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Endoscopic features of low-grade dysplastic Barrett's

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Authors
Tony He[1,2], Kiran Gopinath Iyer[1], Mark Lai[1], Eloise House[3], John L Slavin[3], Bronte Holt[1,2], Edward H Tsoi[4,2], Paul Desmond[1,2], Andrew C F Taylor[1,2]

Institutions
1 Gastroenterology, St Vincent's Hospital Melbourne Pty Ltd, Fitzroy, Australia
2 Faculty of Medicine, The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Melbourne, Australia
3 Pathology, St Vincent's Hospital Melbourne Pty Ltd, Fitzroy, Australia
4 Gastroenterology , St Vincent's Hospital Melbourne Pty Ltd, Fitzroy, Australia

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
MBBS (Hons), FRACP Tony He, St Vincent's Hospital Melbourne Pty Ltd, Gastroenterology, Fitzroy, Australia
tonyhe.714@gmail.com

ABSTRACT

Background and study aims Barrett's esophagus (BE) with low-grade dysplasia (LGD) is considered usually endoscopically invisible and the endoscopic features are not well described. This study aimed to: 1) evaluate the frequency of visible BE-LGD; 2) compare rates of BE-LGD detection in the community versus a Barrett's referral unit (BRU); and 3) evaluate the endoscopic features of BE-LGD.

Patients and methods This was a retrospective analysis of a prospectively observed cohort of 497 patients referred to a BRU with dysplastic BE between 2008 and 2022. BE-LGD was defined as confirmation of LGD by expert gastrointestinal pathologist(s). Endoscopy reports, images and histology reports were reviewed to evaluate the frequency of endoscopically identifiable BE-LGD and their endoscopic features.

Results A total of 135 patients (27.2%) had confirmed BE-LGD, of whom 15 (11.1%) had visible LGD identified in the community. After BRU assessment, visible LGD was detected in 68 patients (50.4%). Three phenotypes were observed: (A) Non-visible LGD; (B) Elevated (Paris 0-IIa) lesions; and (C) Flat (Paris 0-IIb) lesions with abnormal mucosal and/or vascular patterns with clear demarcation from regular flat BE. The majority (64.7%) of visible LGD was flat lesions with abnormal mucosal and vascular patterns. Endoscopic detection of BE-LGD increased over time (38.7% (2009–2012) vs. 54.3% (2018–2022)).

Conclusions In this cohort, 50.4% of true BE-LGD was endoscopically visible, with increased recognition endoscopically over time and a higher rate of visible LGD detected at a BRU when compared with the community. BRU assessment of BE-LGD remains crucial; however, improving endoscopy surveillance quality in the community is equally important.

Introduction

Barrett's esophagus (BE) is an important risk factor for esophageal cancer [1]. Progression occurs in a stepwise manner from non-dysplastic BE to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally to adenocarcinoma [2, 3]. Esophageal cancer is associated with a poor prognosis and early endoscopic recognition of dysplasia represents an opportunity to halt disease progression and decrease cancer-related morbidity and mortality.

With advances in endoscopic imaging and increasing endoscopist experience, data describing the importance of detecting visible dysplastic BE lesions continue to grow. The current TREAT-BE consortium recommends, as a quality indicator, that at least 80% of HGD or cancerous lesions should be detected endoscopically [4]. With regard to BE-LGD lesions, there remain no recommended quality indicators for endoscopic identification. This is likely due to a paucity of data describing the endoscopic features of BE-LGD, compounded by interobserver variability among pathologists regarding the histological diagnosis [5, 6]. This has resulted in a generalized community belief that BE-LGD is most commonly invisible endoscopically. However, recently, in a Dutch cohort of 168 patients with persistent BE-LGD, Nieuwenhuis et al reported visible lesions detected in 7% of patients (n = 12) [7], whereas Tsoi et al, in a cohort of 75 patients with BE-LGD, identified BE-LGD lesions in 18.7% [8]. Furthermore, Hussein et al recently identified that nodular BE-LGD at index endoscopy was associated with progression to neoplasia [9]. Separately, Tsoi et al described a subset of BE-LGD patients with a diffusely nodular, multifocal LGD phenotype (DEVLB) that also appeared to be associated with an increased risk of progression to HGD or cancer [10]. Current guidelines recommend endoscopic resection for all visible dysplastic BE lesions and this may be equally relevant in patients with visible BE-LGD [11, 12].

It is clear that more data are needed to help describe the endoscopic features of BE-LGD and classify the different phenotypes. This will improve physician and endoscopic awareness and result in earlier recognition of BE-LGD, allowing for a timely referral to a Barrett's Referral Unit (BRU) for expert assessment. The aims of this study are to: 1) evaluate the frequency of endoscopically visible BE with LGD; 2) compare the rates of endoscopic detection of BE-LGD in the community versus a BRU; and 3) evaluate the endoscopic features and phenotypes of BE-LGD.

Patients and methods

Study design

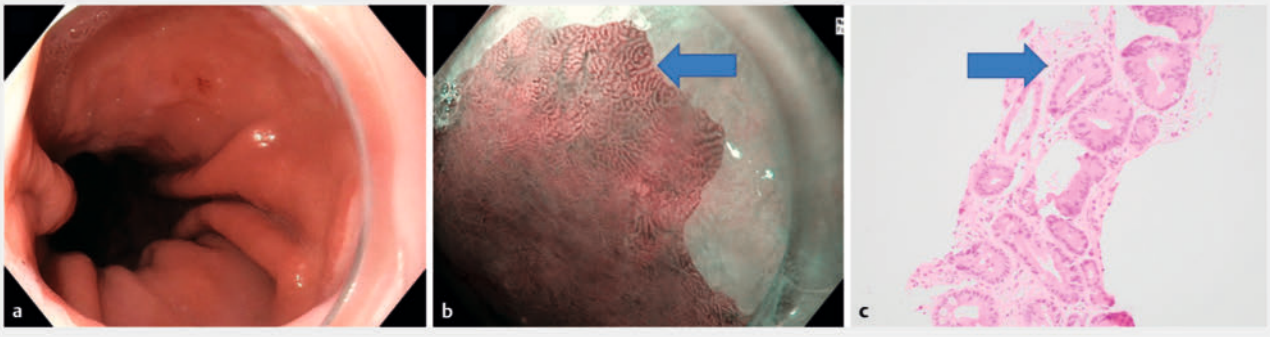
We conducted a retrospective analysis of patients with true low-grade dysplastic Barrett's who were managed at a BRU between November 2008 and November 2022. At our institution, all adult patients (18 years and older) referred with dysplastic BE were prospectively observed and data about them were recorded in an electronic database.

Study definitions

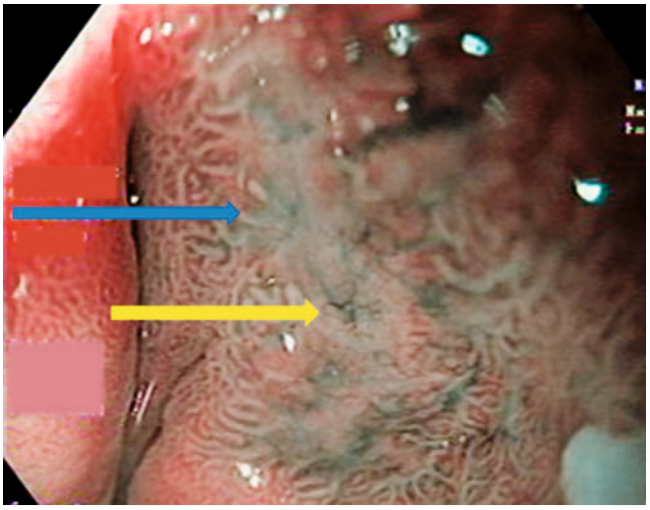
True BE with LGD was defined as confirmation of LGD on referral histology by an expert gastrointestinal pathologist (three at our center), followed by confirmation of LGD (and no worse pathology) at assessment endoscopy at our institution. Non-visible lesions were defined as endoscopically suspicious for BE without features of dysplasia (i. e., flat BE with regular mucosal pattern). Regular mucosal pattern was defined as villous or gyrate pattern with vessels directed along the tubules (▶ **Fig. 1**). Visible lesions were defined as lesions that were endoscopically suspicious for dysplasia (i. e., abnormal mucosal or vascular pattern, nodularity or depression (using the Paris classification [13]) and suspected sub-squamous or buried BE [14]). Abnormal or irregular mucosal pattern was defined as partial or complete absence of villous or tubular surface pattern (▶ **Fig. 2**). Abnormal or irregular vascular pattern was defined as partial or complete absence of vessels or wavy, irregularly branched vessels (▶ **Fig. 2**).

Endoscopic suspicion and features of BE with LGD and histopathology confirmation

During the study period, five experienced endoscopists documented any suspicion of dysplastic BE in the endoscopy report, with a uniform description of visible lesions (i. e., o'clock position with the endoscope in neutral position, the distance measured from the incisors in centimeters, size in millimeters, mu-



▶ **Fig. 1** **a** C0M1 flat, regular Barrett's examined on high-definition white light examination. **b** Barrett's tongue with regular mucosal pattern examined using narrow band imaging. c Seattle protocol biopsy: <1 mm, single focus of LGD.



▶ **Fig. 2** Low-grade dysplastic Barrett's with irregular vascular pattern (yellow arrow) and loss of mucosal pattern (blue arrow) on NBI.

cosal and vascular pattern (regular or irregular), and Paris classification [13]) and photo documentation of regular Barrett's mucosa and any visible lesions. Endoscopic data on BE-LGD lesions were prospectively collected and retrospectively analyzed. ▶ **Fig. 3** shows the study algorithm. All patients with suspected BE-LGD had external and internal histopathology reviewed by one to three expert gastrointestinal pathologists (with more than 5 years' experience) to confirm the diagnosis of LGD.

BRU assessment and treatment protocol for BE with LGD

Our national guidelines currently recommend that patients with suspected LGD in the community be referred to an expert center for assessment [15]. Patients referred to our center with suspected dysplastic BE underwent endoscopic examination with high-definition white light endoscopy (HD-WLE) and narrow band imaging (NBI) with GIF-HQ180 or GIF-HQ190 gastroscopes (Olympus, Tokyo, Japan). Dual image magnification and a transparent cap for image stabilization were used from 2013 onward. Confocal laser endomicroscopy was used between 2008 and 2011. Barrett's extent was documented according to the Prague classification [16]. At assessment endoscopy, endoscopic resection or targeted biopsy samples were obtained from any visible lesions. For flat BE with regular mucosal pattern, Seattle protocol biopsies were collected. All specimens were reviewed by an expert gastrointestinal pathologist and discussed at a Barrett's multidisciplinary meeting to confirm histological diagnosis. After confirmation of true LGD, participant management was individualized and guided by current Australian, European Society of Gastrointestinal Endoscopy, and British Society of Gastroenterology guidelines [15, 17, 18].

Depending on patient comorbidities and preferences, endoscopic eradication therapy was offered when there was confirmed persistent LGD or multifocal LGD. Endoscopic eradication therapy consisted of endoscopic resection of all visible lesions with proven (detected on prior targeted biopsy samples) or suspected dysplasia by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection, followed by radiofrequency ablation (RFA) of residual flat BE. In patients with non-visible (flat and regular Barrett's mucosa) dysplasia, RFA was performed. All patients were prescribed twice-daily high-dose proton pump inhibitors (PPIs) during endoscopic therapy and continued PPIs long-term following treatment.

Study outcomes and statistical analysis

Our primary study outcome was the proportion of patients with visible true BE-LGD lesions detected at our BRU. Our secondary outcomes included the proportion of patients with visible true BE-LGD lesions detected in the community and the endoscopic and histological features of visible LGD lesions. Data were summarized as means (± standard deviation), medians (interquartile range [IQR]) or proportions (%), as warranted. All statistical analysis was performed using STATA Version 17.0 (StataCorp LLC).

Ethics approval

This study was approved by the St Vincent's Hospital Human Research Ethics Committee (HREC-D 161/09).

Results

Patient cohort

A total of 497 patients with suspected dysplastic BE or T1a adenocarcinoma (LGD = 165, HGD = 190, T1a adenocarcinoma = 142) were referred between November 2008 and November 2022.

After expert gastrointestinal pathologist(s) review and BRU endoscopic assessment, 135 patients (27.2%) had confirmed BE with true LGD (14 of 190 patients were downstaged from HGD to LGD and 121 of 165 patients referred with LGD were confirmed to have LGD after review by an expert gastrointestinal pathologist). The cohort with true BE-LGD were included in the final analysis (▶ **Fig. 3**).

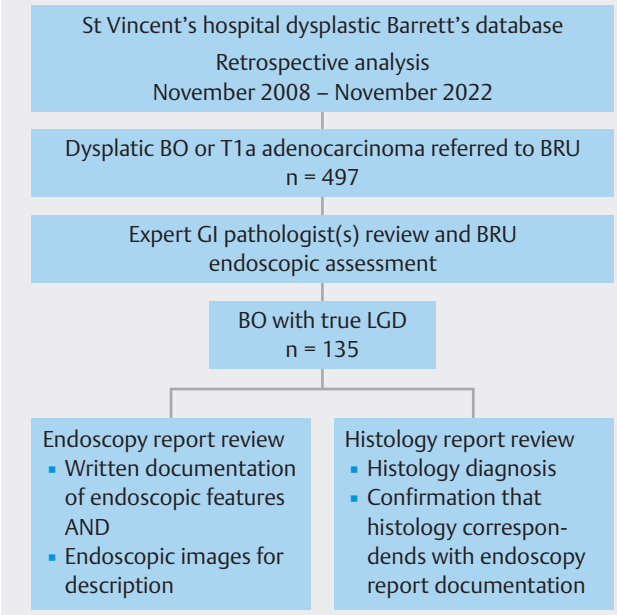
Visible LGD lesions detected in the community and at endoscopic assessment at BRU

Of the 135 patients with true BE-LGD, 15 (11.1%) had endoscopically visible lesions detected in the community, while at our BRU assessment, 68 patients (50.4%) had endoscopically visible lesions confirmed by targeted biopsies or endoscopic resection (▶ **Fig. 4**). In our cohort, the median time (weeks, IQR) between referral endoscopy and expert center endoscopy was 6.1 weeks (range, 3.6–11.5).

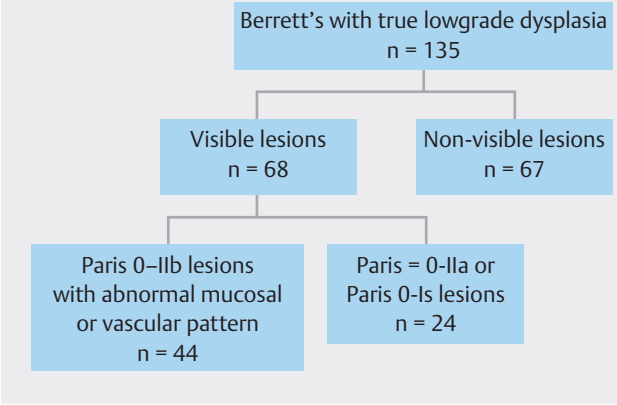
Of the 15 patients who had endoscopically visible lesions detected in the community, 11 (73.3%) were elevated lesions (Paris 0-IIa) and 4 (26.7%) were flat lesions with a depressed component (Paris 0-IIb-IIc).

Visible LGD lesions detected at our BRU over time

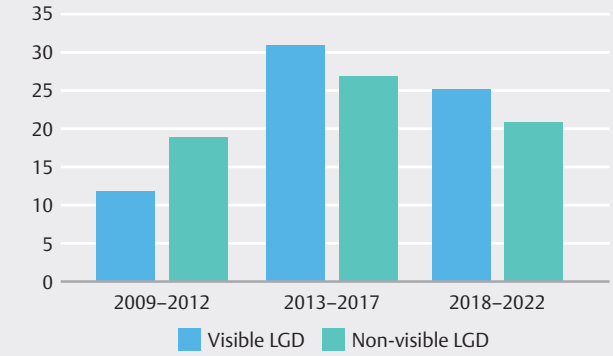
Detection of endoscopically visible BE with LGD between 2009 and 2012 was 38.7% (12 of 31). From 2013 to 2017, the detection of visible BE with LGD increased to 53.4% (31 of 58). Be-



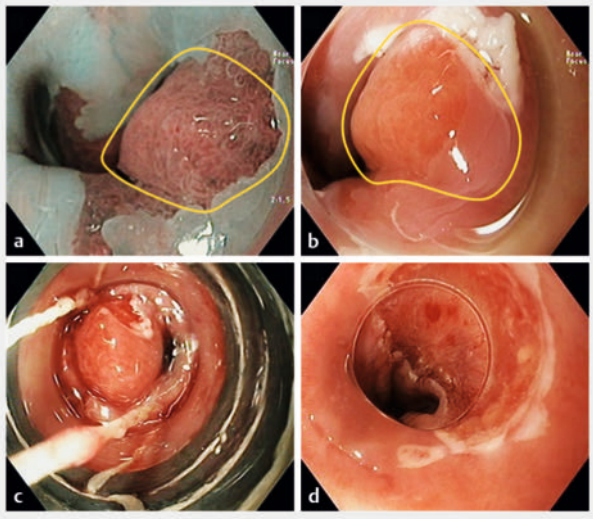
▶ **Fig. 3** Study algorithm.



▶ **Fig. 4** Frequency of endoscopic features suspicious for dysplasia among cases of histologically confirmed Barrett's with LGD.



▶ **Fig. 5** Endoscopically visible versus non-visible BE with LGD over time.



▶ **Fig. 6** **a** 14-mm Paris 0-IIa lesion with regular mucosal pattern examined using narrow band imaging. **b** Edges of the Paris 0-IIa lesion being marked using soft tip coagulation. **c**,**d** Paris 0-IIa lesion removed by endoscopic resection.

tween 2018 and 2022, the frequency of visible BE with LGD identified at assessment endoscopy continued to uptrend to 54.3% (25 of 46) (▶ **Fig. 5**).

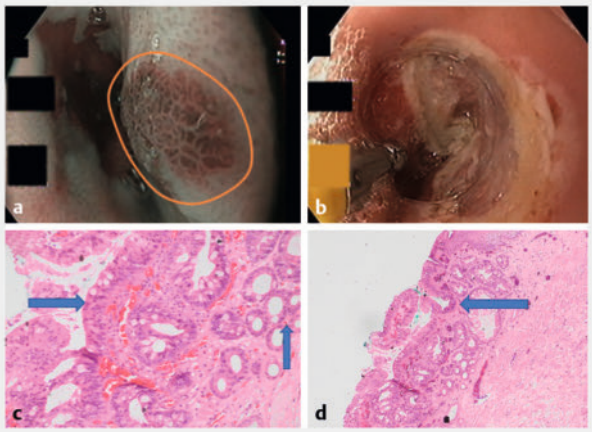
Endoscopic features and phenotypes of BE-LGD

In our cohort, three endoscopic phenotypes were identified: non-visible lesions, elevated lesions (Paris 0-IIa or 0-Is lesions), and flat (Paris 0-IIb) lesions with irregular mucosal or vascular pattern.

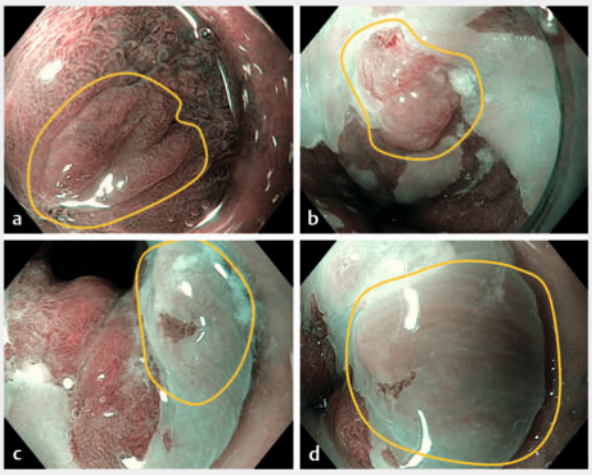
A total of 65 patients (49.6%) had flat Barrett's with regular mucosal and vascular pattern with LGD only detected on random Seattle protocol biopsies (▶ **Fig. 1**). Of the 67 patients with non-visible LGD lesions, 58 patients (86.5%) had a single, small focus of LGD seen histologically (from the Seattle protocol biopsy, ▶ **Fig. 1**).

Isolated Paris 0-IIa lesions with confirmed BE-LGD were detected in 24 patients (17.8%). Within this cohort, two subtypes were identified: B1 - Single elevated lesion with a median (IQR) diameter of 10.6 mm (range, 7.1–15.3), which were seen in 22 patients (91.7%) (▶ **Fig. 6**, **Fig. 7**, **Fig. 8a** and ▶ **Fig. 8b**); and B2 - Elevated de novo Barrett's island with a rim of darker pink squamous epithelium on HD-WL and darker brown squamous mucosa on NBI, confirmed to be sub-squamous BE-LGD (▶ **Fig. 8c** and ▶ **Fig. 8d**), which were seen in two patients (8.3%). The median (IQR) diameter of the BE island was 6.4 mm (range, 4.2–7.1).

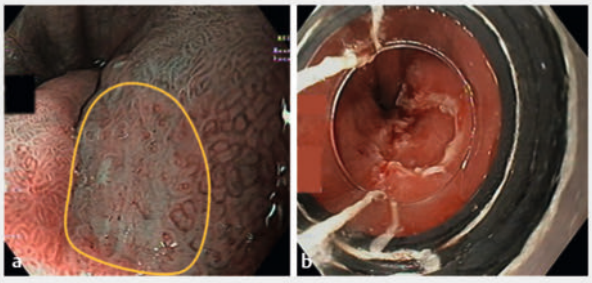
No patients with BE-LGD had Paris 0-Is lesions. Of the 24 patients with single Paris 0-IIa lesions, 17 (70.8%) had either multiple foci of LGD or a larger, continuous area of LGD seen histo-



▶ **Fig. 7** **a** 12-mm Paris 0-IIa lesion with prominent villous pattern, seen using narrow band imaging. **b** Paris 0-IIa lesion removed by endoscopic resection. (**c,d**) EMR specimen: multiple foci of LGD within the Paris 0-IIa lesion (arrows).



▶ **Fig. 8** **a** 8-mm Paris 0-IIa lesion with indistinct mucosal pattern, seen using narrow band imaging. **b** 15-mm Paris 0-IIa lesion central indistinct mucosal and vascular pattern, visualized using narrow band imaging. **c,d** de novo 4-mm Barrett's island with a raised rim of dark brown squamous mucosa with narrow band imaging, suggestive of sub-squamous Barrett's.



▶ **Fig. 9** **a** 8-mm Paris 0-IIb lesion with loss of regular mucosal pattern, detected using narrow band imaging. **b** Endoscopic mucosal resection of visible BE-LGD lesion.

logically (from biopsy or endoscopic resection specimen) (▶ **Fig. 7**).

A total of 44 patients (32.6%) had Paris 0-IIb (flat) lesions with suspicious features for dysplasia and confirmed BE-LGD. All Paris 0-IIb lesions had a clear demarcation line from the flat, regular BE mucosa. Within this cohort, three subtypes were identified: C1 - Flat focal, discrete lesion with loss of villous pattern and indistinct vascular pattern (▶ **Fig. 9**), seen in 30 patients (68.2%), with a median (IQR) lesions diameter of 7.1 mm (range, 4.1–10.3); C2 - Flat discrete lesion with a Paris 0-IIc (depressed component) associated with thickened villous pattern in seven 7 patients (15.9%), with a median lesion diameter (IQR) of 8.3 mm (range, 5.4–12.5); and C3 - Diffusely abnormal mucosa with widespread, subtle bumpy mucosa and patchy loss of or variation in mucosal pattern (▶ **Fig. 10**) with biopsies confirming sheets of multifocal LGD in seven patients (15.9%), which had a median (IQR) length of abnormal mucosa of 58 mm (range, 33.7–75.4) and was akin to the DEVLB phenotype described by Tsoi et al [8].

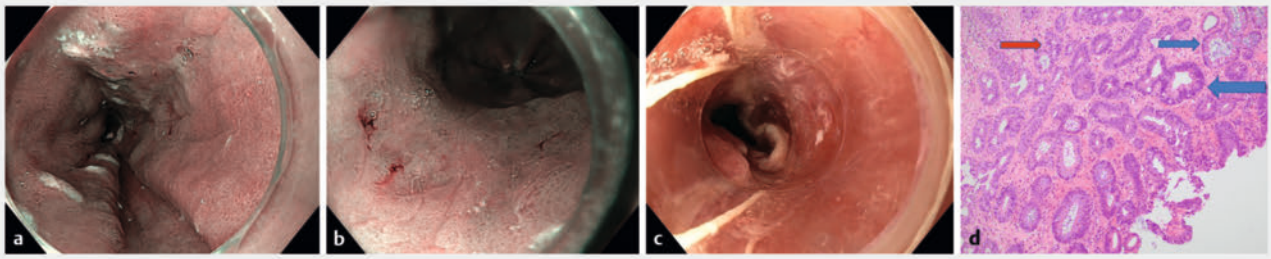
Of the 44 patients with Paris 0-IIb lesions, 34 (77.2%) had multiple foci of LGD or a larger, continuous area of LGD seen histologically (from biopsy or endoscopic resection specimen) (▶ **Fig. 10**). In patients with the DEVLB phenotype, the depth of dysplasia was greater than 1 mm in five patients (71.5%) (▶ **Fig. 10**).

Discussion

This study suggests that LGD can be visualized endoscopically in a significant proportion of patients with true BE-LGD, with three distinct endoscopic phenotypes identified over a 14-year period. The recognition of LGD endoscopically was higher in a BRU setting, when compared with referring community hospitals or clinicians, and the detection of visible LGD increased over time.

These findings are important in provoking discussion on whether LGD is more detectable endoscopically than originally appreciated and whether this should be a marker of quality endoscopy in future guidelines. This is relevant given that LGD, confirmed by an expert gastrointestinal pathologist, carries a 0.4% to 13.4% per patient per year risk for progression to HGD or cancer [9, 11, 12, 19, 20]. In our cohort, 11.1% of patients had a visible LGD lesion detected in the community. This was considerably lower than the 50.4% of visible LGD lesions identified at BRU assessment (in the same cohort). Our high proportion of visible lesions was also significantly more than the current reported rates from other expert Barrett's centers (6.4%–18.7%) [7, 8, 9, 10, 19, 20].

Several aspects may contribute to this difference in the detection rates between our BRU and the community referral hospitals and other Barrett's expert centers. First, it should be recognized that, in contrast to the referring community endos-



▶ **Fig. 10** **a** Diffusely abnormal mucosal pattern and a slightly raised lesion, seen using narrow band imaging, with edges marked with soft tip coagulation. **b** Indistinct mucosal and vascular pattern, visualized using narrow band imaging. **c** Endoscopic resection of abnormal Barrett's mucosa. d EMR specimen: multiple foci of LGD (blue and red arrows) with depth of dysplasia seen up to 1.2 mm from squamous epithelium (red arrow).

copists, our BRU endoscopists were aware of the LGD diagnosis before their assessment endoscopy. The location of the referral biopsy was often documented by the community endoscopist, and as such, the BRU endoscopists were able to focus their attention on a particular Barrett's area. Second, the higher caseload of patients with dysplastic BE at our BRU compared with the community allows for improved endoscopist learning, and may have resulted in increased detection of subtle lesions. This is especially relevant given that the majority of visible LGD lesions in our cohort were in subtle Paris 0-IIb (flat) lesions with irregular mucosal or vascular pattern. Third, the quality of the endoscopy equipment accessible differs from BRU to BRU, and from BRU to community hospitals. At our center, upgrade of the Olympus endoscopes and introduction of a transparent cap for image stabilization in 2013 resulted in a substantial increase in LGD lesions being detected over time. BRU endoscopist experience and awareness also likely contributed to this increase in detection. In keeping with data from Schölvinck et al and Cameron et al, our study underscores the importance of BRU assessment of true BE-LGD [21, 22].

Endoscopist experience and quality endoscopy can result in improved detection of LGD endoscopically. To improve BE surveillance in the community, the focus should continue to be on improving the quality of upper gastrointestinal endoscopy by raising clinician awareness of the endoscopic features of BE-LGD.

At our tertiary center, five BRU endoscopists described three distinct endoscopic phenotypes of BE-LGD: (A) Non-visible lesions; (B1–2) Single elevated lesions (Paris 0-IIa); and (C1–3) Flat lesions (Paris 0-IIb) with abnormal mucosal or vascular pattern. All visible BE-LGD lesions had a clear demarcation line that differentiated abnormal dysplastic mucosa from regular Barrett's mucosa. The BRU endoscopists frequently reported that endoscopic visualization of regular Barrett's mucosa first allowed for easier identification of this demarcation line and allowed the endoscopist to map out the BE-LGD lesion prior to endoscopic therapy. Another important subset of visible BE-LGD is LGD hidden in de novo buried Barrett's adjacent to Barrett's islands. Buried Barrett's is also usually considered endoscopically invisible. However, in our study, two patients had sub-squamous LGD that was detected in slightly raised Barrett's islands with a rim of darker pink squamous mucosa on HD-WL and darker brown squamous epithelium on NBI. These endoscopic features have been described by Yang et al [14]. Identification of these endoscopic features should prompt endoscopic resection to confirm and treat possible sub-squamous dysplastic Barrett's.

These three endoscopic phenotypes also had notable histologic differences. The majority of non-visible lesions detected on protocol biopsies had a single, < 1-mm focus of LGD, while visible LGD lesions often had multiple foci or a larger, continuous area of LGD within the biopsy or resection specimen. Furthermore, our patients with the DEVLB phenotype [10] frequently had LGD that was deeper than 1 mm (▶ **Fig. 9**) and interestingly, did not respond to RFA therapy (the reported controlled treatment depth of RFA is 0.5 to 1 mm [23]). These endoscopic and histologic differences may represent biological differences between BE-LGD phenotypes. It is also plausible that they represent different time points in the natural history of BE-LGD. Perhaps visible lesions are in fact more advanced LGD compared with non-visible lesions. This is in keeping with the recent report from Hussein et al that nodular BE-LGD was an independent risk factor for progression to HGD/cancer [9]. This is also consistent with the previous report from Pech et al that nodular BE lesions often harbor more advanced dysplasia [24]. Future larger prospective studies are required to further characterize the progression risk associated with each phenotype and their optimal therapy.

This study has several strengths. A key strength of a single-center analysis is that the data are homogeneous: endoscopic assessment, location and biopsy reporting, visible lesion description, biopsy sampling techniques, and forceps sizes were all consistent, and surveillance protocols were followed diligently, leading to lower detection bias and decreased sampling error. Importantly also, our definition of true BE-LGD was the same as prior studies and all histology samples were reviewed by expert gastrointestinal pathologists, allowing for generalizability to the real world [2, 5, 6, 7, 8, 9, 10, 11, 12].

This study also has potential limitations. Although our patients were recruited prospectively, some of the data collection was done retrospectively, increasing the risk for information and selection bias. Our data also describe results from an ex-

pert center, potentially limiting the generalizability of our results to the community setting. It does, however, highlight the importance of education to improve awareness and quality of endoscopy.

Conclusions

Our data show that BE-LGD is frequently endoscopically visible. Three main endoscopic phenotypes of BE-LGD were identified; however, more data are required to further clarify their individual risk profile and biologic differences. Identification of visible lesions was higher at a BRU and improved with time, underscoring the importance of quality endoscopy and endoscopist experience. BRU assessment of true BE-LGD is vital; however, improving quality endoscopy in community surveillance programs is arguably more important.

Conflict of Interest

The authors declare that they have no conflict of interest.

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