Barrett’s Esophagus with Epithelial Changes Indefinite for Dysplasia: What we Have Learnt from Recent Studies - 3

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Barrett’s esophagus (BE), a complication of chronic gastroesophageal reflux disease (GERD), is defined as the extension of salmon-colored mucosa into the tubular esophagus ≥1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of intestinal metaplasia, defined by the presence of goblet cells histologically [1]. Patients with BE are at increased risk of esophageal adenocarcinoma (EAC), and as such, need to undergo endoscopic surveillance with biopsy to detect dysplasia or early EAC. Histologic criteria for dysplasia in BE were well described in 1988 by Reid et al. and classified as BE with low grade dysplasia (LGD), BE with high grade dysplasia (HGD) and BE with changes indefinite for dysplasia (IND). Biopsies are classified as IND when the epithelial abnormalities are not sufficient to diagnose dysplasia or the nature of the epithelial abnormalities is uncertain due to inflammation or technical issues. Specific diagnostic criteria for indefinite for dysplasia (IND) are not well established and its clinical significance has not been well studied. Previous studies have focused on the higher end of neoplasia in BE and led to revolutionary changes and improvement in the management of BE with HGD and early EAC. Only recently, the lower end of dysplasia in BE attracted researchers’ interest. This review summarizes the findings in most recent studies on the neoplastic risk and thus the management of BE IND.

ABSTRACT

Barrett’s esophagus (BE), a complication of chronic gastroesophageal reflux disease (GERD), is defined as the extension of salmon-colored mucosa into the tubular esophagus ≥1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of intestinal metaplasia, defined by the presence of goblet cells histologically. Patients with BE are at increased risk of esophageal adenocarcinoma (EAC), and as such, need to undergo endoscopic surveillance with biopsy to detect dysplasia or early EAC. Histologic criteria for dysplasia in BE were well described in 1988 by Reid et al. and classified as BE with low grade dysplasia (LGD), BE with high grade dysplasia (HGD) and BE with changes indefinite for dysplasia (IND). Biopsies are classified as IND when the epithelial abnormalities are not sufficient to diagnose dysplasia or the nature of the epithelial abnormalities is uncertain due to inflammation or technical issues. Specific diagnostic criteria for indefinite for dysplasia (IND) are not well established and its clinical significance has not been well studied. Previous studies have focused on the higher end of neoplasia in BE and led to revolutionary changes and improvement in the management of BE with HGD and early EAC. Only recently, the lower end of dysplasia in BE attracted researchers’ interest. This review summarizes the findings in most recent studies on the neoplastic risk and thus the management of BE IND.

INTRODUCTION

Barrett’s esophagus (BE) is a complication of chronic gastroesophageal reflux disease (GERD); it is defined as the extension of salmon-colored mucosa into the tubular esophagus ≥1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of intestinal metaplasia as defined by the presence of goblet cells histologically [1]. Patients with BE are at increased risk of esophageal adenocarcinoma (EAC), and as such, undergo endoscopic surveillance and biopsy with the goal of detecting dysplasia or early adenocarcinoma. Histologic criteria for dysplasia in BE were well described in 1988 by Reid et al. [2]. Routinely, the biopsies are classified as negative for dysplasia, IND or positive for dysplasia, the latter can be further divided into low-grade (LGd) and high-grade (HGd).

The management of LGD and HGd in BE has been reviewed extensively and discussed in many guidelines. Experienced gastrointestinal pathologists can diagnose HGd and intra-mucosal adenocarcinoma (IMAC) with a high degree of agreement [2]. Many gastrointestinal pathologists can diagnose HGD and intra-mucosal adenocarcinoma (IMAC) with a high degree of agreement [2]. Many gastrointestinal pathologists can diagnose HGD and IMAC, leading to a much improved and less invasive management.

The architecture may be moderately distorted. Nuclear abnormalities are less marked than those seen in dysplasia. Other features that may lead to a diagnosis of IND include more numerous dystrophic goblet cells, more extensive nuclear stratification, diminished or absent mucus production, increased cytoplasmic basophilia, and increased mitoses.

The presence of architectural and cytologic atypia in small and mal-oriented biopsy specimen or those with inflammation or ulceration exceeding those expected for reactive changes. In some cases, it is due to basal dysplasia with surface maturation.

When a diagnosis of genuine dysplasia cannot be made. This is often due to the occurrence of inflammatory changes or when evaluation of surface maturation is not possible.

Cytologic changes similar to those seen in LGD but with surface maturation or presence of inflammation.

Downgraded from BE LGD to BE IND by an expert pathology panel.

Preserved gland architecture, mild crypt distortion, minimal nuclear stratification and slight nuclear atypia or enlargement.

The diagnosis of IND should be limited to cases in which the changes are too marked for negative but not sufficient for the diagnosis of dysplasia.

Cases reviewed by 5 gastrointestinal pathologists. When cases were simplified into negative vs non-negative, the kappa value was 0.33.

When cases were dichotomized, LGD vs negative/IND, the kappa value was 0.45.

All IND slides were validated by a single specialist histopathologist. The kappa value for IND among 3 reviewing pathologists was 0.18.

Abbreviation: BE, Barrett’s esophagus; BE IND, Barrett’s esophagus with epithelial changes indefinite for dysplasia; LGD, low-grade dysplasia.
used when technical issues such as biopsy crushing artifact, thick tissue sectioning, marked thermal artifact and tangential embedding and sectioning precluded a reliable diagnostic interpretation of dysplasia. Occasional cases were secondary to the use of certain types of fixatives. For example, tissue fixation in Hollande’s and Bouin fixatives resulted in vesicular nucleus and prominent nucleolus leading to overinterpretation of IND by pathologists not familiar with this phenomenon [7]. In rare cases, the diagnosis of IND may be due to the so-called “basal crypt dysplasia-like atypia”, where the dysplasia-like atypia is limited to the bases of the crypts, without involvement of the surface epithelium in BE [8].

Despite the attempted description and illustration of BE IND in initial publication [2], BE IND is diagnostically challenging and it is clear that its diagnostic reproducibility is poor [7,9,10]. Histologic criteria used to diagnose BE IND varied in different studies (Table 1) and even more so by pathologists in routine practice. For instance, the criteria for IND described by Reid BJ et al included moderate architectural distortion, nuclear abnormalities less marked than those seen in dysplasia, frequent dystrophic goblet cells, more extensive nuclear stratification, diminished or absent mucus production, increased cytoplasmic basophilia, and increased mitoses. The diagnosis of IND should be limited to cases in which the changes are worrisome but not sufficient for the diagnosis of dysplasia [2]. Using similar criteria, other groups performed intraobserver and interobserver reproducibility studies and found that BE IND has significant interobserver variability [7,11]. In daily pathology practice, the BE IND category appears to expand, one such example being basal crypt dysplasia-like atypia. The concept of basal crypt dysplasia-like atypia remains controversial and is interpreted by some groups as IND while others believe that it truly represents dysplasia without surface involvement.

Clinical significance of BE IND: Regardless of the definition, illustration, and intraobserver interobserver variability, BE IND category is not uncommonly used in daily pathology practice. Several studies recently investigated the clinical significance of BE IND and the results are reviewed and summarized in Tables 2 and 3.

1. Prevalent neoplasia risk in patients with BE IND: The results are summarized in Table 2. Three studies addressed the prevalent neoplasia (defined as LGD, HGD or EAC detected within 1 year of the diagnosis of BE IND), and concluded that it ranged from 12.9% to 25%. Four studies addressed the prevalence of advanced neoplasia as defined by HGD or EAC detected within 1 year of the diagnosis of BE IND and reported that the hazard ratio for combined markers (active inflammation and abnormal DNA flow cytometric results, either DNA aneuploidy and/or 4N fractions greater than 6% of the nuclei) was 18.8 [14]. Sonwalkar SA and al reported that the expression of alpha-methylacyl-CoA racemase (AMACR) in more than 1% of cells predicted progression in BE IND [9]. However, the role of AMACR expression in risk stratifying BE IND was not substantiated in a study by Horvath B et al, and they instead showed that high expression of p53 (defined as intense staining in >5% nuclei) was associated with prevalent advanced neoplasia and progression to advanced neoplasia in BE IND [15].

CONCLUSIONS

In summary, the diagnosis of BE IND is challenging. Recent data reveal that BE IND carries a significant risk of prevalent advanced neoplasia (at least 2.8%, 31 out of 1135 patients, ranging from 0% to 15%) (Table 2). In addition, the diagnosis of BE IND is associated with risk of progression to advanced neoplasia (0.43 to 1.2 cases person-years at risk) (Table 3), similar to the calculated progression risk of LGD without histology review [16], but much lower than the progression risk in consensus diagnosis of LGD [13]. Also, 73% of cases with a diagnosis of BE LGD originally rendered by practicing pathologists were downgraded to BE IND or BE negative for dysplasia by an expert pathology panel [13]. These results strongly suggest that cases with initial impression of BE IND or LGD should be reviewed by additional GI pathologists to confirm the diagnosis. The current knowledge regarding the clinical significance of BE IND as revealed by recent studies supports a close follow-up (short intervals between surveillance within 1 year) after intensive acid suppressive therapy and extensive biopsy sampling to detect prevalent neoplasia. BE IND patients with follow-up biopsies which are negative for dysplasia have low risk of neoplasia progression and may be reverted to routine surveillance as suggested by Kestens C et al., 2015 [17]. Although the length of BE, multifocality of BE IND, older age (>60 years old), abnormal p53 expression, active inflammation, and abnormal DNA content detected by flow cytometry may provide useful information to risk-stratify this patient population, additional large prospective studies are needed to address their role in clinical management of patients with BE IND.
associated with the presence of prevalent advanced neoplasia [15]. *p53 immunohistochemical stain was performed in the BE IND esophageal biopsies from 81 out 85 cases, and expression of p53 in more than 5% nuclei was associated with the presence of prevalent advanced neoplasia [15].

**Expression of AMACR in more than 1% of cells was predictive of progression in BE IND.**

****** Incidence of adenocarcinoma was 0.21 cases per 100 person-years at risk.******

***** Older age (per 10 years) was found to be a risk for developing all neoplasia and advanced neoplasia in this BE IND cohort including 12.1% of prevalent LGD.*****

**** 101 cases of BE IND were diagnosed as BE IND during the first follow-up endoscopy, incidence of advanced neoplasia and adenocarcinoma was 1.10 cases per 100 person-years at risk.****

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### Table 2: Prevalent neoplasia risk in patients with BE IND.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Repeated surveillance EGD rate within 1 year following BE IND diagnosis, N (%)</th>
<th>Prevalent LGD, N (%)</th>
<th>Prevalent HGD, N (%)</th>
<th>Prevalent adenocarcinoma, N (%)</th>
<th>Prevalent neoplasia, N (%)</th>
<th>Prevalent advanced neoplasia, N (%)</th>
<th>Risk factors for prevalent advanced neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horvath B et al. 2015</td>
<td>107</td>
<td>85 (79.4%)</td>
<td>7 (8.2%)</td>
<td>2 (2.35%)</td>
<td>2 (2.35%)</td>
<td>11 (12.9%)</td>
<td>4 (4.7%)</td>
<td>p53*</td>
</tr>
<tr>
<td>Montgomery E et al. 2001</td>
<td>7</td>
<td>Not known</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (15%)</td>
<td>1 (15%)</td>
<td>At least 1 (15%)</td>
<td>Ulceration noted at the time of BE IND</td>
</tr>
<tr>
<td>Choi W-T et al. 2015</td>
<td>96</td>
<td>Not known</td>
<td>At least 14 (14.5%)</td>
<td>Not known</td>
<td>Not known</td>
<td>24 (25%)</td>
<td>At least 10 (10%)</td>
<td>No data</td>
</tr>
<tr>
<td>Kestens C et al. 2015</td>
<td>842</td>
<td>842 (100%)</td>
<td>101 (12.1%)</td>
<td>Not known</td>
<td>Not known</td>
<td>117 (13.8%)</td>
<td>16 (1.9%)</td>
<td>No data</td>
</tr>
<tr>
<td>Singh P et al., 2015</td>
<td>83</td>
<td>Not known</td>
<td>Not known</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>Not known</td>
<td>0 (0%)</td>
<td>No data</td>
</tr>
<tr>
<td>Sonwalkar et al. 2010</td>
<td>41</td>
<td>Not known</td>
<td>At least 1 (2.4%)</td>
<td>0 (0%)</td>
<td>At least 1 (2.4%)</td>
<td>At least 2 (4.8%)</td>
<td>At least 1 (2.4%)</td>
<td>No data</td>
</tr>
<tr>
<td>Total</td>
<td>1176</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At least 32 (2.7%)</td>
</tr>
</tbody>
</table>

Abbreviation: BE IND, Barrett’s esophagus with epithelial change indefinite for dysplasia; LGD, low-grade dysplasia; HGD, high-grade dysplasia.

*p53 immunohistochemical stain was performed in the BE IND esophageal biopsies from 81 out 85 cases, and expression of p53 in more than 5% nuclei was associated with the presence of prevalent advanced neoplasia [15].

### Table 3: Incident neoplasia risk in patients with BE IND.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Follow up in months (range)</th>
<th>Incident LGD</th>
<th>Incident HGD</th>
<th>Incident adenocarcinoma</th>
<th>Incident rate of all neoplasia (cases per 100 person-years at risk)</th>
<th>Risk of progression to all neoplasia</th>
<th>Incident advanced neoplasia (cases per 100 person-years at risk)</th>
<th>Risk factors for progression to advanced neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horvath B et al. 2015</td>
<td>82</td>
<td>Mean 59 (13-182)</td>
<td>14 (8.3%)</td>
<td>3 (2.3%)</td>
<td>2 (2.3%)</td>
<td>4.5</td>
<td>Length of BE and multifocality of BE IND*</td>
<td>1.2</td>
<td>p53**</td>
</tr>
<tr>
<td>Kestens C et al., 2015</td>
<td>631</td>
<td>Not known</td>
<td>No data</td>
<td>10 (1.6%)</td>
<td>6 (1.0%)</td>
<td>No data</td>
<td>No data</td>
<td>0.43***-1.10*****</td>
<td>Age*****</td>
</tr>
<tr>
<td>Singh P et al., 2015</td>
<td>83</td>
<td>Mean 68.4 (SD: 37.2)</td>
<td>No data</td>
<td>3 (3.6%)</td>
<td>1 (1.2%)</td>
<td>Not done</td>
<td>Not done</td>
<td>0.86*****</td>
<td>Not done for BE IND group</td>
</tr>
<tr>
<td>Duits LG et al., 2015</td>
<td>40</td>
<td>Median 31 (16-59)</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>0.9</td>
<td>Not done</td>
<td>0.9</td>
<td>Not done</td>
</tr>
<tr>
<td>Sonwalkar SA et al., 2010</td>
<td>37</td>
<td>Median 38.7 (6-122)</td>
<td>3 (8.1%)</td>
<td>0 (0%)</td>
<td>3 (8.1%)</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Expression of AMACR *****</td>
</tr>
</tbody>
</table>

Abbreviation: BE IND, Barrett’s esophagus with epithelial change indefinite for dysplasia; LGD, low-grade dysplasia; HGD, high-grade dysplasia; SD, standard deviation; AMACR, alpha-methylacyl-CoA racemase.

* Univariate analysis revealed that BE length and multifocality of BE IND were associated with progression to all neoplasia. Multivariate analysis was not performed due to the small number of events [12].

**p53 immunohistochemical stain was performed in the BE IND esophageal biopsies from 79 out 82 cases, and expression of p53 in more than 5% nuclei was associated with the progression to advanced neoplasia with a hazard ratio of 12 (95% confidence interval (CI): 1.43-100) by univariate analysis. Multivariate analysis was not performed due to the small number of events [15].

*** 330 cases of BE IND were downgraded to negative for dysplasia, incidence of advanced neoplasia and adenocarcinoma were 0.43 cases and 0.18 cases per 100 person-years at risk, respectively.

**** 101 cases of BE IND were diagnosed as BE IND during the first follow-up endoscopy, incidence of advanced neoplasia and adenocarcinoma was 1.10 cases per 100 person-years at risk.

***** Older age (per 10 years) was found to be a risk for developing all neoplasia and advanced neoplasia in this BE IND cohort including 12.1% of prevalent LGD.

****** Incidence of adenocarcinoma was 0.21 cases per 100 person-years at risk.

*******Expression of AMACR in more than 1% of cells was predictive of progression in BE IND.

### REFERENCES


