Developments in molecular and advanced endoscopic imaging in esophageal cancer

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Today's mistakes and tomorrow's wisdom in endoscopic imaging of Barrett's esophagus.

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ABSTRACT

Background

Esophageal adenocarcinoma (EAC) is one of the main causes of cancer-related deaths worldwide and its incidence is rising. Barrett's esophagus (BE) can develop low- and high-grade dysplasia which can progress to EAC overtime. The golden standard to detect dysplastic Barrett's esophagus (DBE) or EAC is surveillance with high-definition white-light endoscopy (HD-WLE) and random biopsies according to the Seattle protocol. However, this method is time-consuming and associated with a remarkable miss rate. Therefore, there is great need for the development of novel reliable techniques to optimize surveillance strategies and improve detection rates.

Summary

Optical chromoendoscopy (OC) techniques like Narrow band imaging (NBI) have shown improved detection of DBE and EAC compared to HD-WLE and random biopsies. Most recent OC techniques, including iScan Optical Enhancement system and linked color imaging, showed improved characterization of DBE and EAC retrospectively. Fluorescence molecular endoscopy (FME) presented promising results to highlight DBE and EAC. Moreover, with the establishment of well-performing delineation computer aided diagnosis (CAD) algorithms and the first real-time CAD system for EAC, we expect clinical application of CAD in the near future.

Key messages

Despite impressive progress made in the development of advanced endoscopic techniques, combined HD-WLE/OC followed by random biopsies remains the golden standard for BE surveillance. Surveillance depends on appropriate mucosal cleansing, sufficient inspection time, and competence of the performing gastroenterologist to improve detection of EAC. In addition, to facilitate the clinical implementation of advanced endoscopic techniques, multi-center prospective clinical studies are demanded for OC and FME. Meanwhile, further optimization of CAD algorithms, the education of gastroenterologists, and analysis of the interaction between the clinician and the computer should be performed.

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide while rising in terms of incidence [1]. Esophageal adenocarcinoma (EAC) follows a devastating prognosis with an estimated five-year survival between 15 – 20% [2]. Barrett's esophagus (BE) predisposes EAC. Screening and surveillance endoscopy is the golden standard to detect dysplastic BE (DBE) and early stage EAC to improve patient outcomes [3]. This is momentarily achieved with high-definition white-light endoscopy (HD-WLE) and collecting biopsies according to the Seattle protocol. This protocol is costly and time-consuming while risking a potential high miss rate of 9% - 35% [4,5]. Meanwhile, poor adherence to surveillance guidelines is observed in clinical practice resulting in variable sensitivity and specificity of the current standards [6]. Optical chromoendoscopy (OC) has been implemented in many medical centers, however inconsistent results compared to HD-WLE are reported for detection of DBE and EAC [4,7,8]. Therefore, there remains a great need for novel reliable imaging techniques to improve surveillance protocols and thereby improving detection rates of DBE and early stage EAC. In this review several promising novel techniques are discussed and evaluated.

Chromoendoscopy

Chromoendoscopy includes dye-based chromoendoscopy and OC. After being sprayed onto the surface mucosa, the dye methylene blue, acetic acid or indigo carmine enhances visualization of esophagus mucosal patterns to improve distinction of dysplasia and cancer [9,10]. Dye-based chromoendoscopy has been available since the late 1980s, however large and recent validation studies on BE surveillance remain nonexistent [10]. A meta-analysis on methylene blue-based chromoendoscopy reported no significant improvement in the diagnostic yield of DBE compared to HD-WLE and random biopsies [11]. Limitations such as additional costs and procedure time as well as poor surface coating are reported consistently [11, 12]. Different from dye-based chromoendoscopy, optical chromoendoscopy often focuses mainly on lesion characterization more than improving detection of lesions. However, a meta-analysis showed 34% increase of detecting DBE and EAC compared to HD-WLE and random biopsies, consequently decreasing the risk of missing dysplasia which signifies its role in BE surveillance [13].

OC includes narrow-band imaging (NBI), flexible spectral imaging color enhancement (FICE), I-SCAN, blue light imaging (BLI) (Fujifilm, Japan) and linked color imaging (LCI). All major manufacturers incorporate OC within the standard endoscope, explaining its widespread use [14]. NBI (Olympus, Japan) uses an optical filter to highlight microvascular structures of the esophageal mucosa. This technique is associated with an improved sensitivity of 80% and specificity of 88% in predicting the absence or presence of dysplasia and EAC after the new NBI classification system was introduced [15]. Unlike NBI, FICE (Fujifilm, Japan) and I-SCAN (Pentax, Japan) enhance mucosal and microvascular patterns by modifying the spectrum of collected white-light images. In a prospective pilot study, a sensitivity of 92% for detection of DBE by FICE was reported compared to the dysplastic lesions found by acetic acid chromoendoscopy and FICE together [10]. A recent retrospective study applied the updated I-SCAN system, namely iSCAN Optical Enhancement system. This showed an improved sensitivity and specificity of 78% and 81% for I-SCAN compared to 69% and 70% for HD-WLE concerning the detection of dysplasia [16]. Prospective clinical results with regard to the surveillance of BE lesions with either FICE or I-SCAN remain rather limited. The latest BLI platform integrated linked color imaging (LCI), enabling both narrow spectrum illumination and computational image modification. Although improved visualization on DBE was shown with this platform, results on diagnostic sensitivity and specificity are still lacking [17]. An overview of the different systems and manufactures is given in Table 1.

Table 1. Overview of the different optical chromoendoscopy systems, their geographic distribution and manufactures [14].

Technique	Company	Name	Geographic distribution
Narrow band imaging (NBI)	Olympus	Lucera Spectrum/ Lucera Elite	Japan, UK
		Exera II/ Exera III	Rest of the world
Flexible spectral imaging color enhancement (FICE) (also Fujinon Intelligent Chromo Endoscopy)	Fujifilm	EXP-4400 system	Worldwide
i-Scan digital contrast (I-SCAN)	Pentax	EPK-i	Worldwide
Blue light imaging (BLI)	Fujifilm	Lasereo	Japan, China, South America, Asian-Pacific, Europe
Texture and color enhancement imaging (TXI)	Olympus	EVIS X1	Worldwide

Endomicroscopy

Confocal laser endomicroscopy (CLE) provides endoscopists with real-time *in vivo* visualization of superficial mucosal layers at high magnification which results in a real-time microscopy image. Endoscope-based CLE (eCLE, Pentax, Tokyo, Japan) provides a wider field of view, higher resolution images and better performance compared to probe-based CLE (pCLE, Mauna Kea Technologies, Paris, France). However, eCLE is not commercially available anymore. Targeted biopsies guided by pCLE showed a pooled sensitivity of 90% and specificity of 77% [18]. The reported sensitivity and specificity of real-time pCLE optical biopsy was 67% and 98%, respectively [19]. Therefore, in accordance with the Preservation and Incorporation of Valuable endoscopic innovations (PIVI) [20], neither pCLE real-time optical biopsy nor targeted biopsy could replace random biopsies following the Seattle protocol at this moment. However, pCLE can add value, like OC, in providing histological information of suspected lesions detected by HD-WLE to assist in differentiating between DBE and non-dysplastic BE (NDBE) [21].

Volumetric laser endomicroscopy

Unlike the narrow-field magnified imaging of pCLE, volumetric laser endomicroscopy (VLE) provides wide-field magnified imaging at high speed. VLE incorporates optical

frequency domain imaging technology and provides *in vivo* cross-sectional structural information at real-time, shown in Figure 1. After inserting the balloon-centered probe through the working channel, the inflated balloon circumferentially scans 6 centimeters of the esophagus in 90 seconds, to a depth of around 3 millimeters [22]. Histologically correlated VLE results showed a sensitivity of 83-86% and a specificity of 71-88% [23, 24]. Larger clinical trials are warranted to validate these preliminary results. However, the company NinePoint Medical filed for bankruptcy in 2020, consequently making VLE currently unavailable.

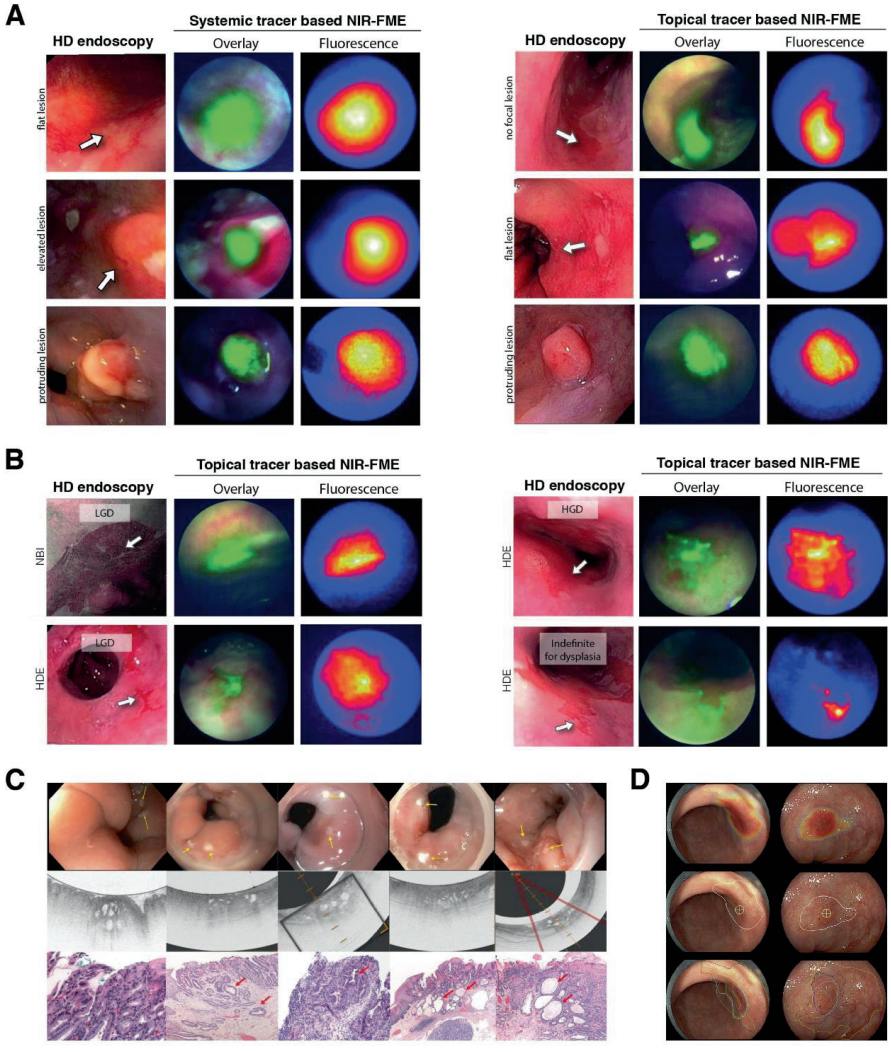

Figure 1. Representative results of fluorescence molecular endoscopy, volumetric laser endomicroscopy and computer-aided detection.

(A) Examples of the systemic tracer based and the topical tracer results, summarizing that all lesions could be visualized with real-time VEGFA-targeted NIR-FME, including one EAC area which was not visible during HD inspection (displayed in first row, right panel). Reprinted with permission from Nagengast et al. [29] (B) Additionally identified dysplastic areas during real-time VEGFA-targeted NIR-FME, which were missed during HD-NBI inspection. All fluorescence signals presented here are uncorrected; overlay images display the high intensities only. Reprinted with permission from Nagengast et al. [29] (C) Five examples of complex glands seen on VLE with the corresponding laser marks and histology. The top row is the endoscopic images with laser marks (yellow arrows). The middle row is the VLE images that correspond to the above endoscopy image. The bottom row is the H&E-stained histology images that correlate to the VLE images above them. Red arrows refer to complex glands. Columns 1, 2, 4, and 5 are from the endoscopic mucosal resection images. Column 3 is from a biopsy. Reprinted with permission from Trindade et al. [44] (D) Example of 2 neoplastic lesions with the heatmap visualization by the CAD system (the top row), and its corresponding delineation and biopsy site indicator (the middle row). Ground truth is established by expert delineations (the bottom row). Reprinted with permission from de Groof et al. [31]. CAD, computer-aided detection; EAC, esophageal adenocarcinoma; HD, high-definition; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NIR-FME, near-infrared fluorescence molecular endoscopy; NBI, narrow-band imaging; VEGFA, antibody against vascular endothelial growth factor; VLE, volumetric laser endomicroscopy.

Fluorescence molecular endoscopy

Molecular imaging could potentially improve the sensitivity and specificity compared to HD-WLE by targeting disease-specific molecules to highlight neoplastic changes at molecular level even before macroscopic morphological changes occur, hereby providing additional information compared to HD-WLE [25].

Initially, *ex vivo* fluorescence imaging using lectins in the visible spectrum was performed which identified lower fluorescence signals in DBE due to reduced cell-surface glycans [26]. One of the first *in vivo* studies evaluating fluorescence molecular endoscopy (FME) in BE was with topical administration of ASY - fluorescein isothiocyanate (FITC) which operated in the visible spectrum (400 - 700 nm). With this, a sensitivity of 76% and a specificity of 94% in detecting high grade dysplasia and EAC was reported [27].

Compared to the visible spectrum, the near infrared (NIR) spectrum (700 - 1700 nm) shows deeper tissue penetration and lower background noise signals due to less tissue absorption, autofluorescence and scattering [28]. Near-infrared FME (NIR-FME) could highlight specific targets at real-time *in vivo* and minimizes noise signal. A phase-I trial with NIR-FME targeting vascular endothelial growth factor A (VEGF-A) showed a promising 33% improved detection of early EAC through topical application of bevacizumab-800CW when compared to HD-WLE and NBI [29]. Different lesion types in this study visualized with FME in combination with the tracer bevacizumab are shown in Figure 1. The phase-II trial is ongoing (NCT03877601) to assess sensitivity and specificity of NIR-FME targeting VEGF-A for detection of early EAC within 60 patients.

One of the advantages of fluorescence imaging is that multiple fluorophores exciting light at different wavelengths could be potentially used, and thus multiple targets of dysplasia can be highlighted. A multispectral FME system that enables concurrent targeting of multiple molecules was recently developed and seems promising for molecular imaging to improve the sensitivity and specificity [30]. A phase I trial confirmed the feasibility of multispectral imaging to detect early EAC by targeting two different molecules [30]. However, the tissue optical properties, scattering and absorption, were not corrected for within this trial. Integrating fluorescence imaging into standard endoscopes as well as further validation with larger sample sizes are examples of technical improvements that are needed to translate multispectral FME into clinical practice.

Computed aided detection

Advanced endoscopic techniques generate a myriad of detailed images that are overwhelming to endoscopists for real-time interpretation. Computer aided detection (CAD) enables automatic characterization and classification of millions of endoscopic images which are impossible for the human brain to process. CAD could also capture subtle or invisible variation which might be missed by the human eyes.

A newly developed CAD system of deep residual learning performs better at EAC detection than general endoscopists do with HD-WLE images, resulting in a sensitivity

of 93% versus 72% and a specificity of 83% versus 74%. This CAD system also delineates EAC comparable to BE experts [31]. Another CAD algorithm showed improvement to a sensitivity of 96% and a specificity of 94%, with the potential for real-time diagnosis. The system localizes EAC with annotated boxes, thereby not providing information about the delineation of lesions, but is sufficient for lesion detection [32]. The first real-time CAD system to differentiate EAC from NDBE was built in 2020. The cancerous probability is shown as the spatial distribution of color density overlapped on HD-WLE images. However, the image sets of BE and EAC which are applied to fine-tune the algorithm are still rather small. The promising 83% sensitivity and 100% specificity are based on validation within a small cohort with elevated BE lesions [33]. CAD assessment of HD-WLE images compared to expert assessment is shown in Figure 1.

DISCUSSION

OC outclasses dye-based chromoendoscopy as it avoids uneven distribution of dyes and is less dependent on operator experience [11]. Dye-based chromoendoscopy uses non-targeted dyes and merely visualizes the mucosal pattern of the esophagus. In contrast, OC visualizes the mucosal patterns and enables detailed microvascular characterization when adjusted to the magnified mode [14]. NBI and BLI differ from computational post-processing of white-light images in I-SCAN and FICE. The spectrum of I-SCAN and FICE images are flexible, in contrast with the fixed spectrum of NBI and BLI images [14]. NBI is the most frequently studied OC method. However generalized analysis of NBI-based studies on BE is hampered by the variations of classification criteria [34]. Another limitation is that the majority of studies on OC are based on retrospectively collected data with mostly still images [15,16]. Nevertheless, a large meta-analysis showed improved detection of OC compared to HD-WLE [13]. In addition, consistent results indicate that OC can assist in characterization of BE lesions [18].

Recently, texture and color enhancement imaging (TXI) was embedded into HD-WLE). TXI aims to increase brightness in dark areas, improve color contrast, and enhance subtle tissue morphology differences [35]. Despite lack of TXI research in BE surveillance, superior visibility compared to HD-WLE was shown in serrated colorectal

polyps [36]. TXI combined with dye-based chromoendoscopy or OC might be able to improve detailed visualization and BE lesion detection [37].
In contrast to chromoendoscopy and endomicroscopy techniques, which are limited to morphology changes in lesions, FME could target underlying biological processes of dysplasia or specific tumor subtypes and serve as a wide-field “red-flag” technique for endoscopists. To transform FME systems widely into clinical practice, the major hurdles are integration of fluorescence imaging in standard endoscopes, correction of noise signals at video rate, interpretation of signals by for instance artificial intelligence and real-time semi-quantification of fluorescence intensities to prevent operator dependent interpretation [38].

Regardless of imaging techniques used, it has been shown that BE expert centers achieve a significantly higher detection rate of DBE and EAC compared to community hospitals, 87% vs 60% respectively [39]. As the performance of CAD could reach the level of BE experts in image interpretation, the implementation of CAD in community hospitals could bridge the gap with BE expert centers [31]. HD-WLE images and NBI images were assessed with the same CAD algorithm. It was found that the NBI-based CAD system outperformed the HD-WLE-based CAD system regarding binary classification between DBE and NDBE, showing sensitivity and specificity per image of 92% versus 99% and 99% versus 89%, respectively [32]. The algorithm trained on HD-WLE images with improved image sharpness displayed better performance in DBE and NDBE classification, with a specificity of 98% versus 90% [32]. Therefore, besides optimization of artificial intelligence algorithms, development of endoscopes that show better image quality with improved visualization of cancerous tissue seems promising. Current CAD systems of BE feasible for real-time application still need to be validated in prospective multi-center large cohort studies and evaluated by different manufacturers for implementation. To facilitate clinical implementation of CAD, education of clinicians on artificial intelligence and further research on interaction between clinicians and CAD systems are of vital importance [40].

Despite many advances that have been made in current endoscopic imaging and upcoming promising techniques, several parameters always need to be considered to reach optimal surveillance of BE. The clear visibility of esophageal mucosa is often impaired by bubbles and mucus on the surface of the esophagus. Pre-endoscopy

cleansing with defoaming and mucolytic solution improved the mucosal visibility necessary for optimal assessment of the mucosa [41]. In addition, longer endoscopic inspection time was associated with higher detection rates of DBE. Inspecting over one minute per centimeter of BE segment was suggested to improve the surveillance quality [42]. Frequent cardiac peristalsis increases the difficulty of endoscopic visualization. HD-WLE biopsies assisted by a transparent cap improved the detection accuracy of BE by suctioning and stabilizing the mucosa compared to non-cap assisted biopsies [43].

CONCLUSION

Implementation of novel imaging techniques is promising and might result in a multimodality strategy for BE surveillance. Currently, HD-WLE combined with OC and random biopsies is still the standard in BE surveillance. OC techniques are improving, such as I-SCAN and LCI, showing enhanced capability for detailed characterization of BE lesions. In addition, HD-WLE and OC might be combined in the future with FME to improve wide-field surveillance. These techniques assisted by artificial intelligence show potential to improve detection rates of DBE and to make the Seattle protocol redundant. However, until well-designed clinical trials show clear improvements in performance, BE surveillance outcomes depend on appropriate mucosal cleansing, sufficient inspection time and subsequent random biopsies.

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