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How should we describe, diagnose and observe the Barrett's esophagus?

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ABSTRACT

Barrett's esophagus (BE) is one of the major complications of gastroesophageal reflux disease (GERD) commonly encountered in gastroenterology clinics. A consensus has not been achieved yet with respect to the definition of BE in published guidelines. It is advised to use the Prague classification and not to use the definition of short and long segments for the endoscopic standardization of BE. Undertaking biopsies with white-light endoscopy from each of the 4 quadrants at 2-cm intervals is the standard method for the diagnosis of BE. Because of the ability to perform targeted biopsies, the available data indicate that advanced endoscopic techniques may reduce the number of biopsies needed for diagnoses. In the presence of severe esophagitis along with BE, the biopsies should be taken after 8 weeks of PPI therapy. The evidence values of the suggestions about the surveillance requirements and surveillance frequencies are low because the available data mostly rely on retrospective studies. We suggest that all the patients with BE should be referred to specialized centers for surveillance in Turkey. Considering the additional risk factors of the patient, endoscopy surveillance intervals of the patients with BE without dysplasia should be in a range of 3-5 years and annual surveillance should be made in BE with low-grade dysplasia. In the presence of BE with high-grade dysplasia (HGD), the patients should be referred to specialized centers for treatment within 3 months at the latest.

Keywords: Barrett's esophagus, gastroesophageal reflux disease, proton pump inhibitor, dysplasia

A universal consensus on the definition Barrett's esophagus (BE) has not been achieved yet. Different definitions were made in the British Society of Gastroenterology (BSG) 2013 and *American Gastroenterological Association* (AGA) 2011 guidelines (1,2). With reference to the former, while the presence of any columnar epithelium between the gastroesophageal junction and squamocolumnar junction (fundic, cardiac, or specialized intestinal metaplasia (SIM)) is sufficient for the diagnosis of BE. The presence of SIM is required for the diagnosis, according to AGA 2011.

There are some retrospective studies showing that cardiac- or fundic-type columnar epithelium is precancerous at the same rate with SIM (3,4). In addition, it was put forward in published histochemical and genetic studies that SIM and the other two columnar epithelia showed similar DNA abnormalities and the other columnar epithelia showed intestinal differentiation like SIM. A conclusion was made that the other columnar epithelia were a precursor lesion for SIM (5,6). However, population-based cohort studies with large numbers of patients have revealed that SIM-positive patients carry a much greater risk than SIM-negative patients in terms of the development of LGD, HGD, and esophagus adenocarcinoma (EAC) (7-9). While the annual progression rate to the EAC of SIM-positive patients was 0.24% in the analyses performed in this study, this rate was found to be 0.04% in SIM-negative patients. These results indicate that the presence of SIM is necessary for the diagnosis of BE.

On the other hand, the definition of BE should be disassociated from the concept of irregular Z-lines. An ir-

regular Z-line is known to be seen more frequently in GERD patients (10). Although SIM has been observed in the biopsies taken from the irregular Z-line patients, the clinical significance of this is not very clear (11). In a study in which SIM-positive patients with a segment length over 1 cm and patients with SIM in the gastroesophageal junction were followed in terms of the risk of EAC development, it was observed-after a long-term follow-up-that EAC did not develop in any of the patients with SIM in the gastroesophageal junction (12). It is assumed to be more accurate not to accept lesions smaller than 1 cm as BE due to its clinical insignificance and the lack of consistency among endoscopists.

Since Sharma et al. (13) developed the Prague classification in 2006, short- (<3 cm) and long-segment (>3 cm) terms, which are the traditional classification of BE, have no longer been used. According to the Prague classification system, determining the 3 endoscopic points is of paramount importance: they are the squamocolumnar junction, gastroesophageal junction (the line where the gastric folds end at the proximal), and diaphragmatic hiatus. Following the identification of these 3 areas during endoscopy, the circumferential extension (circumferential: CM) between the squamocolumnar junction and gastroesophageal junction and the maximum length (M) between the most proximal point of the columnar epithelium and the gastroesophageal junction are measured. In validation studies, a perfect consistency was formed between endoscopists regarding the Prague classification, particularly for lesions over 1 cm and on the detection of the 3 important endoscopic points (κ=0.21<1 cm, κ=0.72≥1cm). Moreover, this perfect consistency is independent of the experience of the endoscopist.

If there is severe esophagitis with BE suspicion in patients who were endoscopically evaluated, BE can get masked in the biopsies due to the abundance of inflammation. Therefore, the primary aim for this group should be the reduction of inflammation, and the biopsy should be postponed. In a study, biopsies taken during the first endoscopy of patients with erosive esophagitis and the biopsies taken during the second endoscopy after the treatment with a double dose of PPI for 8 weeks on an average were evaluated. After an average of 8 weeks of standard double-dose PPI treatment (e.g., pantoprazole 40 mg bid, lansoprazole 30 mg bid, and omeprazole 20 mg bid), it was observed that the erosive esophagitis of 75% patients with advanced esophagitis (LA classification C, D) regressed and the basal 12.5% prevalence of BE increased to 24.6% (14,15).

In large and small-scale studies conducted until today, it has been shown that the undertaken biopsies confirmed the diagnosis in a maximum of half the cases with endoscopically suspected BE (16-21). This ratio is even lower in the case of the female gender, hiatal hernia, advanced age, presence of segment lengths shorter than 3 cm, and esophagitis (16-19). As previously mentioned, the presence of SIM should be demonstrated in biopsies for the diagnosis of BE. Taking a biopsy from each of the 4 quadrants at 2-cm intervals is the standard method (20,21).

Studies comparing advanced endoscopic procedures with taking targeted biopsies and taking random biopsies through standard white-light endoscopy are being conducted for the purpose of increasing the diagnostic value of endoscopy and reduce the number of biopsies that are required to be taken. In the meta-analysis in which the studies done with methylene blue were collected, it has been shown that chromoendoscopy performed with methylene blue and targeted biopsies do not provide any additional benefit in comparison to standard white-light endoscopy and random biopsies (22). Indigo–carmine magnifying endoscopy and targeted biopsies were not found to be superior to standard endoscopy and random biopsy methods in detecting dysplasia (23). Out of 2 studies that were performed by using acetic acid and published in the same year, while they were found superior to standard endoscopy and random biopsies in detecting SIM in a study conducted on 31 patients, no statistically significant difference was detected between both groups in the other study which was a larger randomized controlled trial evaluating 137 patients (24,25). Eventually, advanced endoscopic methods and targeted biopsies did not provide distinct advantages over standard white-light endoscopy and random biopsies. The number of biopsies that are required to be undertaken can be reduced by taking targeted biopsies by means of advanced endoscopic methods.

Our knowledge about the surveillance of BE is based on retrospective surgical series. Surgical retrospective analyses indicate that the patients from the observation arm are significantly better in terms of the stage of cancer and recovery in comparison to patients studied when the symptoms occur (26-35).

The frequency of surveillance in BE is determined by the presence and degree of dysplasia. The surveillance in BE without dysplasia should be performed every 2 years according to the BSG 2013 guidelines and in every 3-5 years according to the AGA 2011 guidelines (1,2). In the study of cost-effectivity in patients with BE, it was found that the rate of disease progression should be over 0.5% in order to make endoscopic surveillance at a frequency under 5 years (36). Although the annual progression rate of BE without dysplasia to HGD/EAC is demonstrated at different rates in studies, there is no study that shows it to be more than 0.5% (7,18,37-48). Considering the additional risk factors such as Prague M>3, male gender, Caucasian race, advanced age, smoking history, and central obesity, it is assumed that endoscopic surveillance should be made in BE patients who do not have dysplasia due to the low rate of progression at 3-5-year intervals by taking a decision particular to the patient's characteristics.

Both AGA 2013 and BSG 2011 guidelines recommend annual surveillance in BE with low-grade dysplasia (1,2). The annual progression rate from LGD to HGD/EAC occurred in a wide

range between 1.1% and 12.8% in different studies (7,8,37-50). Considering the annual progression rate, annual surveillance is recommended in BE with LGD.

In the meta-analysis showing the annual progression rate from HGD to EAC, the annual progression rate was found to be 5.57% (51). In the meta-analysis of HGD patients who underwent esophagectomy, the ratio of hidden EAC comorbidity was found to be 39.9% (0%-73%) in pathological samples of the patients in whom esophagectomy was performed due to HGD (52). BE-diagnosed patients with HGD should be referred to specialized centers for treatment without delay due to the high progression rate and the risk of occult invasive cancer.

RECOMMENDATIONS

- Barrett's esophagus (BE): Moving of the squamocolumnar junction (endoscopic Z-line) toward the proximal of gastroesophageal junction (the line where the gastric folds end at the proximal) at least 1 cm in the esophagus and the presence of specialized intestinal epithelium in this place instead of multi-layered squamous epithelium (level of evidence: 5).
- Prague classification should be used for the endoscopic standardization of BE. The following three anatomical regions should be noted in the report of endoscopy (level of evidence: 5).
  - Squamocolumnar junction (Z-line)
  - The line where the gastric folds end at the proximal (gastroesophageal junction)
  - Diaphragmatic hiatus
- Definitions of short and long segments are no longer used (level of evidence: 5).
- If there is severe esophagitis accompanied by BE (Los Angeles (LA) classification C, D), these patients should be given proton pump inhibitors (PPI) at a standard dose of 2 times a day and biopsies should be taken by performing endoscopy 8 weeks later (level of evidence: 2b).
- White-light endoscopy and biopsies are the standard methods for the diagnosis of BE (level of evidence: 2b). Biopsies should be taken from each of the 4 quadrants at 2-cm intervals (level of evidence: 5).
- Advanced endoscopic methods (conventional chromoendoscopy, virtual chromoendoscopy NBI, and magnifying endoscopy) may reduce the number of biopsies needed for diagnosis because targeted biopsies can be taken (level of evidence: 1a, 1b).
- After the diagnosis of BE is established, surveillance is recommended (level of evidence: 3b).
- Considering the additional risk factors such as Prague M>3, male gender, Caucasian race, advanced age, smoking history, and central obesity, the endoscopic surveillance intervals of BE patients without dysplasia should be 3-5 years by taking a decision particular to the patient's characteristics (level of evidence: 5)
- Annual surveillance should be made in BE with low-grade dysplasia (LGD) (level of evidence: 5)
- All the patients with BE are proposed to be referred to specialized centers for surveillance in Turkey (level of evidence: 5).
- In the presence of BE with HGD, the patients should be referred to specialized centers for treatment within 3 months at the latest (level of evidence: 5).

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