AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Diagnosis and Management of Low-Grade Dysplasia in Barrett’s Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association

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The purpose of this clinical practice update expert review is to define the key principles in the diagnosis and management of low-grade dysplasia (LGD) in Barrett’s esophagus patients. The best practices outlined in this review are based on relevant publications, including systematic reviews and expert opinion (when applicable).

**Practice Advice 1:** The extent of Barrett’s esophagus should be defined using a standardized grading system documenting the circumferential and maximal extent of the columnar lined esophagus (Prague classification) with a clear description of landmarks and visible lesions (nodularity, ulceration) when present.

**Practice Advice 2:** Given the significant interobserver variability among pathologists, the diagnosis of Barrett’s esophagus with LGD should be confirmed by an expert gastrointestinal pathologist (defined as a pathologist with a special interest in Barrett’s esophagus-related neoplasia who is recognized as an expert in this field by his/her peers).

**Practice Advice 3:** Expert pathologists should report audits of their diagnosed cases of LGD, such as the frequency of LGD diagnosed among surveillance patients and/or the difference in incidence of neoplastic progression among patients diagnosed with LGD vs nondysplastic Barrett’s esophagus.

**Practice Advice 4:** Patients in whom the diagnosis of LGD is downgraded to nondysplastic Barrett’s esophagus should be managed as nondysplastic Barrett’s esophagus.

**Practice Advice 5:** In Barrett’s esophagus patients with confirmed LGD (based on expert gastrointestinal pathology review), repeat upper endoscopy using high-definition/high-resolution white-light endoscopy should be performed under maximal acid suppression (twice daily dosing of proton pump inhibitor therapy) in 8–12 weeks.

**Practice Advice 6:** Under ideal circumstances, surveillance biopsies should not be performed in the presence of acute inflammation (erosive esophagitis, Los Angeles grade C and D). Pathologists should be informed if biopsies are obtained in the setting of erosive esophagitis and if pathology findings suggest LGD, or if no biopsies are obtained, surveillance biopsies should be repeated after the anti-reflux regimen has been further intensified.

**Practice Advice 7:** Surveillance biopsies should be performed in a four-quadrant fashion every 1–2 cm with target biopsies obtained from visible lesions taken first.

**Practice Advice 8:** Patients with a confirmed histologic diagnosis of LGD should be referred to an endoscopist with expertise in managing Barrett’s esophagus–related neoplasia practicing at centers equipped with high-definition endoscopy and capable of performing endoscopic resection and ablation.

**Practice Advice 9:** Endoscopic resection should be performed in Barrett’s esophagus patients with LGD with endoscopically visible abnormalities (no matter how subtle) in order to accurately assess the grade of dysplasia.

**Practice Advice 10:** In patients with confirmed Barrett’s esophagus with LGD by expert GI pathology review that persists on a second endoscopy, despite intensification of acid-suppressive therapy, risks and benefits of management options of endoscopic eradication therapy (specifically adverse events associated with endoscopic resection and ablation), and ongoing surveillance should be discussed and documented.

**Practice Advice 11:** Endoscopic eradication therapy should be considered in patients with confirmed persistent LGD with the goal of achieving complete eradication of intestinal metaplasia.

**Practice Advice 12:** Patients with LGD undergoing surveillance rather than endoscopic eradication therapy should undergo surveillance every 6 months up to 2 years, then annually unless there is progression to nondysplastic Barrett’s esophagus. Biopsies should be obtained in 4-quadrants every 1–2 cm and from any visible lesions.

**Practice Advice 13:** In patients with Barrett’s esophagus-related LGD undergoing ablative therapy, radiofrequency ablation should be used.

**Practice Advice 14:** Patients completing endoscopic eradication therapy should be enrolled in an endoscopic surveillance program. Patients who have achieved complete eradication of intestinal metaplasia should undergo surveillance every year for 2 years and then every 3 years thereafter to detect recurrent intestinal metaplasia and dysplasia. Patients who have not achieved complete eradication of intestinal metaplasia should undergo surveillance every 6 months for 1 year after the last endoscopy, then annually for 2 years, then every 3 years thereafter.

**Practice Advice 15:** Following endoscopic eradication therapy, the biopsy protocol of obtaining biopsies in 4 quadrants every 2 cm throughout the length of the...
original Barrett’s esophagus segment and any visible columnar mucosa is suggested. **Practice Advice 16: Endoscopists performing endoscopic eradication therapy should report audits of their rates of complete eradication of dysplasia and intestinal metaplasia and adverse events in clinical practice.**

Barrett’s esophagus (BE), a complication of chronic gastroesophageal reflux disease and a well-established risk factor for esophageal adenocarcinoma (EAC), is defined by the replacement of normal squamous epithelium by columnar lined epithelium with intestinal metaplasia.1,2 EAC is a highly lethal cancer with an overall median survival of <1 year especially in cases with advanced stage of disease. The incidence of EAC has increased during the past 5 decades, and in 2014 there were approximately 18,170 incident cases of esophageal cancer in the United States, 59.9% of which were EAC.3–5 BE is believed to affect 1%–2% of the general population6,7 and is thought to progress to invasive EAC in a step-wise and probabilistic fashion through the histopathologic stages of low-grade dysplasia (LGD), and high-grade dysplasia (HGD).8–11 Despite all the recent advances in genetic and molecular markers, the degree of dysplasia is the best current biomarker to predict progression to EAC and determine further management. Several issues (interobserver variability among pathologists, variable natural history outcomes between different populations, need for risk stratification, and determining ideal candidates likely to benefit from endoscopic eradication therapy compared with surveillance) continue to make the management of LGD highly controversial. Defining the optimal management strategy for LGD patients is clinically relevant as 15%–40% of BE patients are diagnosed with LGD at some point during follow-up.12

The purpose of this clinical practice updates review from the Clinical Practice Updates Committee from the American Gastroenterological Association is to provide practice advice regarding the diagnosis and management of BE-associated LGD. The target audience is all clinicians, and the target patient population includes individuals diagnosed with BE-associated LGD. A formal systematic review for all relevant aspects regarding diagnosis and management of LGD was not performed with the exception of natural history of LGD (Tables 1 and 2) and predictors for progression to HGD and EAC (Table 3). A panel of experts was convened to create a document that highlights the current controversies in LGD, provides practice advice based on the best available evidence, including systematic reviews and recent guidelines, and provides a framework for future research in this field. The discussion around presence or absence of intestinal metaplasia is not part of this publication.

### Histopathologic Diagnosis of Low-Grade Dysplasia

The revised Vienna classification for gastrointestinal (GI) mucosal neoplasia and the World Health Organization classification of GI tumors are the most commonly utilized grading systems to categorize patients with and without dysplasia in BE.13,14 The characteristic changes associated with LGD include presence of crypts with relative preservation of glandular architecture. Epithelial cell nuclei are oval or elongated and generally retain polarity or associated with mild loss of polarity. The nuclei are elongated, slightly enlarged, hyperchromatic and have mild irregularity of nuclear membrane contour. Nuclear stratification is present, and the nuclei usually occupy the lower half of the epithelium with absence of full thickness stratification. Other recognizable features include mucin depletion, decreased number of goblet cells and increased mitotic figures. Importantly, there is loss of surface maturation such that cytologic atypia extends from the deeper glands to the surface epithelium. It should be noted that changes resembling LGD can be seen in regenerating epithelium and overdiagnosis of LGD should be avoided.15–17

Classification of patients in this category is challenging for several reasons.18 These include variation in criteria for evaluation of LGD, differences in thresholds for dysplasia/neoplasia diagnosis and geographic variation in practice patterns. The current classification systems do not clarify thresholds for diagnosis of LGD and reactive atypia and also do not account for the intestinal and gastric or mixed pathways in the Barrett’s epithelium. As such, there is significant interobserver and intra-observer variability among community and expert pathologists; especially in the differentiation between no dysplasia, indefinite for dysplasia and LGD.8,19–21 A reproducibility study showed that the interobserver agreement was only fair for LGD (k = .32) and slight for indefinite for dysplasia (k = .15).19 A US multicenter cohort study showed that the interobserver agreement among 2 expert central GI pathologists for LGD diagnosis was slight (k = .14).8 Available data from a multicenter international study suggest that interobserver agreement among pathologists is greater for endoscopic resection (ER) specimens compared to biopsy specimens (k = .33 vs k = .22; P < .001).20 An exception to this has been documented by a set of expert pathologists in the Netherlands with good interobserver agreement.22 Although the British Society of Gastroenterology states that routine staining for p53 may improve the diagnostic reproducibility,17 aberrant p53 staining among cases classified as LGD in the largest study to date had only 71% sensitivity and 68% specificity for neoplastic progression.23 Thus, the role of adding p53 immunohistochemistry to the histopathologic assessment of LGD in routine clinical practice needs further clarification.

The proportion of consecutive BE patients diagnosed with LGD may be a surrogate for quality of pathologic

### Abbreviations used in this paper: BE, Barrett’s esophagus; CE-IM, complete eradication of intestinal metaplasia; CI, confidence interval; EAC, esophageal adenocarcinoma; ER, endoscopic resection; GI, gastrointestinal; HGD, high-grade dysplasia; HR, hazard ratio; LGD, low-grade dysplasia; NBI, narrow band imaging; OR, odds ratio; RFA, radiofrequency ablation.

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evaluation indicating the presence of overdiagnosis of LGD in practice. In a study that included pathology slides from 147 patients with LGD from 6 community hospitals whose slides were reviewed by 2 expert pathologists, after review, 75% of the patients diagnosed with LGD by community pathologists were downgraded to nondysplastic BE.21 Individuals with a confirmed diagnosis of LGD had a higher rate of progression to HGD/EAC compared with those downgraded to nondysplastic BE (13.4% per year vs 0.49% per year). Another recent study by the Amsterdam group showed that after an expert pathology panel review, 73% of the 293 LGD patients were downgraded to nondysplastic BE or indefinite for dysplasia. Among patients with confirmed LGD, the risk of progression to HGD/EAC was 9.1% per year compared with 0.6% in the down-graded nondysplastic BE group.22 Thus, this phenomenon of LGD overdiagnosis has a significant impact on the reported rates of progression in LGD patients 8,21,24–26 and, in turn, ultimately impacts appropriate management of this patient population. A recent systematic review and meta-analysis showed a

Table 1. Systematic Review of Studies Reporting on Progression Rates to High-Grade Dysplasia and Esophageal Adenocarcinoma in Barrett’s Esophagus Patients With Low-Grade Dysplasia

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Diagnosis confirmed by 2nd pathologist</th>
<th>N BE</th>
<th>N BE-LGD</th>
<th>% LGD</th>
<th>Incidence HGD/EAC per 1000 p-y (95% CI)</th>
<th>Incidence EAC per 1000 p-y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcedo</td>
<td>2009</td>
<td>Spain</td>
<td>Single Center</td>
<td>No</td>
<td>340</td>
<td>32</td>
<td>9.4%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dulai</td>
<td>2005</td>
<td>US</td>
<td>Multicenter</td>
<td>No</td>
<td>575</td>
<td>134</td>
<td>23.3%</td>
<td>12.8</td>
<td>3.6</td>
</tr>
<tr>
<td>de Jonge</td>
<td>2010</td>
<td>Netherlands</td>
<td>Population</td>
<td>NR</td>
<td>16333</td>
<td>4132</td>
<td>25.3%</td>
<td>3.6 (2.5, 4.2)</td>
<td>4.1</td>
</tr>
<tr>
<td>Schouten</td>
<td>2011</td>
<td>Netherlands</td>
<td>Population</td>
<td>No</td>
<td>626</td>
<td>92</td>
<td>14.7%</td>
<td>4.1</td>
<td>5.1 (3.0, 8.6)</td>
</tr>
<tr>
<td>Hvid-Jensen</td>
<td>2011</td>
<td>Denmark</td>
<td>Population</td>
<td>No</td>
<td>11028</td>
<td>621</td>
<td>5.6%</td>
<td>5.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Miro</td>
<td>1991</td>
<td>Australia</td>
<td>Single Center</td>
<td>No</td>
<td>81</td>
<td>20</td>
<td>24.7%</td>
<td>13.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Bhat</td>
<td>2011</td>
<td>Northern Ireland</td>
<td>Population</td>
<td>NR</td>
<td>8522</td>
<td>323</td>
<td>3.8%</td>
<td>14.0 (9.9, 19.7)</td>
<td>10.1 (9.4, 15.1)</td>
</tr>
<tr>
<td>Den Hoed</td>
<td>2011</td>
<td>Netherlands</td>
<td>Single Center</td>
<td>Yes</td>
<td>133</td>
<td>27</td>
<td>20.3%</td>
<td>17</td>
<td>4.2 (2.9, 9.8)</td>
</tr>
<tr>
<td>Wani</td>
<td>2011</td>
<td>US</td>
<td>Multicenter</td>
<td>Yes</td>
<td>2264</td>
<td>210</td>
<td>9.3%</td>
<td>18.3 (12.3, 27.4)</td>
<td>4.4 (2, 9.8)</td>
</tr>
<tr>
<td>Kestens</td>
<td>2016</td>
<td>Netherlands</td>
<td>Population</td>
<td>Partial</td>
<td>1579</td>
<td>21</td>
<td>1.7%</td>
<td>11.9 (9.6, 14.8)</td>
<td>11.9 (9.6, 14.8)</td>
</tr>
<tr>
<td>Gatenby</td>
<td>2009</td>
<td>UK</td>
<td>Single Center</td>
<td>Yes</td>
<td>1329</td>
<td>146</td>
<td>11.0%</td>
<td>22 (12, 38)</td>
<td>14 (6, 27)</td>
</tr>
<tr>
<td>Thota</td>
<td>2015</td>
<td>US</td>
<td>Single Center</td>
<td>Yes</td>
<td>2370</td>
<td>299</td>
<td>12.6%</td>
<td>27 (19, 36)</td>
<td>6 (3, 12)</td>
</tr>
<tr>
<td>Lim</td>
<td>2007</td>
<td>UK</td>
<td>Single Center</td>
<td>Yes</td>
<td>357</td>
<td>34</td>
<td>9.5%</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Weston</td>
<td>2001</td>
<td>US</td>
<td>Single Center</td>
<td>Yes</td>
<td>283</td>
<td>48</td>
<td>17.0%</td>
<td>30.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Picardo</td>
<td>2015</td>
<td>Ireland</td>
<td>Single Center</td>
<td>Yes</td>
<td>1033</td>
<td>73</td>
<td>7.1%</td>
<td>31.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Kastelein</td>
<td>2013</td>
<td>Netherlands</td>
<td>Multicenter</td>
<td>Yes</td>
<td>720</td>
<td>223</td>
<td>31.0%</td>
<td>42 (28, 59)</td>
<td></td>
</tr>
<tr>
<td>Duits</td>
<td>2015</td>
<td>Netherlands</td>
<td>Single Center</td>
<td>Yes</td>
<td>293</td>
<td>91</td>
<td>31.0%</td>
<td>42 (28, 59)</td>
<td></td>
</tr>
<tr>
<td>Montgomery</td>
<td>2001</td>
<td>US</td>
<td>Multicenter</td>
<td>Yes</td>
<td>138</td>
<td>26</td>
<td>18.8%</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Reid</td>
<td>2000</td>
<td>US</td>
<td>Single Center</td>
<td>NR</td>
<td>322</td>
<td>43</td>
<td>13.4%</td>
<td>24 (8, 68)</td>
<td></td>
</tr>
<tr>
<td>Tavakkoli</td>
<td>2016</td>
<td>US</td>
<td>Single Center</td>
<td>Partial</td>
<td>2887</td>
<td>202</td>
<td>7.0%</td>
<td>112 (17, 53)</td>
<td>30 (83, 150)</td>
</tr>
<tr>
<td>Curvers</td>
<td>2010</td>
<td>Netherlands</td>
<td>Multicenter</td>
<td>Yes</td>
<td>1198</td>
<td>122</td>
<td>10.2%</td>
<td>134 (35, 232)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Sorted by incidence. Incidence correlates roughly with whether there was a 2nd pathologist review, but even among those with review, the incidence varies by an order of magnitude.

BE, Barrett’s esophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; NR, not reported.

Table 2. Studies Highlighting the Difference in Progression Rates Among Barrett’s Esophagus Patients With Low-Grade Dysplasia After Expert Pathology Review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>% of BE initially diagnosed as LGD</th>
<th>% of LGD confirmed</th>
<th>Progression to HGD/EAC with expert downgrading</th>
<th>Progression to HGD/EAC with expert confirmation of LGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curvers</td>
<td>2010</td>
<td>Netherlands</td>
<td>Multicenter</td>
<td>122</td>
<td>10.2%</td>
<td>18.0%</td>
<td>4.9 per 1000 p-y (95% CI 0, 13)</td>
</tr>
<tr>
<td>Duits</td>
<td>2015</td>
<td>Netherlands</td>
<td>Single Center</td>
<td>293</td>
<td>27.0%</td>
<td>6 per 1000 p-y (95% CI 2, 13)</td>
<td>91 per 1000 p-y (95% CI 58, 136)</td>
</tr>
<tr>
<td>Lim</td>
<td>2007</td>
<td>UK</td>
<td>Single Center</td>
<td>34</td>
<td>9.5%</td>
<td>41.2%</td>
<td>21% (4/19)</td>
</tr>
<tr>
<td>Wani</td>
<td>2011</td>
<td>US</td>
<td>Multicenter</td>
<td>210</td>
<td>9.3%</td>
<td>46.5%</td>
<td>9.4 per 1000 p-y</td>
</tr>
<tr>
<td>Skacel</td>
<td>2000</td>
<td>US</td>
<td>Single Center</td>
<td>25</td>
<td>68.0%</td>
<td>0% (0/8)</td>
<td>8 per 1000 p-y if 2 agreed 456 per 1000 p-y if 3 agreed</td>
</tr>
</tbody>
</table>
higher rate of progression to EAC among studies with 
LGD/BE ratio of <0.15 compared with those with a ratio of
>0.15 (0.76% per year vs 0.32% per year).27 While the
threshold for LGD/BE ratio has not been de
fined, experts
believe that this should be <0.05.28 A number of studies
have demonstrated that patients with LGD con
firmed by an
expert pathologist have a greater risk of progression
(Table 2).
Given the significant interobserver variability
among pathologists, the diagnosis of BE with LGD should be
confirmed by an expert GI pathologist. A working definition of
such an expert is a pathologist with a special interest in
BE-related neoplasia and who is recognized as an expert in
this field by his/her peers. Providing practice advice on
detailed criteria that pathologists should use for making a
diagnosis of LGD or of how consensus diagnosis should be
reached is not a part of this document. Expert pathologists
should report audits of their diagnosed cases of LGD, such as
the proportion of LGD diagnosed among surveillance patients
and/or the difference in incidence of neoplastic progression
among patients diagnosed with LGD vs nondysplastic BE.
While case-mix and referral patterns may lead to differences
in these rates, and further research is needed to identify the
ideal target for these metrics, reporting the results of such
audits is an important first step in improving the quality and
efficiency of care in BE. To be useful, the audit results
should be readily available to endoscopists, such as posted
online and/or accompanying a pathology report of LGD.

Natural History and Predictors
of Progression
Incidence of High-Grade Dysplasia and
Esophageal Adenocarcinoma
Variable rates of progression of LGD to end points of HGD/
EAC and EAC alone have been reported with progression rates
ranging from 0.4% to 13.4% per year.8,11,21,24–37 These vari-
able rates stem from inclusion of relatively small number of
patients with LGD in the vast majority of the studies, lack of
expert or central pathology panel review limiting reliability of
LGD diagnosis, variability in pathologic diagnosis of LGD,
analyses not distinguishing prevalent from incident dysplasia,
referral and selection bias, and limited endoscopic follow-up data especially for survival analyses.\textsuperscript{22,38} A systematic review and meta-analysis that included 24 studies with 2694 LGD patients reported a pooled annual incidence rate of 1.73\% (95\% confidence interval [CI], 0.99–2.47) for the end point of HGD/EAC and 0.54\% (95\% CI, 0.32–0.76) for EAC.\textsuperscript{27} However, substantial heterogeneity in the results was a major limitation of this study.

A systematic review was performed to address 3 research issues among patients with LGD: incidence of EAC, incidence of HGD/EAC as a combined end point, and predictors of progression to HGD/EAC in BE patients with LGD. A literature search of Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Embase, and the Cochrane Library from 1980 to January 31, 2016 was performed using search terms such as Barrett’s esophagus, Precancerous conditions, Disease Progression, Early Diagnosis, Incidence, among others. The search was limited to English-language, non-animal studies and comments, editorials, letters, and case reports were excluded (Table 1 and Supplementary Appendix).

A noteworthy feature, as demonstrated in several studies, in the natural history data of LGD patients is the phenomenon of regression where follow-up endoscopic biopsies after an initial diagnosis of LGD do not demonstrate LGD and the diagnosis is downgraded to nondysplastic BE.\textsuperscript{35–37,39,40} The potential reasons for this phenomenon include interobserver variability among pathologists, sampling errors, misdiagnosis, removal of the dysplastic focus by biopsies and perhaps even true regression of the dysplastic area. This clearly has significant implications related to daily practice and impacts healthcare costs, morbidity related to increased number of endoscopies and biopsies and patient’s quality of life.\textsuperscript{15}

**Clinical Predictors of Progression**

As highlighted in our systematic review of the published literature (Tables 2 and 3), a limited number of studies identified predictors of progression in BE-associated LGD patients, whereas others were unable to identify any significant predictors in their reported cohorts.\textsuperscript{8} Improved risk stratification with reliable predictors of progression has the potential to better define individuals at the highest of progression to HGD/EAC and most likely to benefit from endoscopic eradication therapy.

Review of pathology slides by an expert GI pathologist has been shown to "purify" the group of LGD patients by downgrading the vast majority of cases to nondysplastic BE. Studies have demonstrated that individuals with confirmed LGD (defined by confirmation of diagnosis by an expert GI pathologist or panel) are at a higher risk of progression to EAC and HGD/EAC.\textsuperscript{21,22,24} In addition, patients with LGD confirmed by multiple pathologists instead of a single pathologist diagnosis may be associated with a higher risk of progression to HGD/EAC.\textsuperscript{25,41} Persistent LGD (defined by the presence of LGD on 2 consecutive endoscopies) has also been identified as a risk factor for progression, or as a risk factor for failure to regress subsequently. A recent study showed that the number of pathologists confirming the diagnosis of LGD (odds ratio [OR], 47.14; 95\% CI, 13.1–169.7 when all 3 pathologists agreed) and persistent LGD (OR range, 4.48–11.33 for individual pathologists) were predictors associated with progression of LGD.\textsuperscript{11} A Dutch study showed a statistically significant difference in the rates of progression to HGD/EAC between cases with and without confirmed LGD (confirmed incidence rate: 5.18; 95\% CI, 3.63–7.19) per 100 person-years vs 1.85; 95\% CI, 1.52–2.22) per 100 person-years; \( P < .001 \). Persistent LGD was the only independent risk factor for the development of HGD/EAC (hazard ratio [HR], 3.5; 95\% CI, 1.48–8.28).\textsuperscript{42} A multicenter US study showed that the presence of nodularity (HR, 3.12; 95\% CI, 1.18–8.25) and multifocal dysplasia defined as evidence of dysplasia on at least 2 specimens taken from different locations in the BE segment on the same endoscopy (HR, 3.09; 95\% CI, 1.49–6.41) were independent predictors of progression whereas factors associated with regression included shorter BE length, active smoking status, and proton-pump inhibitor use.\textsuperscript{36} Multivariable analysis from a recent multicenter randomized controlled study identified the following independent predictors associated with progression: the number of years since diagnosis of BE (OR, 0.84; 95\% CI, 0.72–0.98), number of endoscopies with dysplasia (OR, 1.44; 95\% CI, 1.03–2.03), and circumferential BE length (OR, 1.35; 95\% CI, 1.04–1.76).\textsuperscript{37} A single-center study showed that prevalent cases of LGD (HR, 2.9; 95\% CI, 1.6–5.2) and index biopsy of LGD compared with indefinite for dysplasia (HR, 2.8; 95\% CI, 1.01–8.1) had a higher risk of progression to HGD/EAC. Factors associated with regression include incident LGD, older age, and shorter BE segments.\textsuperscript{40} Similarly, another study showed that predictors associated with a higher risk of progression to HGD/EAC were presence of prevalent LGD (OR, 7.57; 95\% CI, 1.9–30.2) and persistent LGD (OR, 7.25; 95\% CI, 1.28–41.1), whereas increasing body mass index was inversely associated with progression (OR per increments of 5 kg/m\(^2\), 0.52; 95\% CI, 0.28–0.94). Unifocal LGD was associated with the phenomenon of regression.\textsuperscript{35} Aside from pathologist confirmation of LGD and persistent LGD, no other factor appears to be reproducibly associated with progression.

**Biomarkers as Predictors of Progression**

Several biomarkers have been studied to improve the current risk-stratification approach and identification of patients at the highest risk for progression. These include detection of DNA content abnormalities (aneuploidy or increased 4N fraction), mutation or loss of heterozygosity of the p53 and p16 genes, chromosomal abnormalities, methylation-based biomarkers among others.\textsuperscript{43–48} A recent study identified an expression pattern of 90 genes in esophageal tissue with low or high-risk for progression and has the potential to risk stratify LGD patients.\textsuperscript{49} However, none of these biomarkers are widely available and ready for application in clinical practice and require validation in large prospective multicenter studies.
Endoscopic Evaluation and Management Strategies

Endoscopic Evaluation

Endoscopy in patients referred for management of LGD should be performed using high-definition white-light endoscopy when reflux symptoms are controlled. The use of high-definition white-light endoscopy should be considered the standard of care and the first critical step in the evaluation of BE patients undergoing surveillance or being considered for endoscopic eradication therapy, a recommendation endorsed in other guidelines and consensus documents.1,17,50,51 Indirect evidence suggests that high-definition white-light endoscopy is more sensitive compared with standard-definition white-light endoscopy in the detection of BE-related neoplasia.52-54 Careful inspection of the BE segment should begin after the mucosa has been cleaned and all mucosal debris is removed. Adequate inspection time should be spent inspecting the entire BE segment.55 The extent of BE should be defined using a standardized grading system documenting the circumferential and maximal extent of the columnar lined esophagus (Prague classification)56 with a clear description of landmarks and visible lesions (nodularity, ulceration, plaques, areas of depression, strictures, areas of mucosal discoloration), no matter how subtle, when present. Cognitive knowledge regarding the endoscopic appearance of subtle lesions during upper endoscopy is essential. Surveillance biopsies should be performed in a systematic manner with four-quadrant biopsies every 1–2 cm with target biopsies first from visible lesions (Seattle protocol).57,58 A post-hoc analysis of 2 randomized controlled trials showed that the proximal most half of the BE segment is almost twice as likely to demonstrate dysplasia as the distal-most quartile. Monte Carlo simulations of an altered biopsy regimen (higher number of biopsies in the proximal BE segment) suggested an increased sensitivity of dysplasia detection.59 These results need to be confirmed in future prospective trials before current surveillance biopsy protocols can be changed.

Under ideal circumstances, surveillance biopsies should not be performed in the presence of active inflammation (erosive esophagitis, Los Angeles grade C and D). Pathologists should be informed if biopsies are obtained in the setting of erosive esophagitis and if pathology findings suggest LGD, or if no biopsies are obtained, surveillance biopsies should be repeated after the antireflux regimen has been further intensified (high-dose twice daily proton pump inhibitor therapy) in 8–12 weeks to exclude the possibility of over-diagnosis related to inflammation, exclude the presence of synchronous lesions with higher grades of dysplasia (HGD/EAC) and confirm the diagnosis of LGD. Similarly, in BE patients with confirmed LGD (based on expert GI pathology review) at initial endoscopy, repeat upper endoscopy using high-definition white-light endoscopy should be performed under maximal acid suppression (twice daily dosing of PPI therapy) in 8–12 weeks. A recent systematic review and meta-analysis reported a substantial missed EAC (defined as EAC diagnosed within 1 year of initial endoscopy) rate of 25.3% (95% CI, 16.4–36.8) in cohorts of patients with nondysplastic BE and BE with LGD.60 These results call for an improvement in the endoscopic evaluation of BE and the need to spend adequate time inspecting the BE segment using high-definition white-light endoscopy, obtaining target biopsies from visible lesions and complying with the Seattle protocol for surveillance biopsies. The confirming endoscopy should be performed by an endoscopist experienced in the management of dysplastic BE, typically one who has experience with endoscopic resection as they have the most experience recognizing subtle mucosal abnormalities.

Role of Advanced Imaging Techniques

The current surveillance strategy has several limitations, including the associated time and labor, costs, non-adherence to Seattle biopsy protocol in routine clinical practice, and sampling errors due to focal distribution of neoplasia.61,62 These factors have provided the necessary impetus for evaluation of several advanced imaging techniques aimed at improving detection and identification of patients with early neoplastic lesions, prediction of histology and real-time diagnosis during endoscopy, and guiding endoscopic eradication therapy by determining lateral extent of lesions.

Optical electronic chromoendoscopy provides enhanced visualization of the mucosa using light filters and computer processing technology without the need to spray dyes. Narrow band imaging (NBI) is the most widely studied electronic chromoendoscopy technique that uses blue light with narrow band filters enabling detailed imaging of the mucosal and vascular surface patterns with a high level of resolution and contrast. A recent randomized multicenter study comparing NBI to high-definition white-light endoscopy demonstrated a comparable detection rate of intestinal metaplasia and early neoplasia with fewer biopsies required in the NBI arm.63 A recent meta-analysis showed that advanced imaging techniques (optical chromoendoscopy and chromoendoscopy) increased dysplasia or cancer detection by 34% (95% CI, 20%–56%; P < .0001).64 However, a standardized classification system that includes LGD does not exist. Optical electronic chromoendoscopy (NBI) may have a role in guiding surveillance (although the additional benefit compared with high-definition white-light endoscopy has been debated) and endoscopic eradication therapy (although not adequately studied). Other advanced endoscopic imaging techniques studied include chromoendoscopy, confocal laser endomicroscopy, autofluorescence endoscopy, optical frequency domain imaging, spectroscopy, and high-resolution microendoscopy. The use of these techniques cannot be recommended in the routine clinical management of these patients.

Role of Endoscopic Resection

Endoscopic resection has evolved into an important diagnostic/staging and therapeutic tool in the management
of patients with dysplastic BE. The value of endoscopic resection as a diagnostic/staging tool compared with biopsy specimens is enhanced by the provision of larger and deeper tissue specimens (submucosa and muscularis mucosa present in majority of endoscopic resection specimens) with limited distortion, allowing for an accurate assessment of depth of neoplastic involvement and adequacy of resection. Several studies have demonstrated that endoscopic resection results in a change in the histopathologic diagnosis of BE patients with neoplasia referred for endoscopic eradication therapy. Results from a recent multicenter cohort study showed that ER resulted in a change in diagnosis in 30% of BE patients with early neoplasia. In addition, provision of a larger specimen results in an improvement in interobserver agreement among pathologists compared to biopsy specimens. Based on these data, endoscopic resection should be performed in BE patients with LGD with endoscopically visible abnormalities (no matter how subtle) in order to accurately assess the grade of dysplasia.

**Treatment Options**

While the management strategies for nondysplastic BE (surveillance) and HGD (endoscopic eradication therapy) are clear, management of BE-associated LGD continues to be controversial. This section reviews the merits and drawbacks of the 2 management strategies for this group of patients—surveillance and ablation.

Studies focusing on various endoscopic eradication therapies specifically in this patient population are limited and have predominantly reported on outcomes related to radiofrequency ablation (RFA). Trials frequently included LGD patients in the group of nondysplastic BE or in the HGD group, making it difficult to estimate the impact of endoscopic eradication therapy. Two randomized controlled trials compared RFA with surveillance including patients with LGD. In a multicenter, prospective, randomized, sham-controlled trial, subjects with dysplastic BE were assigned 2:1 to either treatment with RFA or a sham procedure. A total of 127 patients were randomized (84 RFA, 43 sham) and included 64 patients with LGD (42 RFA, 22 sham). At 12 months, complete eradication of LGD was achieved in 90% in the RFA group compared with 23% in the sham group (P < .001), and complete eradication of intestinal metaplasia was achieved in 81% vs 4% (P < .001). Two patients in the RFA group progressed to HGD with none progressing to cancer in either group. At 2-year follow-up study of a subset of the same cohort of patients with LGD, demonstrated complete eradication of dysplasia and intestinal metaplasia in 51 of 52 (98%) and 51 of 52 (98%) subjects, respectively. The study was a crossover design, such that many patients randomized to sham were then treated with RFA. Among subjects with LGD, the annual rate of progression to EAC was 1 per 197 patient-years or 0.51% per patient per year and the annual rate of overall disease progression was 1 per 49 patient-years, or 2.04% per patient per year. With the longer follow-up, 3 patients progressed from LGD to HGD and 1 from LGD to EAC. A recent European multicenter randomized controlled trial, the Surveillance vs Radiofrequency Ablation (SURF) study compared RFA with endoscopic surveillance in patients with BE with confirmed LGD. One hundred and thirty-six patients with confirmed LGD (diagnosis confirmed by expert central pathology panel and qualifying endoscopy within 6 months of enrollment to exclude visible lesions, HGD or EAC) were randomized 1:1 to either RFA or endoscopic surveillance. Patients randomized to RFA underwent ablation every 3 months until complete endoscopic and histologic eradication of BE or to a maximum of 2 circumferential and 3 focal sessions. The patients randomized to surveillance underwent endoscopies at 6 and 12 months, then annually. All patients were followed for 3 years after randomization. A total of 136 patients were randomized and for the primary outcome of neoplastic progression, ablation reduced the risk of progression to a combined endpoint of HGD/EAC compared with surveillance (1.5% vs 26.5%; P < .001) and EAC (1.5% vs 8.8%; P = .03). Thus, ablation reduced the risk of progression to HGD/EAC by 25% (95% CI, 14.1–35.9) with a number need to treat of 4. Ablation reduced the risk of progression to EAC by 7.4% (95% CI, 0–14.7%) with a number need to treat of 13.6. Treatment-related adverse events were noted in 19.1% of patients treated with ablation with strictures being the most common. The results may not be generalizable to other populations because the cohort randomized to surveillance in the study experienced a rather high rate of neoplastic progression; 8.8% using the end point of EAC and 26.5% using a composite end point of HGD and EAC. This may reflect better risk stratification in this study that was accomplished by confirmation of the diagnosis by central pathologists. Despite the high rate of neoplastic progression, all but one of the cases of progression in the surveillance arm were ultimately able to be treated by endoscopic eradication therapy. Patients undergoing RFA received a median of 3 excess procedures compared with the surveillance group, and 19% experienced an adverse event, 2.9% considered serious. The most commonly reported adverse event was stricture formation causing dysphagia; others included chest pain and bleeding. Results from a recent systematic review and meta-analysis evaluating adverse events associated with RFA with and without endoscopic resection demonstrated a pooled adverse event rate of 8.8% (95% CI, 6.5–11.9) with a stricture rate of 5.6% (95% CI, 4.2–7.4). Although the efficacy of RFA has been shown in these clinical trials, effectiveness data in clinical practice are limited. A recent multicenter retrospective study demonstrated a lower rate of progression of LGD to HGD/EAC after RFA compared with endoscopic surveillance (0.77% vs 6.6%, adjusted HR, 0.06; 95% CI, 0.008–0.48) with a number need to treat of 3. Studies reporting outcomes associated with endoscopic eradication therapy have been underpowered to address the end point of incidence of invasive EAC, EAC-specific mortality, and all-cause mortality. In a recent multicenter study that included 4982 patients treated with RFA (LGD 20%), 2% developed EAC.
Management Post-Endoscopic Eradication Therapy

While the effectiveness of endoscopic eradication therapy in achieving CE-IM has been demonstrated in multiple studies, recurrence of dysplasia and intestinal metaplasia post CE-IM has been reported in several studies.\(^7^3,7^9-8^6\) Variability in reported rates of recurrence has been attributed to several factors including study design, treatment and surveillance protocol, duration of follow-up and definitions of CE-IM and recurrence (whether intestinal metaplasia at or just below the neo-squamocolumnar junction is included as recurrences). A recent systematic review and meta-analysis showed that the pooled incidence of any recurrence was 7.3/100 patient-years (95% CI, 5.9-8.8) with a pooled incidence of intestinal metaplasia recurrence rate of 4.7/100 patient-years (95% CI 3.6-5.8) and dysplasia recurrence rate of 1.7/100 patient-years (95% CI 1.2-2.2). The vast majority of recurrences were amenable to repeat endoscopic eradication therapy.\(^9^7\) These data suggest that recurrence rates post-endoscopic eradication therapy are not inconsiderable and reinforce the importance of close surveillance after achieving CE-IM; it is important to discuss these recurrence estimates with patients before embarking on endoscopic eradication therapy. Predictors associated with recurrence are not well defined. The associations between the presence of erosive esophagitis, older age, non-Caucasian race and pretreatment BE length and recurrence needs to be explored and confirmed in future studies.\(^8^1,8^8-9^0\) Surveillance after CE-IM should entail careful inspection of the esophagus (neosquamous epithelium) and gastroesophageal junction using high-definition white-light endoscopy and electronic chromoendoscopy (NBI) for detection of recurrence of intestinal metaplasia and dysplasia. The surveillance intervals and biopsy protocol is based on expert opinion. Patients with LGD who have achieved CE-IM should undergo surveillance every year for 2 years and then every 3 years thereafter, unless recurrent dysplasia is identified. Patients who have not achieved CE-IM should undergo surveillance every 6 months for 1 year, then annually for 2 years, then every 3 years thereafter, unless recurrent dysplasia is identified. While the optimal biopsy protocol during surveillance endoscopy is unknown, the biopsy protocol of obtaining biopsies in 4-quadrants every 2 cm throughout the length of the original BE segment and any visible columnar mucosa is suggested. At the present time, given the risk of recurrence several years after CE-IM, discontinuation of surveillance after negative surveillance endoscopies cannot be recommended.

Quality Indicators, Training, and Competence

There are limited and conflicting data regarding learning curves and competence in the management of BE patients with dysplasia. A single study showed that higher RFA volume was associated with an increased rate of CE-IM,\(^8^1\) whereas another study found no appreciable learning curve associated with RFA.\(^9^2\) Recent data suggest that
Figure 1. An algorithmic approach to Barrett’s esophagus patients with low-grade dysplasia. EGD, esophagogastroduodenoscopy.
increasing experience of endoscopists and centers (threshold of 30) was associated with a lower number of treatment sessions required to achieve CE-IM. There was no significant association between case volume and safety or efficacy outcomes. Another study evaluating the efficacy and safety of endoscopic resection showed an unacceptably high rate of perforation of 5% in the first 120 esophageal endoscopic resections performed by 6 participants, despite an intense, structured training program suggesting that 20 procedures are insufficient in achieving competency in esophageal endoscopic resection. As demonstrated in the field of other advanced endoscopic procedures, emphasis should be shifted away from the number of procedures performed to achieve competency and toward well-defined and validated competency thresholds (such as CE-IM and adverse event rates). In addition to being competent in ablation and ER, endoscopists need to be competent in the recognition of visible lesions that may harbor neoplasia and merit endoscopic resection.

Quality indicators for management of BE patients and specifically with regards to endoscopic eradication therapy are lacking. These are critical given the significant variation in quality of endoscopy delivered and the recent shift from volume-based to value-based practice. Two recent studies have addressed this important issue and relevant indicators pertinent to this document are as follows: (i) dysplasia diagnosis is confirmed by an expert GI pathologist; (ii) centers performing endoscopic eradication therapy should have high-definition white-light endoscopy; (iii) endoscopists that perform mucosal ablation and ER; (iv) complete endoscopic resection is performed in patients with visible lesions; (v) rate at which CE-IM and CE-D is achieved by 18 months after embarking on endoscopic eradication therapy; (vi) surveillance occurs after achieving CE-IM; (vii) and adverse events are tracked and documented.

Future Directions and Areas of Uncertainty

There is a need for international standardization and validation of histologic criteria for LGD (best accomplished by identifying LGD patients who progressed within the first 2 years of diagnosis) followed by creation of a uniform reporting system that can allow comparison of results across all studies. Future studies need to better define the true risk of progression and predictors associated with progression to HGD and EAC in BE patients with LGD. Techniques to overcome the issue of sampling bias during surveillance endoscopy are required. Further research is required to clarify the role of novel techniques, such as wide-area transepithelial sampling to reduce sampling errors and reduce interobserver variability among pathologists. There is clearly an urgent need for risk stratification and development of reliable and objective predictive models using a combination of clinical features, endoscopic findings (including advanced imaging modalities), histopathologic assessment, and biomarkers. This should accurately identify those most likely to progress and benefit from endoscopic eradication therapy those who may be managed conservatively and those who may benefit from chemoprevention. Future prospective studies that use standardized definitions for study end points and focus on recurrence risk as the primary outcome should more precisely define the annual recurrence risk and predictors associated with recurrence. Biomarkers that predict malignant progression post-endoscopic eradication therapy merit further investigation. Evidence-based best practice advice with regard to surveillance endoscopic and biopsy protocols after CE-IM are needed with the goal of stopping or reducing frequency of surveillance in low risk individuals and enrolling high-risk individuals in surveillance protocols. There is a need to continue to refine and evaluate quality indicators and address challenges germane to the process of measurement and evaluation, such as feasibility of measurement, variability in case mix and referral patterns, implementation costs and unintended consequences of implementation of quality indicators in clinical practice.

Conclusions

An algorithmic approach to BE patients with LGD is highlighted in Figure 1. As adherence to the practice advice statements provided in this document is improved, this will result in improved patient outcomes. Finally, quality indicators need to be an important aspect of clinical practice, which is driven by the common desire and vision to promote best practices among gastroenterologists and pathologists and foster evidence-based care for patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.09.040.

References


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GASTROENTEROLOGY ARTICLE OF THE WEEK
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1. A 59 year old male with Barrett’s esophagus C3 M5 is undergoing dysplasia screening. Two of the biopsies show low grade dysplasia. Next step should be (choose only one):
   a. Repeat EGD in 3 months
   b. Perform RFA
   c. Repeat EGD now and obtain additional biopsies
   d. Have slides reviewed by expert pathologist

2. A patient with Barrett’s esophagus C2 M3 has a subtle nodule. Biopsy shows LGD confirmed by two pathologists. Next step should be
   a. Double dose PPI, repeat endoscopy in 8-12 weeks
   b. Repeat endoscopy in 6 months
   c. Endoscopic resection
   d. Radiofrequency ablation

3. A patient with Barrett’s esophagus C4 M4 is undergoing surveillance with high definition white light endoscopy. No nodules or mucosal abnormalities are found. Protocol biopsies show LGD in 4 of 12 biopsies, confirmed by expert pathologist. The next endoscopy should be done in
   a. 6 months
   b. 1-2 months
   c. 2-3 months
   d. 12 months

True or False

4. The standard of care for the evaluation of Barrett’s esophagus is high definition upper endoscopy using NBI

5. In long-segment Barrett’s dysplasia is more likely to be found in the distal portion of the Barrett’s epithelium

6. After eradication of BE with RFA, surveillance endoscopies should be done once a year for 2 years, then every 3 years

7. The presence of LGD confirmed by a second expert pathologist is associated with a higher risk of progression to adenocarcinoma compared to LGD diagnosed only by the initial pathologist

8. Surveillance biopsies obtained during visible inflammation are as accurate for dysplasia detection as those obtained when no visible inflammation is present

9. RFA should be considered for the therapy of LGD if it is confirmed by a 2nd pathologist and persists on repeat endoscopy after high dose acid suppression