Research supports the concept that crypt dysplasia falls on the dysplasia pathway such that Barrett’s esophagus progresses from erosive esophagitis to nondysplastic Barrett’s esophagus, crypt dysplasia, low-grade dysplasia, high-grade dysplasia, adenocarcinoma in situ, and, finally, invasive adenocarcinoma. Further research into this progression will help clarify the risk associated with crypt dysplasia and the best method of treatment and surveillance given this risk.

In 2018, an estimated 17,290 cases of esophageal cancer were diagnosed in the United States. With 5-year survival less than 20%, esophageal cancer takes an undeniably heavy toll. Of esophageal cancers, esophageal adenocarcinoma (EAC) is the most prevalent histologic type in Western countries, including the United States, with risk factors including male sex and gastroesophageal reflux disease. The latter factor is associated with a 10% to 15% risk for Barrett’s esophagus (BE), which, in turn, is the precursor to most cases of EAC. Given this, much research has gone into identifying and classifying BE to prevent and treat EAC at as early a stage as possible. The pathway from erosive esophagitis to invasive adenocarcinoma has been the subject of significant research because of the poor prognosis associated with EAC. This pattern of progression from BE to EAC is of the utmost importance for early diagnosis and treatment.
Dysplasia: The Basics

Dysplasia is defined as morphologically abnormal changes seen with a microscope that are not cancer and, thus, the gold standard for diagnosis of dysplasia is histologic. Dysplasia in BE is characterized histologically by architectural and cytologic abnormalities. Generally, disease progresses along a continuum from BE without dysplasia to LGD, HGD, and adenocarcinoma. In LGD, there is relative preservation of glandular architecture despite the cellular changes, whereas HGD is characterized by marked cellular atypia and complex architectural changes.

There are 3 main types of dysplasia seen in BE: adenomatous, or intestinal, dysplasia; nonadenomatous, or foveolar type, dysplasia; and basal crypt dysplasia (CD). Basal CD is differentiated from the other types of dysplasia by the presence of retained surface maturation; that is, dysplastic changes are seen only in the crypt bases but may be either low or high grade. Traditionally, dysplasia limited to the crypts has been identified as indefinite for dysplasia (IND), with some pathologists arguing that surface maturation is “the most characteristic feature of nondysplastic epithelium” in BE. Recent research, however, has shown the importance of CD as its own entity along the dysplasia sequence, despite its current place as a provisional diagnosis that does not formally fall along the histopathologic continuum.

Criteria for Diagnosis

If CD is to be its own category of dysplasia, it must have a standard definition such that pathologists can reliably categorize it. Coco et al set out to study the criteria and reproducibility of the diagnosis of CD for just this reason. This study defined CD as “cytologic atypia in the crypts equal to traditional LGD or HGD but without surface epithelium involvement.” The findings were notable for moderate interobserver agreement among gastroenterology pathologists for the diagnosis of CD. Among pathologists, the highest interobserver agreement occurred in diagnosing BE without dysplasia and HGD. The lower interobserver agreement in the diagnosis of intermediate levels of mucosal lesions such as CD demonstrates that there are limitations and inconsistencies in the definition of this entity. This study highlights the need for further refinement of the histologic criteria for CD to increase the reliability of the diagnosis.

Crypt Dysplasia: Significance

Whether CD truly has a place along the metaplasia-to-carcinoma pathway is still debatable, but in recent years several studies were conducted on the topic. In 2006, Lomo et al published a discovery study that identified, for the first time, the biological significance of CD as a true precursor lesion in the progression to EAC. In a study of 206 consecutive patients with BE, 15 were found to have CD in at least 1 biopsy—defined by the presence of LGD or HGD features in the bases of crypts, with a lack of involvement of the upper half of the crypt and/or the surface epithelium—and all of the cases showed morphologic evidence of surface maturation. There was a significantly higher prevalence of traditionally defined dysplasia or adenocarcinoma among patients with CD than those without CD. About half of the CD cases were histologically high grade. In addition, the rate of positivity for the tumor suppressor gene \( p53 \) was higher in CD than in nondysplastic BE but lower in CD than in LGD, suggesting that CD falls between nondysplastic BE and LGD on the continuum of dysplasia; however, this difference was not statistically significant.

During the study period, 87% of patients with CD also had LGD, HGD, or adenocarcinoma. There was a significant association with dysplasia and cancer in patients with CD compared with controls. Thus, CD may be not only a precursor to more advanced stages of dysplasia but perhaps also a marker of this progression.

More recently, Ma et al conducted a study of 106 patients with a diagnosis of IND without a prior or concurrent diagnosis of dysplasia. In follow-up endoscopy in this cohort within 1 year of IND diagnosis, 8.0% of patients had prevalent dysplasia and 5.7% were...
diagnosed with HGD or EAC. Similarly, Kestens et al conducted a large cohort study that found an incidence of progression from IND to HGD or EAC of 1.4 per 100 person-years (95% CI, 1.0-1.9 per 100 person-years); Sinh et al reported that the incidence of HGD and EAC among patients with IND did not differ significantly from that of LGD to HGD or EAC; and Srivastava et al found that the majority of patients with CD had synchronous or metachronous conventional dysplasia or cancer on follow-up. In addition, Horvath et al identified 85 patients with a diagnosis of IND who had a surveillance biopsy within 12 months of diagnosis and found that 12.9% had dysplasia of any kind, with a 4.7% prevalence of HGD or EAC. Over a median of 54 months of follow-up, 23.2% of patients developed dysplasia of any kind, including EAC. This finding correlates with a neoplasia incidence of 4.5 cases per 100 person-years. The findings of these recent studies argue strongly for the place of CD as a precursor and/or marker of conventional dysplasia and EAC.

**Additional Markers of Dysplasia**

In dysplasia in BE, the number of mitoses is increased. Phosphorylated histone H3 is a surrogate marker of mitotic figure. Goodarzi et al conducted a retrospective study to quantify mitotic figures using phosphorylated histone H3 in tissue samples of all stages along the BE dysplasia pathway. The investigators found no significant difference in anti-phosphorylated histone H3-positive mitotic counts between patients with BE without dysplasia and those with a diagnosis of IND. However, surface anti-phosphorylated histone H3-positive mitotic counts were higher in patients with LGD and HGD than in those with IND, and they were higher still in patients with EAC. This finding shows that CD may be less of a risk factor for EAC than the previously discussed studies implied. However, because histology is the gold standard for diagnosis of dysplasia, the presence of mitotic figures as an indicator of dysplasia is not as reliable as a diagnosis from an expert pathologist.

**Inflammation or Dysplasia?**

Notably, inflammation can induce changes that are similar to those seen in CD and act as a possible confounder in the diagnosis of CD. In this situation, a biopsy specimen may be labeled as IND, not as a proxy for CD but as a separate entity that is, in fact,
indefinite.11 This overlap and unclear definition of IND are critical to understanding the current evidence on the importance of CD.

**Treatment and Next Steps**

If biopsy specimens are identified as IND, the American College of Gastroenterology recommends repeating endoscopy after 3 to 6 months of acid-suppressive therapy.3 If the patient is still IND after repeat endoscopy, surveillance endoscopy at an interval of -12 months is recommended.3 Similarly, the American Society for Gastrointestinal Endoscopy recommends antisecretory therapy aimed at resolving esophageal inflammation followed by repeat esophagogastroduodenoscopy with biopsy to clarify the status of dysplasia.18

Data on the clinical significance of CD is still limited. Research supports the concept that CD falls on the dysplasia pathway, such that BE evolves from erosive esophagitis to nondysplastic BE, CD, LGD, HGD, adenocarcinoma in situ, and ultimately invasive EAC. Further research is needed on a larger scale to better classify CD and its significance in the dysplasia-to-adenocarcinoma continuum.

**References**