Barrett's Esophagus

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Given that endoscopic findings can be used to predict the potential of neoplastic progression in Barrett's esophagus (BE) cases, the detection rate of dysplastic Barrett's lesions may become higher even in laborious endoscopic surveillance because a special attention is consequently paid. However, endoscopic findings for effective detection of the risk of neoplastic progression to esophageal adenocarcinoma (EAC) have not been confirmed, though some typical appearances are suggestive. In the present review, endoscopic findings that can be used predict malignant potential to EAC in BE cases are discussed. Conventional results obtained with white light endoscopy, such as length of BE, presence of esophagitis, ulceration, hiatal hernia and nodularity, are used as indicators of a higher risk of neoplastic progression. However, there are controversies in some of those findings. Absence of palisade vessels may be also a new candidate predictor, as that reveals degree of intense inflammation and of cyclooxygenase-2 protein expression with accelerated cellular proliferation. Furthermore, an open type of mucosal pattern and enriched stromal blood vessels, which can be observed by image-enhanced endoscopy including narrow band imaging, have been confirmed as factors useful for prediction of neoplastic progression of BE because they indicate more frequent cyclooxygenase-2 protein expression along with accelerated cellular proliferation. Should the malignant potential of BE be shown predictable by these endoscopic findings, that would simplify methods used for an effective surveillance, because patients requiring careful monitoring would be more easily identified. Development in the near future of a comprehensive scoring system for BE based on clinical factors, biomarkers and endoscopic predictors is required.

Keywords: Barrett's esophagus ; esophageal adenocarcinoma ; endoscopic predictor ; biomarkers ; endoscopic surveillance

1. Introduction

In Western populations, patients with esophageal adenocarcinoma (EAC) derived from Barrett's esophagus (BE) have shown a marked increase in recent decades. Furthermore, the clinical outcome of EAC has been reported that the prognosis worsens as the stage progresses, although a 5-year survival is around 47% for localized EAC ^{[1][2][3][4]}. The annual incidence of EAC arising from BE has reported to be 0.33% in a meta-analysis ^[5], and 0.36% in a prospective study ^[6]. Desai M at al. reported there was a significant increase in the detection of high-grade dysplasia and EAC (1990–1994, 5.1%; to 2005–2009, 6.3%; and 2010+, 16.3%) ^[7]. Thus, calculated rates of incidence of neoplastic progression in BE cases have never shown a reduction, this been suggested that endoscopic surveillance is essentially required for affected patients, as stated in guidelines presented by the British Society of Gastroenterology and American Colleague of Gastroenterology ^{[8][9]}. The American Society for Gastrointestinal Endoscopy (ASGE) standard of practice committee has reported that most patients with EAC are diagnosed in a later stage of the disease and performance of BE surveillance is associated with a 25% reduction in mortality ^[10]. However, endoscopic surveillance of BE is considered to be laborious and costly, as the protocol requires obtaining several biopsy specimens from quadrant areas, each with a 1 or 2 cm interval. Therefore, a more effective and simpler endoscopic surveillance method for clinical practice is anticipated to assist management of patients with BE.

Understanding of available information regarding the potential of neoplastic progression in BE prior to endoscopic surveillance is inevitably important. While several clinical risk factors, such as male gender, aging, smoking, high-fat diet, obesity, reflux esophagitis, colon neoplasms, as well as others, are well-known important predictors of Barrett's carcinogenesis ^{[11][12][13][14][15][16][17][18]}, they are not considered to be fully reliable indicators of neoplastic progression in all patients with BE. However, presence of erosive esophagitis or recurrent gastroesophageal reflux disease (GERD) symptom have been reported to be important predictors for neoplastic progression in BE as described below ^{[19][20]}, and subsequently, proton pump inhibitor (PPI) use was protective against the progression ^{[12][21][22]}. Recently, biomarkers including epigenetics and miRNA analysis findings, DNA content abnormalities, and loss of heterozygosity noted in biopsy findings have been reported to be additional reliable predictors of malignant transformation in affected patients ^[23]. One of the most important biomarkers is aberrant expression and/or mutation of p53 ^{[24][25]}. Some of these biomarkers become to

be detectable by specialized endoscopic devices such as autofluorescence endoscopy, optical coherence tomography, endocytoscopy, confocal endomicroscopy, or near-infrared imaging endoscopy, although use of these novel markers is difficult in clinical settings because of the complicated biochemical procedures required. On the other hand, various findings obtained with white light endoscopy (WLE), such as length of BE segment and presence of esophagitis, ulceration, and hiatal hernia, along with others, can be used for prediction of progression to EAC. Nevertheless, such endoscopic findings must be verified for use in clinical practice before being considered available as a true marker for neoplastic progression. Another significant factor related to Barrett's carcinogenesis is cyclooxynase-2 (COX-2) protein expression, which has been reported to be a key event in transformation to a dysplastic lesion ^[26]. Endoscopic information regarding COX-2 protein expression in BE case can be detected by some endoscopic methods including chromoendoscopy or narrow band imaging (NBI) endoscopy, thus endoscopic surveillance may become to be a more efficacious by the use of these developed devices.

With the development of endoscopic methods and devices, the easier detection of neoplastic lesions of BE may be currently applicable for the clinical practice. Among them, NBI endoscopy that can be evaluated micro-mucosal and micro-vascular patterns is considered to be one of the representative candidates. In the present review, the contributions of endoscopic findings including WLE and image-enhanced endoscopy (IEE): chromoendoscopy, acetate-enhanced endoscopy, NBI endoscopy, and molecular imaging endoscopy, for prediction of the malignant potential of BE, were investigated. Furthermore, a new concept for efficient endoscopic surveillance of BE along with a targeting biopsy method instead of a random biopsy procedure is also discussed. Findings presented in this review were obtained with procedures conducted in accordance with the Declaration of Helsinki.

2. Efficient Method for Surveillance of BE

Patients with EAC have been gradually increasing in Asian countries, and those with BE are known to share similar risk factors for neoplastic progression as demonstrated in Western populations ^{[27][28]}. In Japan, EAC has not been well known in clinical practice, different from esophageal squamous cell carcinoma, though EAC cases have been steadily increasing in association with increases of erosive esophagitis and BE ^[29]. According to the annual report of the Japanese Association for Thoracic Surgery, the ratio of EAC to squamous cell carcinoma cases had increased to 9.4:100 in 2017 ^[30]. Moreover, a cohort study conducted by the Japan Gastroenterological Endoscopy Society showed that the annual rate of incidence of EAC arising from Barrett's esophagus greater than 3 cm in length was 1.2%, though this study was a small number and a short period observation ^[31]. Therefore, Japanese endoscopists have recently been encouraged to pay adequate attention to accurate and effective management of patients with BE.

A multicenter study conducted in Japan (Japan EAC study) reported that 247 (79%) of 311 superficial Barrett's carcinoma cases were derived from SSBE, and the total rate of lymph node and/or another organ metastasis was 15.7%, with a 5-year survival rate of 81% ^[32]. Therefore, some SSBE patients should be followed regularly as same as those with LSBE, albeit all the SSBE cases do not require strict annual surveillance. An efficient survey system is essential for consideration of grading for risk of neoplastic progression.

In Western countries, a random biopsy procedure with 4 quadrants and 1 or 2 cm intervals is recommended for endoscopic surveillance of BE ^{[B][9]}, though that is time consuming and expensive, and also increases risk associated with the large number of biopsy samples obtained. Given that endoscopy findings can predict the malignant potential of BE, they may provide a more efficient and feasible surveillance method in clinical practice. Based on findings presented in this review, we concluded that a simpler surveillance method to avoid unnecessary biopsy procedures may be possible by use of endoscopic findings with WLE, IEE, and MIE. Sharma P et al. reported that a NBI targeted biopsy can detect more areas with dysplasia as compared to WLE with random biopsied areas ^[33]. Although a model to determine clinical risk factors of neoplastic progression in patients with BE has already been demonstrated ^[34], it will be necessary to conduct additional analyses of endoscopic findings to reveal more suitable and novel techniques. Thus, in near future, it may be allowed to propose that a targeting biopsy method combined with IEE and/or MIE plays an important role in surveillance yield of BE cases instead of the Seattle protocol.

3. Conclusions

The risk of neoplastic progression in BE appears to be predictable by WLE, IEE, and MIE observations. It is anticipated that a predictive endoscopic scoring system to detect potential neoplastic progression in affected patients will be established in the near future.

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