Barrett's esophagus with low-grade dysplasia: high rate of upstaging at Barrett's esophagus referral units suggests progression rates may be overestimated

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Background and Aims: The reported progression rate from low-grade dysplasia (LGD) in Barrett's esophagus (BE) to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) ranges from .4% to 13.4% per year. We hypothesize that some reported progression rates may be overestimated because of prevalent HGD or EAC that was not identified during endoscopic assessments performed in the community. Our aim is to determine the proportion of prevalent HGD or EAC detected by BE referral units (BERUs) in patients referred from the community with a recent diagnosis of LGD.

Methods: All patients referred from the community to 6 BERUs with a diagnosis of BE with LGD were identified. Patients with an assessment endoscopy performed at BERUs more than 6 months from their referral endoscopy in the community were excluded. Visible lesions and histology outcomes were compared between the community referral endoscopy and the assessment endoscopy performed at BERUs.

Results: The median time between BERU assessment and referral endoscopy was 79 days (interquartile range, 54-114). Of the 75 patients referred from the community with LGD, BERU assessment identified HGD or EAC in 20 patients (27%). BERU assessment identified more visible lesions than referral endoscopy performed in the community (39 [52%] vs 9 [12%], respectively; $P = .029$).

Conclusions: BERU assessment endoscopy identified more visible lesions than community referral endoscopy and identified HGD or EAC in 27% of patients referred from the community with a recent diagnosis of LGD. Reported progression rates from LGD to HGD or EAC may be overestimated. (Gastrointest Endosc 2021;94:902-8.)

Abbreviations: BE, Barrett's esophagus; BERU, Barrett's esophagus referral unit; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IMC, intramucosal carcinoma; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; SMC, submucosal adenocarcinoma.

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There is controversy in the literature concerning the rate of progression of Barrett's esophagus (BE) with low-grade dysplasia (LGD). The reported incidence of esophageal adenocarcinoma (EAC) arising in patients with LGD has varied greatly, from no more than the progression rate in nondysplastic BE (NDBE) to much higher rates. A systematic review,[1] conducted in 2009 to assess the rate of progression to EAC of LGD, high-grade dysplasia (HGD), and NDBE, demonstrated that the weighted average incidence rate for progression to cancer from LGD was 17 of 1000 patient-years compared with 6 of 1000 patient-years for NDBE and 66 of 1000 patient-years for HGD.

Three more recent European studies, which evaluated the incidence of progression from LGD to either HGD or EAC, found surprisingly high progression rates. A German study derived from community-based practices demonstrated 19% progression over 2 years.[2] A Dutch study of 147 individuals diagnosed with LGD from nonuniversity hospitals demonstrated that when the slides were reviewed by 2 expert pathologists, only 15%[3] were still considered LGD, with 85% downstaged to NDBE or indefinite for dysplasia (IND). Among those considered to have true LGD, 85% were found to have EAC (2 patients) or HGD (6 patients) over 109 months of follow-up (progression rate of 13.4% per year).[3] The same researchers, along with other European groups, performed a randomized controlled trial of radiofrequency ablation versus surveillance and found progression to HGD or EAC in 26.5% of individuals in the surveillance group at 3 years.[4]

These high rates of progression and evidence of reduced progression rates with radiofrequency ablation[4] have led to recommendations in several published guidelines that endoscopic therapy, generally radiofrequency ablation, should be undertaken in individuals with confirmed LGD, especially if it is present on repeated endoscopic examinations.[5-7] Several studies have shown that in individuals with HGD on random biopsy specimens taken in the community setting, repeated examination by experienced endoscopists using high-definition endoscopy and narrow-band imaging can often identify visible focal lesions that may contain adenocarcinoma.[8,9] However, there are no published data to date directly examining whether more-advanced lesions can be identified in the expert setting in individuals with LGD identified on biopsy specimens taken in the community setting.

This article seeks to examine this question by evaluating the findings of expert pathology and endoscopy assessment in patients referred to BE referral units (BERUs) after diagnosis of LGD in the community setting. We hypothesize that some cases of apparent progression from LGD to HGD or EAC may be explained by more-advanced lesions that were present at the time of LGD diagnosis but were not identified at that time. Therefore, when the more-advanced disease was identified at a later stage, it may have been inappropriately assumed to be because of progression rather than prevalent advanced disease that had been missed. This information will be useful in further refining the true incidence of progression from LGD and the role of rigorous endoscopic assessment to rule out advanced disease before LGD is confirmed as the most advanced disease. This should be taken into account in future management guidelines. Therefore, this multicenter study aims to determine the proportion of prevalent HGD or intramucosal carcinoma (IMC) detected by BERUs in patients referred from the community with a diagnosis of LGD.

METHODS

BERUs and database

In this retrospective study, each of the 6 BERUs is a major tertiary referral center for management of dysplastic BE within their state. Each comprises a team of endoscopists and expert GI pathologists with extensive experience in the assessment, management, and reporting of Barrett's pathology in a high-volume center.

Each BERU maintained a database with prospectively collected data on patient endoscopy and histology findings, demographics, and referring specialist. Subsequent assessments, treatment, and follow-up endoscopies performed at the BERUs were prospectively entered into the database.

Patient population

All consecutive patients referred to the 6 BERUs across Australia with a diagnosis of LGD from the community between 2009 and 2017 were identified from the BERU databases. Patient demographics, medical history, endoscopy, and histopathology reports from the community and BERUs were obtained from their individual, respective BERU database. Patients who had an assessment endoscopy performed at a BERU more than 6 months after their referral endoscopy, which was performed in the community, were excluded from the study. Only patients with a diagnosis of LGD confirmed by an expert GI pathologist (after review of their original community slides) were included in the study.

Endoscopic assessment protocol

The initial assessment endoscopy performed at the BERU comprised detailed inspection of the Barrett's segment using high-definition white-light and narrow-band imaging performed with either an H180 or HQ190 gastroscope (Olympus, Tokyo, Japan). A clear distal cap is often used to help examine the folds within the gastroesophageal junction. We did not use confocal laser endomicroscopy or volumetric laser

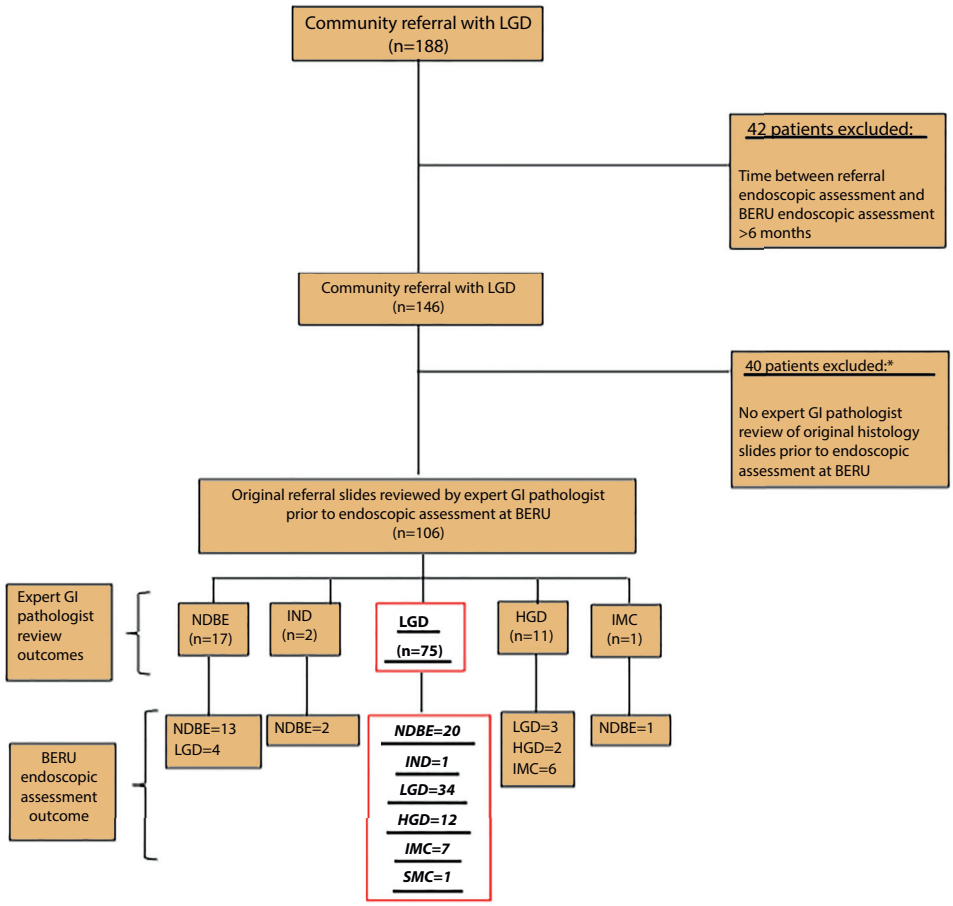

Figure 1. Overall outcomes after endoscopic assessment at Barrett's esophagus referral units (BERUs). Only the 75 patients with confirmed low-grade dysplasia (LGD) by a GI pathologist (*highlighted*) are included in analysis. *Outcomes in 40 patients were excluded from the analysis because of no expert GI pathologist review of original slides before endoscopic assessment at BERUs: nondysplastic BE, 5; indefinite for dysplasia, 3; LGD, 22; high-grade dysplasia, 7; intramucosal carcinoma, 1; submucosal cancer, 2.

endomicroscopy during our assessment. EMR via the Duette system (multiband cap and snare technique) was performed for any visible lesions with features suspicious for dysplasia or neoplasia. Visible lesions included nodules, ulcerations, erosions, and areas of mucosal abnormality. Quadrantic biopsy sampling was then performed as per the Seattle protocol,[8] and the pathologic assessment process was performed by an expert GI pathologist.

Statistical analysis

Statistical analysis was performed using Stata V.16.1 for Mac OS (StataCorp, College Station, Tex, USA). Mean ± standard deviation was used to describe variables with a parametric distribution, whereas median (interquartile range [IQR]) was used for those with a nonparametric distribution. Univariate analysis was performed using a χ^2 test and the Fisher exact test for categorical variables and Student *t* test and Mann-Whitney U test for continuous variables. Ethics approval was granted from the Ethics Committee at each individual site.

RESULTS

Patient demographics

Between 2009 and 2017 there were 188 patients referred from the community to 6 BERUs across Australia with the diagnosis of BE with LGD (site 1, n = 42; site 2, n = 8; site 3, n = 15; site 4, n = 12; site 5, n = 99; and site 6, n = 12). Of these 188 patients, 42 patients were excluded from the study because the time between their assessment endoscopy at BERUs and their original referral endoscopy from the community was more than 6 months. Of the remaining 146 patients, 40 patients were excluded from the analysis because their original histology slides were not reviewed by an expert GI pathologist before an endoscopic assessment at the BERU (see Fig. 1 for outcomes). Of 106 patients who had their LGD histology slide reviewed by an expert GI pathologist before endoscopic assessment at the BERU, 12 patients (11%) were upgraded to HGD (n = 11) and IMC (n = 1), 19 patients (18%) were downgraded to IND (n = 2) and NDBE (n = 17), and 75 patients (71%) had a confirmed diagnosis of LGD. The latter 75 patients

TABLE 1. Endoscopic findings from referral endoscopy in community vs assessment endoscopy from BERUs

	Community Center	BERUs	*P* value
Time between BERU endoscopic assessment and community center assessment, days		79 54-114]	
Circumferential length, cm	3 [0-5]	2 [0-5]	
Maximal length, cm	3 [1-5]	4 [1-7]	
Visible lesions detected	39 (52)	9 (12)	.029
Description of lesion			
Nodule	3	15	
Ulceration	0	8	
Erosion	0	0	
Mucosa abnormality	6	16	
Paris classification			
Is	0	4	
0-IIa	0	11	
0-IIa+c	0	4	
0-IIb	0	14	
0-IIc	0	6	

Values are median [interquartile range], n (%), or n.
BERU, Barrett's esophagus referral unit.

who had a confirmed diagnosis of LGD after an expert GI pathologist review of their original community slides were included in the analysis (Fig. 1). Most of these patients were men (n = 59, 79%) with a mean age of 72 years.

Endoscopic and pathologic assessment at BERUs

All 75 patients with confirmed LGD after GI pathologist review had an endoscopic assessment at a BERU (median time from referral endoscopy performed in the community, 79 days [IQR, 54-114]). After the endoscopic assessment, 20 patients (27%) had a diagnosis of HGD (n = 12), IMC (n = 7), or submucosal cancer (SMC) (n = 1); 34 patients (45%) had LGD, 1 (1%) had IND, and 20 (27%) had NDBE (Fig. 1). The median circumferential and maximal length was 2 cm [IQR, 0-5] and 4 cm [IQR, 1-7], respectively. There was no statistical difference between the median maximal length of those with HGD, IMC, or SMC compared with those with NDBE, IND, and LGD (P = .3486).

Visible lesions detected during referral endoscopy in the community and during endoscopic assessment at BERUs

After assessing all referral endoscopy reports from the community, the median circumferential and maximal length was 3 cm [IQR, 0-5] and 3 cm [IQR, 1-5], respectively. Visible lesions were detected in 9 of 75 patients (12%). These lesions included 3 patients with nodules and 6 patients with mucosal abnormality.

After endoscopic assessment at BERUs, visible lesions were detected in 39 of 75 patients (52%). Four patients had Paris classification 0-Is, 11 patients had Paris classification 0-IIa, 4 patients had Paris classification 0-IIa+c, 6 patients had Paris classification 0-IIc, and 14 patients had Paris classification 0-IIb detected (Table 1). There was a significantly higher detection of visible lesions during an endoscopy performed at a BERU compared with endoscopy performed in the community (39 [52%] vs 9 [12%], respectively; P = .029) (Table 1).

Of the 9 patients with visible lesions detected at referral endoscopy in the community, a subsequent assessment performed at BERUs identified visible lesions in 8 patients (89%), with NDBE identified in 1 patient (13%), LGD in 3 patients (38%), HGD in 2 patients (25%), and IMC in 2 patients (25%). In the remaining 1 patient where a visible lesion was not detected by a BERU assessment endoscopy, an LGD was detected on random biopsy sampling (Fig. 2).

In the 66 patients who did not have a visible lesion detected on referral endoscopy in the community, a subsequent assessment endoscopy performed at BERUs identified visible lesions in 31 patients (47%). Of these 31 patients, 8 (26%) had NDBE, 1 (3%) had IND, 11 (35%) had LGD, 6 (19%) had HGD, 4 (13%) had IMC, and 1 (3%) had SMC. In the remaining 35 patients, where a subsequent assessment endoscopy performed at BERUs did not identify any visible lesions, 11 patients (31%) had NDBE, 19 (54%) had LGD, 4 (11%) had HGD, and 1 (3%) had IMC (Figs. 2 and 3).

There was a significantly higher proportion of patients with HGD, IMC, or SMC in those who had a visible lesion detected at the BERU assessment endoscopy compared with no visible lesions detected at the BERU assessment

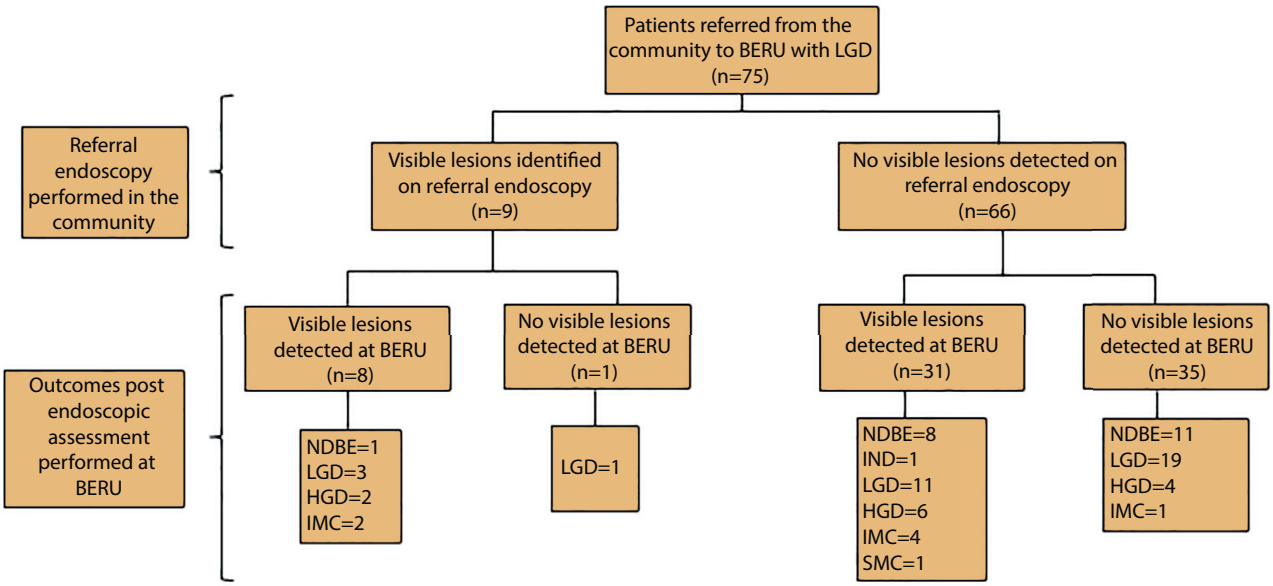

Figure 2. Comparing visible lesions and outcomes from referral endoscopy versus Barrett's esophagus referral unit assessment endoscopy. *BERU,* Barrett's esophagus referral unit; *HGD,* high-grade dysplasia; *IMC,* intramucosal carcinoma; *IND,* indefinite for dysplasia; *LGD,* low-grade dysplasia; *NDBE,* nondysplastic Barrett's esophagus; *SMC,* submucosal adenocarcinoma.

endoscopy (15 [38%] vs 5 [14%], respectively; $P = .016$). Of the 20 patients with HGD, IMC, or SMC, 15 (75%) were diagnosed from an EMR specimen compared with 5 (25%) diagnosed from biopsy specimens ($P < .001$).

DISCUSSION

This is a large multicenter experience on assessment of patients at BERUs after referral from the community with a diagnosis of LGD. Four important conclusions can be inferred from our results. The first is that BERU assessment resulted in a high detection of HGD and EAC in patients referred from the community with a recent diagnosis of LGD. Second, this likely represents prevalent HGD or EAC rather than rapid progression, therefore partly explaining the wide range of progression rates in the literature. Third, BERU assessment resulted in a higher detection of visible lesions compared with referral assessments in patients referred with a diagnosis of LGD from the community. Finally, there was a relatively higher proportion of confirmed LGD when the original community slides were reviewed by an expert GI pathologist compared with previously published data.[3] Interestingly, a significant number of patients had their diagnoses upgraded to HGD or IMC, confirming the importance of GI pathologist review before endoscopic assessment at BERUs.

There is a paucity of data looking at LGD in the community and how best to assess these patients. In this study we specifically assessed the difference in detection of visible lesions, HGD, or EAC between community centers and BERUs in patients referred from the community with a confirmed diagnosis of LGD by an expert GI pathologist. We demonstrated that endoscopic assessment performed at BERUs resulted in detection of HGD, IMC, or SMC in 27% of patients who had a recent diagnosis of LGD in the community. Given the short duration between BERU and community center assessments (median time, 79 days [IQR, 54-114]), patients with more-advanced dysplasia identified on endoscopic assessment at the BERUs likely represent prevalent HGD, IMC, or SMC rather than true progression. This may have led to an overestimate of reported LGD progression rates.

Endoscopic assessment at BERUs resulted in a higher detection of visible lesions compared with endoscopic assessment performed in community centers in patients with a community diagnosis of LGD. This finding is similar to that of Scholvinck et al[9] in their 198-patient cohort from 37 European community centers with histologic diagnoses of HGD or IMC. They showed that expert centers had a higher visible lesion detection rate than community centers (87% vs 60%, respectively; $P < .001$). This may be attributed to expert endoscopists being more likely to use advance imaging techniques and spend more time on inspection during the assessment. They may also be more likely to have the experience and knowledge in identifying subtle visible lesions of early neoplasia in BE and thereby performing more targeted and Seattle protocol biopsy sampling compared with community centers. Cameron et al[8] highlighted that the use of advanced imaging and quadrantic biopsy sampling as per the Seattle protocol was low in community centers at 14% and 20%, respectively.

Moreover, when a community endoscopist detected a visible lesion on referral endoscopy with a biopsy sample yielding LGD, a subsequent BERU endoscopic assessment

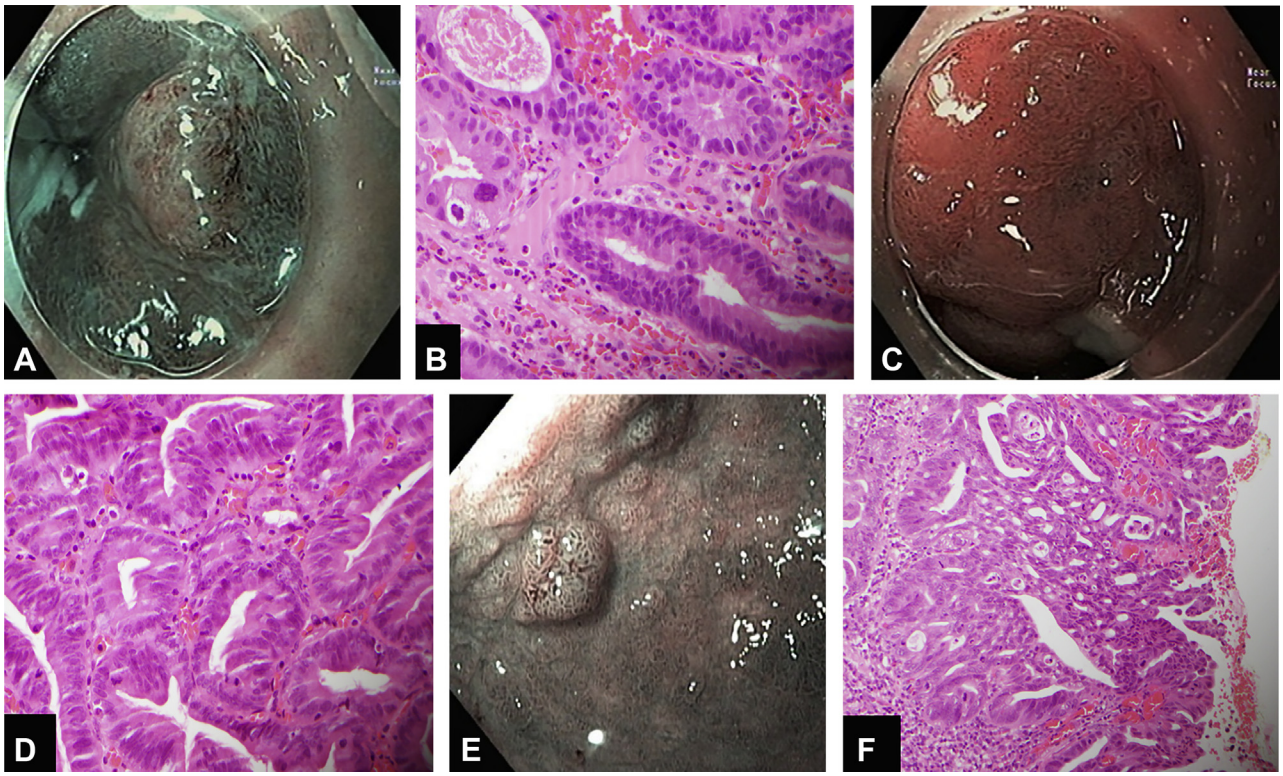

Figure 3. Endoscopic assessments performed at Barrett's esophagus referral units. **A,** Nodule (Paris 1s) identified on narrow-band imaging (NBI). **B,** EMR specimen showing Barrett's metaplastic epithelium with intestinal metaplasia and evidence of focal high-grade cytologic dysplasia. **C,** Paris 0-IIa+c, mucosal abnormality seen on high-definition white-light imaging. **D,** EMR specimen demonstrating an area of ulcerated high-grade dysplasia with architecturally dysplastic glands, high-grade cytologic atypia, and numerous mitoses. **E,** Nodule (Paris 1s) identified on NBI. **F,** EMR specimen showing extensive high-grade architectural atypia, back-to-back glands, and marked cytologic atypia consistent with an area of intramucosal adenocarcinoma.

identified HGD or IMC in 44% of these patients, suggesting there should be a high degree of suspicion for advanced dysplasia when a visible lesion is detected, even if the biopsy sample revealed LGD. However, even when there was no visible lesion detected on referral endoscopy in the community, a subsequent BERU endoscopic assessment identified a visible lesion in 47% of these patients and identified 16 patients (24%) with HGD, IMC, or SMC. This suggests that patients with a biopsy sample yielding LGD, with or without visible lesions identified in the community, should be referred to BERUs for further endoscopic assessment.

A relatively higher proportion of confirmed LGD was found in our cohort when the original community slides were reviewed by an expert GI pathologist. Of the 106 patients who had their original community slides reviewed by an expert GI pathologist, 12 patients (11%) were upgraded to HGD (n = 11) and IMC (n = 1), 19 patients (18%) were downgraded to IND (n = 2) and NDBE (n = 17), and 75 patients (71%) had a confirmed diagnosis of LGD. This finding is significantly higher than that reported by Curvers et al,[3] who reported confirmed LGD in only 15% of cases. The main difference between Curvers et al's methodology and our study is that Curvers et al had used 2 expert GI pathologists to independently review all histology slides. In case of disagreement, a consensus diagnosis was reached between both pathologists in a dedicated consensus meeting. In our study, we had 1 GI pathologist review the original community slides as part of the patients' standard of care.

Having an extra expert GI pathologist and a dedicated consensus meeting may have partly contributed to the difference in the number of confirmed LGD. In addition, there may be a higher interobserver agreement between community and expert GI pathologists in Australia. A study that involved 7 expert GI pathologists (4 from the United States and 3 from Europe) demonstrated that European pathologists tended to diagnose fewer cases of LGD and more cases of NDBE than American pathologists.[10] Wani et al[11] in their multicenter study of 210 patients with BE with LGD showed that the agreement between the local pathologist with at least 1 expert central GI pathologist was 85% and agreement between local pathologist and both expert central GI pathologists was 47%. It is important to note that in the study by Wani et al, the local pathologist also had a special interest in BE.[11] Although our 71% of cases with confirmed LGD was higher than that reported by Curvers et al,[3] it was still in line with that published by Wani et al.[11]

Another interesting finding was that we had a significant proportion of patients with their histology upgraded to HGD or IMC after having a GI pathologist review the community slides. Twelve patients (11%) had their diagnosis upgraded to HGD (n = 11) or IMC (n = 1) after review by a GI pathologist. Of these 12 patients, a subsequent BERU assessment identified 1 patient (8%) with NDBE, 3 patients (25%) with LGD, 2 patients (17%) with HGD, and 6 patients (50%) with IMC. If these patients did not have their original slides reviewed before endoscopic assessment, 4 patients (1 with NDBE and 3 with LGD) would have had surveillance initially and been classified as rapid progressors on their next surveillance endoscopy when advanced dysplasia was identified. This therefore highlights the importance of having an expert GI pathologist review the original histology slides before endoscopic assessment at BERUs as part of the standard of care.

Limitations to this study are the retrospective study design and that not all BERUs routinely reviewed all community histology slides by a GI pathologist before endoscopic assessment. This has resulted in a smaller sample size because we believe this step is extremely important in diagnosing LGD.

This is an important study because it suggests that the wide range of reported LGD progression rates in the literature may be significantly influenced by inadequate endoscopic and histopathologic assessment in the community. Further research is needed to define the true progression rate of LGD; however, advanced dysplasia must be confidently excluded by endoscopic and histopathologic assessment at BERUs before enrolling patients in subsequent follow-up studies.

In conclusion, endoscopic assessment at BERUs resulted in a higher detection of visible lesions, HGD, and EAC compared with community centers. We believe that some of the reported LGD progression rates in the literature may be overestimated because many studies have included prevalent HGD or EAC during their analysis of the LGD progression rate. However, a community diagnosis of LGD is not benign because in our cohort 1 in 4 patients with a community diagnosis of BE with LGD was a "missed" HGD or EAC. Further prospective studies are required on the assessment of BE with LGD in the community. However, until then we suggest that all patients with a community diagnosis of LGD be referred to BERUs for further assessment and management.

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