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EDITORIAL

Risk stratification in Barrett's esophagus patients with diagnoses of indefinite for dysplasia: the definite silver bullet has not (yet) been found

In Barrett's esophagus (BE), both endoscopic surveillance interval and treatment recommendations are based on the presence and grade of histopathologically diagnosed dysplasia, because dysplasia currently best predicts the risk of progression to esophageal adenocarcinoma (EAC). Owing to the low risk of progression, periodic endoscopic surveillance is recommended in nondysplastic BE (NDBE), whereas a more intensive surveillance or even preventive ablation can be considered in patients with low-grade dysplasia (LGD). By contrast, the risk of progression in BE patients with diagnoses of indefinite for dysplasia (IND) and as a consequence their further treatment remain controversial.

In this issue of *Gastrointestinal Endoscopy*, Krishnamoorthi et al[1] report the results of a systematic review in which 8 studies originating from both Europe and North America including a total of 1441 BE patients with a diagnosis of IND and a reported outcome of high-grade dysplasia (HGD) and/or EAC were identified. In the subsequent meta-analysis, a pooled incidence rate of HGD, EAC, or both of 1.5 per 100 person-years and a slightly lower incidence rate of EAC alone of 0.6 per 100 person-years were estimated. No substantial differences in incident rates were found in the subgroup analysis of HGD, EAC, or both if studies were compared regarding their origin (Europe vs North America, 1.6 vs 1.4 per 100 person-years, respectively) or study quality (medium vs high, 1.7 vs 1.3). When progression to EAC alone was analyzed, a significantly higher incidence rate of 0.9 versus 0.4 per 100 patient-years was observed if studies from Europe were compared with those from North America, respectively. A moderate to substantial heterogeneity of the included studies was noted in all analyses. The authors conclude a similar incidence rate of BE-IND and LGD and therefore recommend an intensified surveillance program.

However, the complexity behind the term "IND" raises the question whether the underlying data allow one to draw an adequate conclusion on how to treat these patients.

Two fundamental questions have to be adressed in every systematic review and meta-analysis. First, are the included patient populations homogeneous enough to be summarized? Second, can the findings be transferred to an equal patient population? Both may be questioned in this report. All included samples were analyzed retrospectively, with the majority being collected at tertiary referral centers. In particular, the second limitation is highly biased toward an increased progression risk for IND: Does a patient with a diagnosis of IND in a center with experienced gastroenterologists and GI pathologists carry the same progression risk as a patient identified in a community hospital (where most BE care is given)?

Although showing some promising results, the use of biomarkers is not (yet) part of the guidelines recommended by the GI societies. So what should we do if we are confronted with a patient with a diagnosis of IND?

Inasmuch as none of the studies included a pathologist's definition of IND within the methods section, how should we avoid painting different entities with the same brush? In addition to differing levels of experience, this may be another reason for the reported poor interobserver agreement among pathologists in diagnosing IND, and it may partly explain the different progression risks when studies from Europe and North America are compared.

Nevertheless, the authors can hardly be critizied for including a highly varied population of patients with diagnoses of IND, because this might be a logical consequence of the vague definition of the term "IND" itself.

Before 2000, the use of both conventional Western and Japanese classification systems resulted in large interobserver differences in the diagnosis of GI tumors, mainly caused by a varying focus on cytologic and architectural features between Western and Japanese pathologists. The adoption of the revised Vienna criteria[2] created a uniform 5-tier classification system based on a combination of architectural and cytologic features and invasion status. All participating pathologists agreed that this classification should include the new category "indefinite for dysplasia" when one cannot decide whether a lesion is dysplastic.

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In nondysplastic biopsy specimens next to a preserved architecture, the cytologic aspect appears nearly normal, and surface maturation can be seen.[3] By contrast, LGD architecture can be slightly altered and surface maturation is distorted, accompanied by mild but diffuse cytologic changes, reflected by nuclear hyperchromasia and mild to moderate increase in size and shape (often enlongated but retaining basal orientation). Logically, in the presence of preserved architecture and surface maturation but altered cytologic changes such as increased mitoses in the deeper glands and mild nuclear atypia, a distinction between absence or presence of dysplasia might be difficult, and a diagnosis of IND may be reasonable. Additionally, inflammation and regenerative changes after epithelial injury can both cause significant cellular and nuclear changes that closely mimic dysplasia. Because in IND, elements from both reactive nondysplastic changes and aspects from "true" dysplasia could be present, it is likely that IND patients constitute a very heterogeneous group that includes patients without dysplasia but reactive changes and a very low risk of progression, and patients with true dysplasia and consecutively higher risk for progression to cancer.

The experience of a pathologist is one of the key factors in separating these 2 subgroups. Obviously, the distinction between these subtle changes is even harder for pathologists who do not see BE biopsy specimens very frequently. Consequently, a less-experienced pathologists may diagnose IND rather than reactive nondysplastic changes so as not to miss patients at risk for progression. By contrast, an expert GI pathologist may be able to identify patients with true dysplastic changes. With the inclusion of additional patients with reactive changes into the IND category, the true risk of progression in IND patients will be diluted. In a similar manner, one would expect additional patients to receive "overdiagnoses" of LGD in comparison with the diagnoses applied by a highly experience GI pathologist. This was shown in a Dutch study published in 2015, in which 293 patients with a community-based diagnosis of LGD were reviewed by 3 expert GI pathologists.[4] The majority of patients were downstaged to NDBE (59%), whereas 14% received diagnoses of IND and 27% had a confirmed diagnosis of LGD. This resulted in a low risk of HGD/EAC of 0.6% and 0.9% per patient-year in NDBE and IND patients, respectively, compared with a significantly increased risk of HGD/EAC of 9.1% per patient-year in confirmed LGD cases. This study highlights the need for expert GI pathologist review for a diagnosis of IND. Although an accepted definition of the term "expert GI pathologist" is lacking and the term itself remains vague, the same Dutch study group developed benchmark criteria for pathologists who aspire to join a core group of experienced BE pathologists.[5] Although this selection may be subjective, a low number of IND diagnoses was 1 out of a total of 4 criteria.

European guidelines (British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy) and the American College of Gastroenterology (no specific recommendations are made by the American Gastroenterological Association) slightly differ. All guidelines advise repeating the endoscopy after 6 months of intensified antireflux therapy after a confirmed diagnosis of IND, similar to the management of confirmed LGD. The 2 European Guidelines recommend endoscopically surveying patients with repetitive and expert confirmed IND similar to NDBE every 3 to 5 years, whereas the American College of Gastroenterology suggests applying the same annual surveillance interval as in confirmed LGD. In none of the guidelines is preventive ablative therapy in the presence of IND recommended.

Although review by an expert pathologist is significantly better than diagnosis by a less-experienced pathologist, it is still a subjective grading of subtle changes, resulting in an at best moderate interobserver agreement in patients with IND or LGD. To complicate matters, some pathologists use IND in slightly different settings, for example, in the setting of massive inflammation where cells can look highly atypical (resembling HGD) whereas others use it for mild changes when they cannot decide whether or not it is sufficient for LGD. Additionally, new sampling techniques, such as wide-area transepithelial brush sampling, are gaining more interest, and the larger tissue areas sampled may increase the number of diagnoses with (yet) "indefinite" significance (such as basal crypt dysplasia).[6]

More objective tools are clearly needed to facilitate risk stratification in patients with IND and LGD. Critchley-Thorne et al[7] combined immunofluorescence-based analysis of epithelial and stromal biomarker features such as p53, HER2, COX2, and AMACR with morphologic changes using an automatized whole slide image analysis algorithm. The resulting 3-tier classifier accuratly risk stratified NDBE, IND, and LGD into low risk, intermediate risk, or high risk for progression to HGD/EAC. This classifier provided independent prognostic information that outperformed the histopathologic risk prediction based on analysis by a GI expert. Other approaches based on somatic chromosomal alterations have also been shown to predict progression independent from the histopathologic diagnosis of dysplasia. Li et al[8] used a risk prediction model containing 29 somatic chromosomal alterations that outperformed prediction made by histopathology and immunohistochemistry. Recent work suggests that *TP53* may be an early event in the cascade to progression to EAC, which is able to dinstinguish between BE patients who experience progression and those who do not.[9] Their genomic analysis using formalin-fixed paraffin-embedded tissue blocks demonstrated that almost half of the patients who experienced progression in their case-control study had *TP53* mutations, whereas such mutations were found in only 5% of the control individuals who did not experience progression.

Although showing some promising results, the use of biomarkers is not (yet) part of the guidelines recommended by the GI societies. So what should we do if we are confronted with a patient with a diagnosis of IND?

We likely do not have the tools yet to accurately risk stratifiy these patients, inasmuch as the term "IND" reflects less an accurate diagnosis and more a diagnosis of uncertainty by the pathologist. This diagnostic gap is therefore an interim step until the true nature of the lesion reveals itself by either progressing to "true" dysplasia or downstaging to NDBE. Nevertheless, because the limited data that we have suggest that a minority of the patients with community-diagnosed IND either already harbor LGD or will experience progression to LGD, reviewing the initial diagnosis by an expert pathologist seems to be the most logical step. If the diagnosis is subsequently downstaged or upstaged to NDBE or LGD, respectively, the surveillance interval should follow that diagnosis. In those rare cases in which the expert review still results in the diagnosis of IND, repeated endoscopy after 6 months along with intensified antireflux therapy to minimize interfering inflammation seems a logical aproach. In the majority of cases, the true nature of IND (either NDBE or LGD) will then show its face. Very few patients will have a persistent diagnosis of IND over the course of multiple surveillance endoscopies.

DISCLOSURE

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Abbreviations: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus.

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