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BRIEF REVIEW

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The Clinical Consequences of Advanced Imaging Techniques in Barrett's Esophagus

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Evaluation of patients with Barrett's esophagus (BE) using dye-based chromoendoscopy, optical chromoendoscopy, autofluorescence imaging, or confocal laser endomicroscopy does not significantly increase the number of patients with a diagnosis of early neoplasia compared with high-definition white light endoscopy (HD-WLE) with random biopsy analysis. These newer imaging techniques are not more effective in standard surveillance of patients with BE because the prevalence of early neoplasia is low and HD-WLE with random biopsy analysis detects most cases of neoplasia. The evaluation and treatment of patients with BE and early-stage neoplasia should be centralized in tertiary referral centers, where procedures are performed under optimal conditions, by expert endoscopists. Lesions that require resection are almost always detected by HD-WLE, although advanced imaging techniques can detect additional flat lesions. However, these are of limited clinical significance because they are effectively eradicated by ablation therapy. No endoscopic imaging technique can reliably assess submucosal or lymphangio-invasion. Endoscopic resection of early-stage neoplasia in patients with BE is important for staging and management. Optical chromoendoscopy can also be used to evaluate lesions before endoscopic resection and in follow-up after successful ablation therapy.

Keywords: Barrett's Esophagus; Neoplasia; Endoscopic Imaging; Endoscopic Therapy.

The incidence of esophageal adenocarcinoma in the Western world has increased 6-fold over the past 3 decades, and patients with this disease have a dismal prognosis when it is detected at a symptomatic stage.[1] Adenocarcinoma develops through a precursor lesion called Barrett's esophagus (BE) in a sequence of gradually evolving, histologically recognizable steps: intestinal metaplasia, low-grade dysplasia, high-grade dysplasia, intramucosal carcinoma, and eventually invasive carcinoma. These intermediate grades of dysplasia offer a window of opportunity for curative therapy.

In the past decade, endoscopic therapy has been the treatment of choice for early Barrett's neoplasia (ie, high-grade dysplasia and intramucosal carcinoma), with an excellent prognosis and safety profile compared with surgical resection.[2] A prerequisite for endoscopy therapy is adequate patient selection; only patients with high-grade dysplasia and intramucosal carcinoma have a virtually absent risk of lymph node metastasis and are therefore amenable for endoscopic therapy.[3]

In patients with known BE, regular surveillance endoscopy with random biopsies is recommended to detect early neoplastic lesions at a curable stage.[4] However, these lesions are often small, focally distributed, and poorly visible endoscopically (Figure 1). Random 4-quadrant biopsies may easily miss early lesions, because only approximately 5% of the Barrett's segment is sampled.[5] Moreover, this process is laborious and many endoscopists do not adhere to the protocol.[6]

In recent years, many advanced imaging techniques have been developed to improve the detection of early Barrett's neoplasia. In this review, we discuss how these techniques may affect clinical management of BE by either improving the primary detection of early neoplastic lesions, allowing real-time diagnosis and decision making during endoscopy, or guiding the endoscopic workup and treatment.

Primary Detection of Early Neoplasia

For primary detection of early neoplastic lesions in BE, wide-field imaging techniques are required that allow detection of lesions in an overview to "red flag" areas of interest. As stated in current guidelines, advanced imaging techniques should be superimposed on high-resolution white light endoscopy (WLE) using high-definition (HD) systems. The currently available HD-WLE systems have a spatial resolution of less than 10 μm and offer high-quality imaging that is the basis for endoscopy in BE.[7–9]

Chromoendoscopy

In chromoendoscopy, stains are applied to the mucosa to improve the visualization of neoplastic lesions. In general, 2 types of dye are available: vital and contrast stains. Vital stains (eg, methylene blue) are actively absorbed by the

Abbreviations used in this paper: **AFI, autofluorescence imaging; BE, Barrett's esophagus; BLI, blue laser imaging; CLE, confocal laser endomicroscopy; ETMI, endoscopic trimodal imaging; HD, high-definition; iCLE, integrated confocal laser endomicroscopy; NBI, narrow band imaging; OFDI, optical frequency domain imaging; pCLE, probe-based confocal laser endomicroscopy; WLE, white light endoscopy.**

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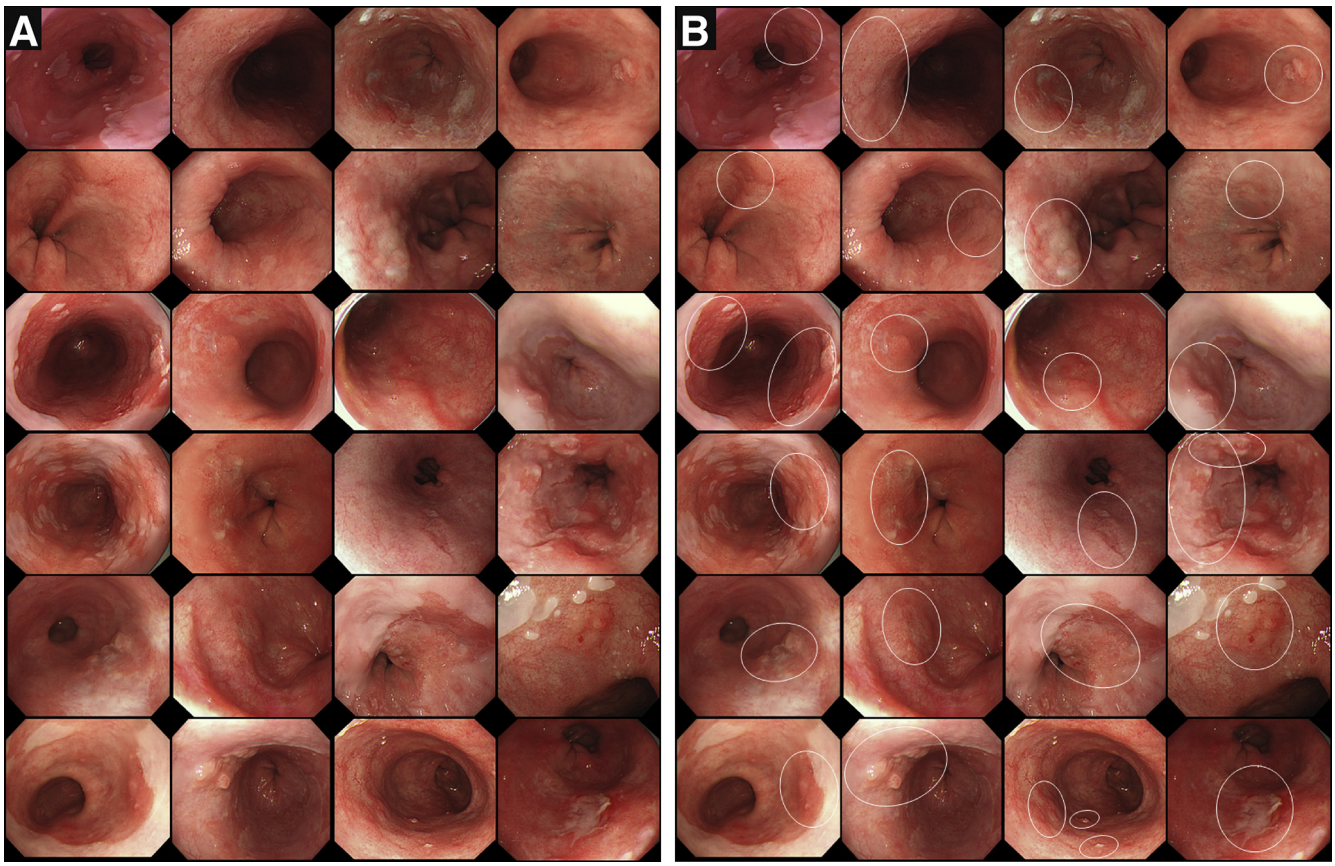

Figure 1. (*A*) Examples of subtle neoplastic lesions in BE. (*B*) The neoplastic lesions are indicated with *circles*. Reproduced with permission from www.endosurgery.eu.

epithelium. Contrast stains (eg, indigo carmine) accumulate in pits and grooves along the epithelial surface, highlighting the superficial mucosal architecture (Supplementary Figure 1). Early studies of methylene blue chromoendoscopy suggested increased detection of early neoplasia,[10] yet a recent meta-analysis of 9 studies showed that there is no incremental yield for methylene blue chromoendoscopy over standard WLE.[11] Acetic acid is an inexpensive agent that increases the contrast of the mucosal pattern (Supplementary Figure 1). Recent publications have suggested that acetic acid may be beneficial for identification of early neoplasia.[12,13] However, no randomized (crossover) controlled studies have been performed comparing acetic acid with standard practice, and other studies have questioned the additional value of acetic acid over HD-WLE.[14]

Chromoendoscopy techniques are not widely used in Barrett's endoscopy; it is questionable whether they really increase the detection of early neoplasia over HD-WLE, many endoscopists consider chromoendoscopy a cumbersome procedure, and correct application of dyes and interpretation of the images are operator dependent.

Optical and Digital Chromoendoscopy Techniques

Optical and digital chromoendoscopy techniques improve the visualization of mucosal morphology without the use of dyes. This can be done with preprocessing techniques (optical chromoendoscopy) such as narrow band imaging (NBI; Olympus, Tokyo, Japan), or blue laser imaging (BLI; Fujifilm, Tokyo, Japan). The mucosal imaging is enhanced by using blue light, which only penetrates superficially into the tissue and causes less scattering. In addition, blue light encompasses the maximum absorption wavelength of hemoglobin, which results in better visualization of vascular structures.[15]

Digital chromoendoscopy techniques that are based on postprocessing (Fuji Intelligent Chromo Endoscopy [Fujifilm] and i-scan [Pentax, Tokyo, Japan]) use normal white light excitation. The reflected image is then reprocessed by a proprietary algorithm. In our opinion, preprocessing techniques have a better signal-to-noise ratio, resulting in images with a higher resolution and brightness compared with postprocessing techniques (Figure 2).

Most studies on optical chromoendoscopy techniques in BE have used NBI. Regular mucosal and vascular NBI patterns have been shown to correlate with nondysplastic BE, while irregular features are associated with early neoplasia.[15,16]

The yield of NBI for the detection of early neoplasia has been investigated in 3 randomized studies. Kara et al compared HD-WLE plus NBI with HD-WLE plus indigo carmine chromoendoscopy in a randomized crossover design.[17] NBI and indigo carmine both increased the targeted detection of neoplastic lesions, but all patients with neoplasia had already received a diagnosis of HD-WLE.