression. Test for potential interactions between histologic and endoscopic factors were not statistically significant, indicating that the effects of LGD and Barrett's extent on progression risk are independent. Complete Cox hazard model is shown in Table 3.

Kaplan–Meier curves stratified by a combined variable of LGD status and Barrett's length (<5 cm vs. ≥5 cm) showed a clear gradient of risk (Figure 2). The highest cumulative incidence of progression occurred among patients with both LGD and long segments, whereas those without LGD and short segments exhibited a negligible risk. The global log-rank test confirmed significant differences across groups (*p < 0.001*).

4. Discussion

This longitudinal study provides new insights into progression risk in a real-world cohort of BE patients managed at an expert center in Spain. Over a median follow-up exceeding five years, the global annual risk of progression to HGD or EAC was 1.4% per patient-year, which is higher than the 0.3%-1.2% patient-year previously reported in other series (18–23). This difference likely reflects referral bias and a higher baseline risk in our cohort, which included higher rates of baseline LGD. In addition, part of the increased detection of progression may be attributable to the systematic surveillance (24), where high-definition endoscopy and chromoendoscopy were consistently employed, potentially enhancing the identification of early neoplastic lesions and dysplasia.

LGD detected at any time during surveillance was the strongest predictor of progression. This is consistent with previous studies reporting annual progression risks of 9–13% when LGD is confirmed by expert review (7–9). Contrary to previous reports describing markedly higher progression rates in persistent LGD (9,25), our data showed no significant differences between persistent and non-persistent cases. These findings emphasize the prognostic value of LGD regardless of persistence, provided the diagnosis is confirmed by expert pathology.

In addition to LGD, BE extent was independently associated with progression, consistent with previous evidence (23). We stratified patients by segment length at a 5 cm cut-off, as this reflected the median extent in our cohort and provided better statistical separation of risk groups. Although a 3 cm threshold is often used in surveillance guidelines, this value is arbitrary. Previous studies (5,11,23) have shown a continuous increase in progression risk with each additional centimeter of BE length (HR 1.11–1.15), a finding consistent with our results (HR 1.01–1.3 per cm). In line with this concept, the ongoing BLISS project (NCT06803147) introduced significant changes in the latest Dutch guideline as part of a national initiative to refine BE surveillance based on longitudinal outcomes (26). This program adopted a 5 cm cutoff and considers patients with shorter, low-risk segments (no dysplasia and no family history of EAC) as exempt from surveillance. Using this threshold together with LGD status identified subgroups with markedly different outcomes. Patients with BE ≥5 cm and LGD had the highest incidence of progression, around 4% per patient-year, whereas those with short segments (<5 cm) without LGD had a negligible risk (<0.5% per patient-year). These findings illustrate a graded, additive effect of segment length and dysplasia, and support the integration of both variables into clinical risk models, potentially guiding early endoscopic therapy in those at greatest risk while safely extending surveillance intervals in patients at minimal risk.

Hiatal hernia was associated with BE progression in univariate analysis but not in multivariable models, likely reflecting mediation through segment length or dysplasia. Although hiatal hernia is well recognized as a risk factor for BE development, its role in BE progression has been less consistently reported (10–12,23). Notably, patients with hernia showed greater variability in BE extent across surveillance endoscopies, reflecting the technical challenge of evaluating the gastroesophageal junction in this context. This variability may contribute to misclassification and oversurveillance, underscoring the need for rigorous application of Prague criteria and careful inspection in this subgroup.

Our findings have direct clinical implications. LGD emerged as the strongest predictor of progression, highlighting the importance of surveillance in expert centers where both pathological confirmation and endoscopic evaluation can be reliably performed. Moreover, our data underscore the need for individualized surveillance. The recent BOSS trial (27), did

not demonstrate a survival benefit for routine surveillance in an unselected cohort of BE patients, reflecting the overall low risk of progression in many individuals. By integrating both LGD status over time and BE length into risk stratification, our study identifies patients at highest risk—those most likely to benefit from closer surveillance and timely endoscopic therapy—while allowing safe de-escalation in minimal-risk patients. This approach ensures that resources are focused where they are most likely to impact outcomes. Finally, although current European guidelines (6) recommend ablation for expert-confirmed LGD on at least two separate endoscopies (28–30), our findings shows that even isolated or intermittent LGD carries a significant risk of progression. The protective effect of RFA in our cohort—only 1 of 16 patients (5.9%) progressed after achieving CR-IM compared with 7 of 26 untreated or unsuccessfully treated patients (26.0%)—suggests a favorable impact on the natural history of dysplasia, although these results should be interpreted with caution given the sample size and observational design.

This study has several strengths. It reflects real-world data from a high-volume referral center, with surveillance performed by an expert endoscopist within a structured program and centralized pathology review, minimizing misclassification bias. Exclusion of patients diagnosed with HGD/EAC within six months reduced inclusion of prevalent cases. The long follow-up and relatively large sample size further strengthen the reliability of our estimates.

Limitations should also be acknowledged. The retrospective design and long study period, spanning more than two decades, encompass changes in endoscopic technology, pathology interpretation, and therapeutic strategies. Although we adjusted for calendar period, residual confounding is possible. The relatively small number of progressors limits subgroup analyses and may increase the risk of overfitting in multivariable models. We did not apply competing risk analyses, given the low number of events and minimal censoring due to death. As a referral center, our cohort likely overrepresents patients with advanced or complex disease, which may limit generalizability. Surveillance intervals were sometimes shorter than guideline recommendations, leading to oversurveillance that could have influenced progression estimates. Finally, although previous studies (23,25) identified baseline LGD as a major risk factor for progression, in our cohort, baseline examinations may not always have represented the true first endoscopy, as some patients had been

under surveillance in other centers before referral. In this context, we considered LGD at any time during follow-up as a more accurate measure of attributable risk.

5. Conclusion

In this longitudinal cohort, both LGD and Barrett's length were independent predictors of progression to HGD or EAC. Their combined presence identified a subgroup at particularly high risk, whereas patients with short segments without LGD had a negligible risk. These findings highlight the value of expert pathology review, support early intervention even in non-persistent LGD, and emphasize the need to integrate histologic and anatomic factors into individualized risk models to optimize surveillance strategies.

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Table 1. Study cohort demographics and follow-up characteristics (n = 289)

Age at the start of surveillance, y	57 (48.4-64.7)
Sex	
Male	211 (73%)
Female	78 (27%)
Follow-up, y (IQR)	5.3 (2.5-9.3)
Number of surveillance endoscopies (IQR)	4 (3-6)
Barrett's length	
Circunferential (IQR)	3 (2-7)
Maximal (IQR)	1 (0-5)
Baseline histology	
ND-BE	234 (81%)
LGD	55 (19%)
Hiatal hernia	168 (58.1%)
Esophageal stenosis	13 (4.5%)

BE, Barrett’s esophagus. LGD, Low-grade dysplasia. ND, non-dysplastic.

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Table 2. Progression to HGD or EAC according to LGD status, BE length and hiatal hernia

	Number of patients that progressed to HGD/EAC (n)	Incidence rate per patient-year (95% CI)	*p*-value
LGD status			*<0.001*
Mantained ND-BE	5 (2.8%)	0.56 (0.18 to 1.32)	
Present at any time	17 (15.7%)	2.43 (1.42 to 3.89)	
Non-persistent	8 (12.1%)	2.08 (0.90 to 4.09)	*0.638**
Persistent	9 (21.4%)	2.76 (1.26 to 5.24)	
Barrett's length (3cm cut-off)			*<0.001*
<3 cm	2 (1.75%)	0.33 (0.04 to 1.20)	
≥3 cm	20 (11.4%)	2.16 (1.32 to 3.33)	
Barrett's length (5cm cut-off)			*<0.001*
<5 cm	5 (2.9%)	0.53 (0.17 to 1.23)	
≥5 cm	17 (14.9%)	2.84 (1.66 to 4.55)	
Hiatal hernia			*0.045*
Absent	5 (4.1%)	0.79 (0.26 to 1.85)	
Present	17 (10.1%)	1.87 (1.09 to 2.99)	

BE, Barrett's esophagus. ND, non-dysplastic. LGD, Low-grade dysplasia. HGD, high-grade dysplasia. EAC, esophageal adenocarcinoma

* Comparison between persistent vs. non-persistent LGD.

Table 3. Cox regression analysis of factors associated with progression to HGD/EAC

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	HR	95% CI	*p*-value
LGD at any time	3.89	1.35 to 11.28	*0.012*
BE length (per cm)	1.16	1.01 to 1.33	*0.032*
Presence of hiatal hernia	1.82	0.64 to 5.19	*0.261*
Age at the start of surveillance (per year)	1.00	0.97 to 1.04	*0.717*
Male sex	1.51	0.51 to 4.45	*0.452*
Calendar period (<2018)	1.70	0.58 to 5.02	*0.330*

BE, Barrett's esophagus. CI, confidence intervals. LGD, Low-grade dysplasia. HGD, high-grade dysplasia. EAC, esophageal adenocarcinoma

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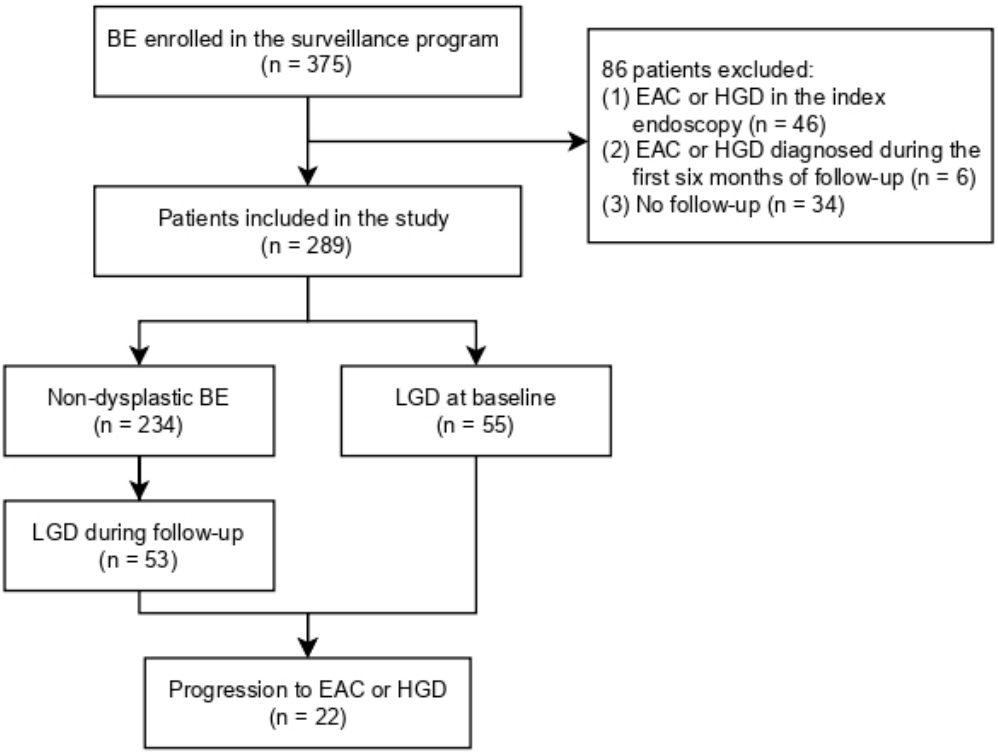

Figure 1. Flow diagram of patient selection for our final study cohort.

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

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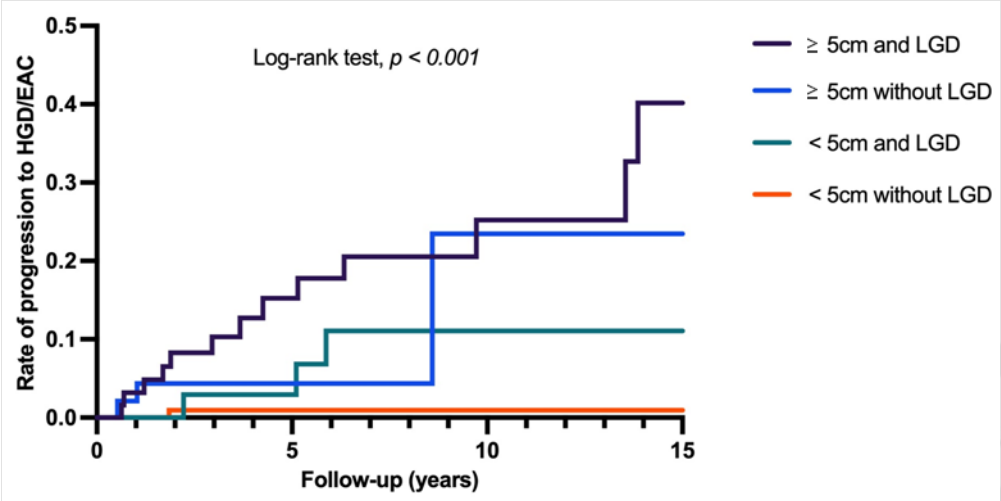

Number at risk at time (years)	0	5	10	15
≥ 5cm and LGD	64	34	16	8
≥ 5cm without LGD	50	23	4	3
<5cm and LGD	44	26	16	5
<5cm without LGD	131	72	32	9

Figure 2. Kaplan–Meier curves stratified by combined categories of LGD status and Barrett's length (<5 cm vs ≥5 cm). Patients with both LGD and long segments showed the highest progression risk, while those without LGD and short segments exhibited negligible risk (log-rank p < 0.001).