REVIEW

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Future of image enhanced endoscopy of esophageal adenocarcinoma

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Barrett's esophagus is a premalignant precursor lesion of esophageal adenocarcinoma that affects approximately 1% of the population worldwide. Esophageal adenocarcinoma has a high mortality rate with a five-year survival of 15% to 20%. Early detection of Barrett's esophagus and dysplasia via endoscopy is crucial for preventing its progression to esophageal adenocarcinoma. New imaging techniques, such as image-enhanced endoscopy, have simplified the identification of Barrett's esophagus, dysplasia, and esophageal adenocarcinoma. Narrow-band imaging, blue-light imaging, and i-Scan are the prominent image-enhanced endoscopic techniques used to detect neoplasia. In Barrett's screening and surveillance, key aspects such as the screening population, tools, and intervals need to be clearly defined and standardized for future guidelines to improve the detection of precursor lesions and reduce the incidence of esophageal adenocarcinoma. Making image-enhanced endoscopy less subjective and enhancing the quality measures during endoscopy are crucial steps. Examples of quality measures include cleaning the esophagus before endoscopy and allowing sufficient time for inspection. Artificial intelligence systems can aid the early identification of lesions and reduce subjectivity.

Keywords: Artificial intelligence; Barrett esophagus; Esophageal neoplasms; Image-enhanced endoscopy; Upper gastrointestinal endoscopy

INTRODUCTION

Barrett's esophagus (BE) occurs in approximately 2.3% to 8.3% of individuals with gastroesophageal reflux disease (GERD) and in approximately 1.2% to 5.6% of those without GERD.[1] It affects approximately 5% of the population in the United States and approximately 1% of the population worldwide. BE is a premalignant precursor of esophageal adenocarcinoma (EAC).[2] BE progresses through a sequence of low-grade dysplasia and high-grade dysplasia (HGD) to EAC. EAC has a high mortality rate with a five-year survival rate of 15% to 20%.[3] The incidence of EAC has been increasing in the Western World.[4] Consequently, it is vital to identify patients who are at risk for developing EAC. Early detection of BE precursor lesions allows treatment that can prevent their progression to EAC. Early detection of BE and dysplasia via endoscopy is crucial.[5]

Screening for BE with endoscopy is recommended for patients with risk factors, and surveillance testing is recommended for BE patients to detect dysplasia.[1] The frequency of HGD and EAC is substantial during BE diagnosis.[6,7] In a meta-analysis analyzing adults with BE, the rate of missed EAC was 25.3%. It was 23.9% in adults with non-dysplastic BE. Missed EAC was defined as EAC diagnosed within 1 year of negative index endoscopy.[8] Most neoplasias (>90%) are detected during or within six months of the index endoscopy. Thus, the quality of the

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index endoscopy and the performance of the endoscopist are crucial to avoid missed diagnoses.[9]

IMPORTANCE OF ENDOSCOPY

White-light endoscopy (WLE) with Seattle protocol biopsy sampling is a routinely used BE surveillance method. The procedure involves taking samples from the BE mucosa in a four-quadrant pattern. When dysplasia is not present, samples are collected every 2 cm, whereas in cases with a history of dysplasia, sampling occurs at 1 cm intervals.[10] The emergence of new imaging techniques, such as image-enhanced endoscopy (IEE), has simplified the identification of HGD and EAC.[11,12] IEE can be divided into chromoendoscopy (dye-based) and virtual chromoendoscopy. Virtual chromoendoscopy techniques include narrow-band imaging (NBI), blue-light imaging (BLI), linked color imaging (LCI), i-Scan, and flexible spectral imaging color enhancement (FICE).[13]

The most recent American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend using chromoendoscopy or virtual chromoendoscopy in addition to WLE and Seattle protocol biopsy sampling.[14] NBI and blue-light imaging BLI are the most prominent types of IEE used in modern endoscopy systems for the detection of neoplasia.[15] Targeted biopsies with NBI and BLI may result in a higher diagnostic accuracy than random biopsies.[11,15]

Chromoendoscopy

Chromoendoscopy (conventional/dye-based) is an endoscopic technique that involves spraying harmless dyes onto the mucosal surface to enhance the visualization of the microstructure and vascular patterns.[13] There are two main types of dyes used: vital and non-vital. Vital dyes, such as Lugol's solution, methylene blue, Congo red, and toluidine blue, are quickly absorbed by normal esophageal squamous epithelial cells. Non-vital dyes, such as indigo carmine and crystal violet, are not absorbed but fill mucosal pits and folds, highlighting irregularities in the gastrointestinal (GI) mucosa.[11] It is used to improve diagnostic accuracy by determining target lesions for biopsy in the screening of malignant and premalignant lesions.[13]

Narrow-band imaging

NBI is an easy-to-use and commonly utilized technique for detecting early neoplasia in patients undergoing BE surveillance.[11,16] Its mechanism of action is based on the penetration properties of light. The blue light filter has a short wavelength (400–430 nm) and penetrates superficially into the mucosa, whereas the green light filter has a longer wavelength (525–555 nm) and penetrates deeper into the mucosa. Thus, the blue light filter better highlights the capillaries in the superficial mucosa.[17] Better detection of epithelial changes using NBI enables targeted biopsies.[11]

Blue-light imaging and linked color imaging

BLI and LCI were developed by Fujifilm and utilize lasers with different wavelengths. BLI uses 410 and 450 nm lasers and allows better visualization of mucosal and vascular patterns.[11,15] LCI can identify color differences in mucosal blood vessels by disrupting the red regions. LCI was shown to improve the visibility of reflux esophagitis compared to white-light imaging (WLI) and BLI.[18] BLI and LCI were preferred over the use of WLE alone in the study by de Groof et al.[15] for visualization of Barrett's neoplasia as it resulted in better delineation performance.

i-SCAN

i-Scan is a software-based digital image-enhancement technology with three functions: surface enhancement, contrast enhancement, and tone enhancement. It was developed by PENTAX[13] and has been shown to improve the identification of minimal changes in GERD.[19] In a recent study, the development of a computer-aided characterization system based on i-Scan showed high sensitivity and specificity for detecting dysplasia in BE.[20]

Flexible spectral imaging color enhancement

FICE uses specific wavelengths of light to better visualize the mucosal structure and microcirculation. The model was developed by Fujinon. The FICE can generate 60 spectral images by sampling the visible light range (400–695 nm) at 5 nm intervals. Each of these images can be further refined into five intensity levels.[13] In patients with non-erosive reflux disease, FICE enables the detection of subtle alterations in the epithelium. Compared with WLE, it demonstrates a higher sensitivity, negative predictive value, and accuracy in identifying "triangular lesions," which are indicative of mild esophagitis.[11]

In BE screening and surveillance, key aspects such as the screening population, tools, and intervals must be clearly defined and standardized for future guidelines. This will help to improve the detection of precursor lesions and reduce the incidence of EAC. Additionally, making IEE less subjective and enhancing the quality measures during endoscopy are crucial. The integration of artificial intelligence (AI) into clinical practice can further assist in recognizing lesions and reducing subjectivity.

FUTURE INSIGHTS

Improvement in quality measures during endoscopy

Perisetti and Sharma[21] highlighted five important points for high-quality endoscopic examination in a recent editorial. These points are cleaning the esophagus, high-quality inspection with adequate inspection time, using virtual chromoendoscopy, improving the education of endoscopists, and using quality metrics, such as neoplasia detection rate (NDR). A summary of these points is presented in Table 1.[21]

1) Clean

The esophageal mucosa should be cleaned using water and carbon dioxide insufflation. Subsequently, it should be examined for landmarks. The use of distal-attachment cap is also suggested. Mucus, saliva, debris, and bubbles should be cleared.[21] Using simethicone and *N*-acetylcysteine prior to the procedure resulted in a statistically significant increase in the mucosal visibility score and decreased need for flushing during the procedure in a randomized controlled trial.[22] Recently, Romańczyk et al.[23,24] proposed a scale (the Polprep: Effective Assessment of Cleanliness in Esophagogastroduodenoscopy [PEACE] system) to assess upper GI cleanliness. Adequate upper GI cleanliness, as assessed using this scale, was associated with a significantly increased clinically significant lesion detection rate.

2) Esophageal inspection time

BE inspection time (BIT) is the amount of time spent examining the BE segment during endoscopy after cleaning the esophagus.[25] A study involving 112 patients published in 2012 showed a statistically significant increase in the number of patients receiving an HGD/EAC diagnosis and BIT. The endoscopist's mean BIT per centimeter was also directly correlated with the diagnosis of HGD/EAC. Additionally, endoscopists with a mean BIT >1 minute per centimeter identified more patients with suspicious lesions.[26] In a more recent study involving 142 BE patients with no visible dysplastic lesions, a longer procedure time was significantly associated with an increased likelihood of detecting dysplasia.[27] Thus, at least one minute should be spent per centimeter of BE length during screening and surveillance. A longer esophageal inspection time is an easy-to-implement quality measure because it does not increase the cost or require additional training.[25]

3) Virtual chromoendoscopy

Detailed information regarding virtual chromoendoscopy is provided above. A meta-analysis including 14 studies and a total of 843 patients revealed that chromoendoscopy significantly improved the diagnostic yield of dysplasia or cancer by 34% ($p<0.0001$) when compared to WLE. Furthermore, this meta-analysis reported no significant differences between dye-based and virtual chromoendoscopy groups ($p=0.45$).[28,29] In a randomized controlled trial by Pohl et al.,[30] which compared virtual and conventional chromoendoscopy for detecting HGD and early cancer, virtual chromoendoscopy was shown to be as accurate as conventional chromoendoscopy. For detecting HGD/early cancer on a per-lesion basis, both conventional and virtual chromoendoscopy demonstrated 87% sensitivity in targeted biopsies. The positive predictive value was calculated at 39% for conventional chromoendoscopy and 37% for virtual chromoendoscopy. Conventional chromoendoscopy showed a sensitivity of 83%, whereas virtual chromoendoscopy exhibited

Table 1. Five important points for a high-quality endoscopic examination

Points	Suggestions
Clean	· Use a distal-attachment cap
	· Clear mucus, saliva, debris, and bubbles
	· Use simethicone and N-acetylcysteine prior to the procedure
Esophageal inspection time	· Spend at least one minute per centimeter of Barrett's esophagus length during screening and surveillance
Virtual chromoendoscopy	· Use virtual chromoendoscopy techniques such as narrow-band imaging/blue-light imaging
Education	· Interactive web-based educational tools and structured training programs can be used to improve endoscopists' performance
Neoplasia detection rate	· Use a quality metric, such as the neoplasia detection rate, at your endoscopy unit

a sensitivity of 92%, with no statistically significant difference between the two in the per-patient analysis (p=0.617).

Compared to conventional chromoendoscopy, virtual chromoendoscopy offers several benefits. It can be activated simply by pressing a button on the endoscope, allowing for easy comparison between white-light and virtual chromoendoscopy images. Also, it is easier to apply, as there are no dyes or spray catheters. In addition, virtual chromoendoscopy allows better visualization of capillaries and neovascularization, which may help in early cancer detection.[30]

The high-definition WLE (HD-WLE) plus Seattle biopsy protocol was compared with NBI plus targeted biopsy in a randomized controlled trial involving 123 patients with BE. The intestinal metaplasia detection rate was the same for both procedures; however, NBI plus targeted biopsy required significantly fewer biopsies per patient. Additionally, NBI identified a significantly higher proportion of areas with dysplasia.[31]

The Barrett's International NBI Group (BING) developed an NBI classification system for detecting dysplasia and EAC in patients with BE. This system is based on mucosal and vascular patterns. Circular, ridged/villous, or tubular mucosal patterns were classified as regular, whereas absent or irregular patterns were classified as irregular. Vessels regularly located along or between mucosal ridges were classified as regular, whereas vessels distributed focally or diffusely and not following the normal architecture of the mucosa were classified as irregular. They then attempted to validate this criterion, which had 85% overall accuracy, 80% sensitivity, 88% specificity, 81% positive predictive value, and 88% negative predictive value in predicting patients with dysplasia. When dysplasia was detected with a high level of confidence, these values increased to 92% overall accuracy, 91% sensitivity, 93% specificity, 89% positive predictive value, and 95% negative predictive value.[16]

In an image-based study by Subramaniam et al.,[32] non-expert endoscopists identified Barrett's neoplasia with a sensitivity, specificity, and accuracy of 85.3%, 88.3%, and 86.8%, respectively. After they were trained with a web-based tool using BLI for Barrett's Neoplasia Classification (BLINC) descriptors, the sensitivity, specificity, and accuracy were 95.7%, 80.8%, and 88.3%, respectively. In another image-based study, the i-Scan optical enhancement system and HD-WLE were compared. The sensitivity, specificity, accuracy, and positive and negative predictive values for i-Scan were 78%, 81%, 80%, 82%, and 78%, respectively, when examined by a cohort including both expert endoscopists and trainees.[33] Studies comparing the accuracy of virtual chromoendoscopy methods such as NBI, BLI, and i-Scan should be conducted in the near future, as this is an important gap in the literature.

The latest ASGE guidelines recommend the use of chromoendoscopy or virtual chromoendoscopy in addition to WLE and Seattle protocol for biopsy sampling. Although targeted biopsies with chromoendoscopy have been shown to be very effective in BE diagnosis, ASGE still recommends WLE and Seattle protocol biopsy sampling, as non-suspicious lesions appearing on chromoendoscopy may still contain dysplasia. It should also be noted that virtual chromoendoscopy is risk-free and commonly available in most endoscopes, resulting in no additional expenses.[14]

4) Education

In a randomized controlled trial, one group received a quality improvement program in cancer care during endoscopy (AQUIRE) training. The control group continued with local standard practices. In the training group, there were statistically significant increases in compliance with the Seattle biopsy protocol and knowledge of BE detection and sampling. However, the change in dysplasia detection rate was not significant.[34] An interactive web-based educational tool was developed to improve the detection of BE-related neoplasia. Educational tools resulted in a statistically significant increase in the detection, delineation, and agreement delineation performance of endoscopists.[35] The use of such tools should be incorporated into early GI fellowship training.

5) Neoplasia detection rate

The NDR was the rate of HGD and EAC during index endoscopy for BE screening. NDR was detected to be around 7% in a meta-analysis published in 2019.[9] In another meta-analysis, every 1% increase in NDR was associated with a 3.5% decrease in missed HGD or EAC detected within one year of negative index screening endoscopy.[36] In a more recent population-based cohort study involving 1066 patients with BE, NDR was detected to be 4.9%. A high NDR results in lower rates of missed dysplasia.[37] NDR can be used as a quality metric in BE endoscopy.[25]

AI in esophageal cancer

Artificial use of AI is becoming increasingly popular in the field of medicine. Deep learning (DL) is the most commonly used sub-discipline for AI in GI endoscopy. They use convolutional neural networks (CNNs) to learn from vast amounts of data.

CNNs identify specific patterns in the input data they receive and generate an output. By analyzing numerous images, DL algorithms can identify common pathological characteristics, potentially facilitating the early identification of BE or EAC lesions.[38,39]

Numerous studies have reported on the development of DL algorithms to aid esophageal endoscopy in BE. These studies included multiple target lesions that were detected using DL algorithms. These lesions were BE, neoplastic BE, dysplastic BE, neoplasia in BE, EAC, and Barrett's neoplasia.[40] We have compiled all the studies that reported the sensitivity and specificity of their algorithms in detecting these lesions in Tables 2.[20,41-58] The data the algorithms were tested on were comprised of images in the majority of the studies; however, in some studies, it was videos. AI systems were used during live endoscopic procedures in two studies.[47,48]

A recent systematic review and meta-analysis, published in 2023, analyzed the effectiveness of AI systems for the endoscopic diagnosis of EAC. This meta-analysis included nine studies and 478 patients. The pooled sensitivity was 93.1% and the pooled specificity was 86.9%.[59]

In the study by Ebigbo et al.,[44] the performance of a DL sys-

Table 2. An overview of studies on the use of artifical intelligence for the detection of Barrett's esophagus and esophageal adenocarcinoma

Study	Year	Light	No. of patients	No. of images/ videos	Sensitivity (%)	Specificity (%)	Accuracy (%)
van der Sommen et al.[41]	2016	WLI	44	100	83	83	Unspecified
Horie et al.[42, a)]	2019	WLI, NBI	97	1,118	77	79	Unspecified
Ghatwary et al.[43]	2019	WLI	39	100	93	93	Unspecified
Ebigbo et al.[44] (Augsburg data set)	2019	WLI	Unspecified	Unspecified	97	88	Unspecified
Ebigbo et al.[44] (Augsburg data set)	2019	NBI	Unspecified	Unspecified	94	80	Unspecified
Ebigbo et al.[44] (MICCAI data set)	2019	WLI	Unspecified	Unspecified	92	100	Unspecified
de Groof et al.[45]	2019	WLI	60	60	95	85	92
de Groof et al.[46] (data set 4)	2020	WLI	80	80	90	88	89
de Groof et al.[46] (data set 5)	2020	WLI	80	80	93	83	88
de Groof et al.[47]	2020	WLI	20	144	91	89	90
Ebigbo et al.[48]	2020	WLI	14	62	84	100	90
Hashimoto et al.[49]	2020	WLI, NBI	39	458	96	94	95
Iwagami et al.[50]	2021	WLI, NBI, BLI	79	232	94	42	66
Struyvenberg et al.[51] (image-based)	2021	NBI	100	183	88	78	84
Struyvenberg et al.[51] (video-based)	2021	NBI	50	157	85	83	83
Hussein et al.[52]	2022	WLI	32	192	92	73	83
Hussein et al.[52]	2022	i-Scan	44	264	91	79	86
Fockens et al.[53] (test set 1)	2023	WLI	200	200	84	66	Unspecified
Fockens et al.[53] (test set 2)	2023	WLI	100	100	100	66	Unspecified
Fockens et al.[53] (test set 3)	2023	WLI	113	200	88	64	Unspecified
Fockens et al.[54] (image-based data set)	2023	WLI	175	400	90	80	Unspecified
Fockens et al.[54] (video-based data set)	2023	WLI	129	188	91	82	Unspecified
Tsai et al.[55]	2023	NBI	86	160	94	94	94
Abdelrahim et al.[56] (image-based data set)	2023	WLI	34	471	95	95	95
Abdelrahim et al.[56] (video-based data set)	2023	WLI	75	75	94	91	95
Hussein et al.[20] (data set with still images)	2023	WLI, i-Scan	57	350	94	86	91
Hussein et al.[20] (data set with video frames)	2023	WLI, i-Scan	575	49,726	92	82	89
Hussein et al.[20] (data set with video sequences)	2023	WLI, i-Scan	57	11,741	92	84	90
Takeda et al.[57]	2024	WLI	96	126	90	76	84
Takeda et al.[57]	2024	LCI	96	137	90	91	91
Meinikheim et al.[58]	2024	WLI	72	96	92	69	81

WLI, white-light imaging; NBI, narrow-band imaging; MICCAI, medical image computing and computer assisted-intervention; BLI, blue-light imaging.
[a)]In the study by Horie et al., only 16% of lesions were esophageal adenocarcinoma, the remaining 84% were esopheageal squamous cell carcinoma.

tem was compared with that of 13 endoscopists in two different datasets that included WLI images. The sensitivity and specificity of the DL system were 97% and 88%, respectively, for one dataset. However, they were 76% and 80%, respectively, for endoscopists. In the other dataset, the sensitivity and specificity were 92% and 100%, respectively, for the DL system and 99% and 78%, respectively, for the endoscopists. The DL system significantly outperformed 11 of the 13 endoscopists in terms of sensitivity, specificity, or both on the first dataset.

The DL system had a sensitivity, specificity, and accuracy of 93%, 83%, and 88%, respectively, while the same values for general endoscopists were 72%, 74%, and 73%, respectively, in the study by de Groof et al.[46] The DL system demonstrated higher accuracy compared to all 53 non-expert endoscopists. In the study by Iwagami et al.,[50] the AI system demonstrated a sensitivity of 94%, specificity of 42%, and accuracy of 66%, whereas expert endoscopists achieved 88%, 43%, and 63% for the same metrics, respectively. The AI system had a higher sensitivity than the experts, but the specificity values were similar.

Takeda et al.[57] compared the performance of an AI system with that of expert endoscopists and trainees. The AI system demonstrated accuracy, sensitivity, and specificity of 84.1%, 89.6%, and 75.5%, respectively, in the WLI group. When using the LCI, these values improved to 90.5%, 90.1%, and 91.1%. In comparison, expert endoscopists demonstrated an accuracy, sensitivity, and specificity of 88.6%, 88.7%, and 88.4% for WLI and 93.4%, 92.6%, and 94.6% for LCI. For trainees, these values were 85.7%, 87.0%, and 83.7% for WLI, and 84.7%, 88.1%, and 79.8% for LCI, respectively.

The DL system had a sensitivity of 84% in test set 1 in a study by Fockens et al.[53] In contrast, general endoscopists had a sensitivity of 63%, which translates to a neoplasia miss-rate of one-third of neoplastic lesions. This suggests that AI-assisted detection could potentially increase neoplasia identification by 33%. In the video-based test set in the study by Abdelrahim et al.,[56] the AI system had a sensitivity, specificity, negative predictive value, and accuracy of 93.8%, 90.7%, 95.1%, and 92.0%, respectively, for detecting Barrett's neoplasia. The same parameters were 63.5%, 77.9%, 74.2%, and 71.8%, respectively, for the endoscopists. The AI system significantly outperformed endoscopists in all these parameters.

DL systems led to statistically significant increases in the performance of general endoscopists when used as assistance in a study by Fockens et al.[54] The sensitivity increased from 74% to 88% in the image test set (p<0.0001) and from 67% to 79% in the video test set (p<0.0001). AI alone was superior to general endoscopists alone for neoplasia detection. AI was also not inferior when compared to expert endoscopists, with a sensitivity of 90% and 91% in image and video test sets, respectively. In comparison, expert endoscopists had a sensitivity of 87% and 86% in the image and video test sets, respectively. AI also improved the performance of non-expert endoscopists in a study by Meinikheim et al.[58] The sensitivity increased from 69.8% to 78.0% and the specificity increased from 67.3% to 72.7%. AI alone was superior to expert endoscopists, with a sensitivity, specificity, and accuracy of 92.2%, 68.9%, and 81.3%, respectively. Meanwhile, expert endoscopists had sensitivity, specificity, and accuracy of 83.3%, 58.1%, and 71.5%, respectively.

AI systems are also used in methods other than endoscopic lesion detection to aid in BE and EAC diagnosis. Wu et al.[60] developed a quality improvement system (WISENSE) to aid endoscopists in everyday esophagogastroduodenoscopy. WISENSE monitors for blind spots, and in this study, the group using WISENSE (5.86%) had a significantly lower blind spot rate compared to the control group (22.46%). DL models are also used to aid pathologists in the histological detection of BE-related dysplasia.[61,62]

The Prague criteria assess the circumferential and maximum extent of a BE lesion to help with endoscopic diagnosis and grading of BE.[1,63] Ali et al.[64] developed a DL algorithm that can calculate the Prague risk scores with high accuracy automatically by creating a 3-dimensional visualization of the esophagus. Iyer et al.[65] used machine learning to develop a risk prediction algorithm for BE and EAC. This model had an area under the curve of 0.84, which was higher than that of pre-existing tools. It also identified novel predictors such as coronary artery disease and electrolytes. Better-developed models in this area can lead to better screening of the BE and EAC.

The use of AI systems and DL to detect BE or EAC lesions is not without limitations. One limitation is that they require high-quality, well-prepared, and extensively labeled data in large quantities for training, which is time-consuming. Ideally, the data used to train AI systems should be labeled by expert endoscopists. The paucity of data that can be used to improve AI models limits their generalizability and improvement. In most studies, the data are retrieved by expert centers that use the best equipment and may not represent community settings where disease prevalence is lower and that do not have access to the best equipment. This limits the generalizability of results to widespread settings.[66] Another potential pitfall is that in the majority of studies, the AI systems were tested on still images or short video sequences that may not represent live real-world scenarios.[67] There is a need for large prospective studies to properly validate the performance and reliability of these AI systems in routine clinical practice.

Novel tools

Several novel tools have been developed to assist in the diagnosis and screening of BE and EAC; however, they do not have widespread use. These tools are less invasive, easier to perform, and cheaper than endoscopy. These tools include tethered capsule endomicroscopy (TCE), non-endoscopic cell sampling devices, circulating microRNAs (miRNAs), microbiome sampling, and volatile organic compounds (VOCs).[68] Screening with these tools can identify better candidates for endoscopy and help increase the detection of BE and EAC.

1) Tethered capsule endomicroscopy

TCE is a swallowable capsule that captures 10 μm resolution cross-sectional optical coherence tomography images of the digestive tract. This procedure is less invasive than esophagogastroduodenoscopy and does not require sedation.[69,70] In a study including 38 patients, Gora et al.[70] reported no adverse events. TCE measurements had a strong to very strong correlation for the circumferential extent and a strong correlation for the maximum extent of Prague classification with endoscopic BE measurements. TCE also showed a strong correlation (r=0.77–0.79) with esophagogastroduodenoscopy for measuring the maximum extent of BE in a multicenter study including 147 patients.[71]

2) Swallowable non-endoscopic sampling devices combined with biomarkers

Non-endoscopic cell sampling devices collect cells from the esophagus, and the cytology data are then analyzed for biomarkers associated with BE and EAC. These biomarkers include trefoil factor 3 (TFF3) and methylated DNA markers (MDM). The cell sampling devices developed for this purpose were Cytosponge, EsophaCap, and EsoCheck. These tests do not require sedation; however, a confirmatory esophagogastroduodenoscopy is required.[68]

Cytosponge is a self-expandable spherical sponge developed by Medtronic.[72] In a multicenter randomized controlled trial including several general practice clinics in England, 13,514 patients were randomly assigned to two groups: usual care and intervention (Cytosponge-TFF3) groups. Intention-to-treat analysis was also performed. A total of 140 participants in the Cytosponge-TFF3 group and 13 in the usual care group were diagnosed with BE. A total of 1654 patients swallowed Cytosponge-TFF3 in the intervention group, 231 of whom had a positive result and were referred for endoscopy. Of the 231 patients, 221 underwent endoscopy and 131 (59%) were diagnosed with BE or cancer.[73] A cost-utility analysis showed that one round of Cytosponge-TFF3 screening in patients with GERD was cost-effective compared with usual care.[74]

In a study by Iyer et al.,[75] EsophaCap, also called a sponge on a string device and a 5 MDM panel, showed accuracy in detecting BE. The sensitivity of the 5 MDM panel was 93% at 93% specificity in the test set. EsophaCap was also well tolerated. EsophaCap and MDM also showed high accuracy in BE diagnosis in a study by Wang et al.[76] EsoCheck is an inflatable silicone balloon used with EsoGuard.[72,77] EsoGuard is a DNA methylation biomarker assay that evaluates methylated vimentin (VIM) and cyclin A1 (CCNA1). EsoGuard was shown to be accurate in detecting BE/EAC in analytical validation studies.[77]

3) Other

Transnasal endoscopy was performed using an endoscope with a diameter <6 mm. It can be performed in an office setting and does not require intravenous sedation.[68] In a 2022 study by Saeian et al.,[78] unsedated transnasal endoscopy had a histopathologic yield comparable to that of conventional upper endoscopy. Transnasal endoscopy use is not widespread in BE or EAC diagnosis, even though it has been around for a long time.[68]

miRNAs are small non-coding RNA molecules. It is possible to measure them in the serum, and circulating miRNA levels in the serum have been used to identify carcinomas.[68,79] Bus et al.[80] reported that circulating miRNAs could be a tool for the non-invasive screening of BE and EAC in the future, as they are differentially expressed in BE and EAC. They reported an increase in the expression of three miRNAs in the EAC and four miRNAs in the BE. They reported a significant increase in miRNA-194-5p and miRNA-451a levels and a significant decrease in miRNA-136-5p levels compared to controls. In EAC, miRNA-382-5p expression was significantly upregulated, whereas miRNA-133a-3p expression was significantly downregulated. Circulating miRNAs successfully differentiated BE from controls, EAC from controls, and BE from EAC when three or more miRNAs were combined.

According to a review by Zhang et al.,[81] sampling of the esophageal or oral microbiome to screen for BE or EAC is a promising approach and can be implemented in the future; however, the data currently available are inconsistent. Currently, the only way to approach the esophageal microbiome is invasive; however, the oral microbiome can be sampled noninvasively. In BE, *Neisseria, Prevotella, Veillonella*, and *Haemophilus* increased in the esophageal microbiome, whereas *Streptococcus, Veillonella*, and *Enterobacteriaceae* species increased in the oral microbiome. In contrast, *Streptococcus* species decreased in the esophageal microbiome, whereas *Neisseria, Lautropia*, and *Corynebacterium* species decreased in the oral microbiome.

Breath testing for VOCs by using an electronic nose device is another novel BE screening method.[82] In a study including 402 patients, VOCs were used to differentiate between patients with and without BE. They differentiated BE with sensitivity, specificity, and area under the curve of 91%, 74%, and 0.91, respectively.[83]

CONCLUSIONS

BE is a premalignant precursor of EAC, which is highly lethal; thus, early detection of lesions via screening and surveillance is critical.[2,3,5] NDR and rates of missed EAC should be minimized. This can be achieved by increasing the quality of endoscopic examinations through standardization, reduced subjectivity, and improved quality measures. Implementing quality measures, such as thorough esophageal cleaning and adequate inspection time (spending at least one minute per centimeter of BE length), can significantly enhance the identification of clinically significant lesions.[23-25] Educational tools for endoscopists can also help increase their detection performance. Targeted biopsies using advanced imaging techniques such as virtual chromoendoscopy and chromoendoscopy may result in higher diagnostic accuracy.[11,15] Further studies comparing virtual chromoendoscopy methods are needed. According to the most recent ASGE guidelines, chromoendoscopy or virtual chromoendoscopy should be used in addition to WLE and Seattle protocol biopsy sampling.[14] Classification systems, such as the BING criteria, and quality metrics, such as NDR, should be implemented.[9,16] AI systems have been extensively researched in this area and have been shown to have high accuracy. The implementation of AI systems in clinical practice can result in decreased subjectivity and improved endoscopist performance. However, AI systems require improvements before widespread implementation because they are still limited in their generalizability to real-world settings. Large prospective studies are required to validate their performance, reliability, and applicability in routine clinical practice. Future efforts should focus on reducing the subjectivity of IEE, integrating AI technologies, and improving the quality of Barrett's endoscopy to decrease the incidence and mortality associated with EAC.

Conflicts of Interest

Dr. Prateek Sharma reported receiving research grants from Fujifilm, ERBE Medical, and Ironwood Pharmaceuticals; being a consultant for Olympus Corporation, Boston Scientific, Salix Pharmaceuticals, Cipla, Medtronic, Takeda, Samsung Bioepis, CDx, and Exact Science. The authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: OO, PS; Methodology: MC, PS; Project administration: MC, OO, PS; Supervision: PS; Writing–original draft: KP; Writing–review & editing: all authors.

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