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Barrett's esophagus: A review

Harleen Kaur Chela, Mustafa Gandhi, Mohammad Hazique, Hamza Ertugrul, Karthik Gangu, Ebubekir Daglilar

Abstract

Barrett's esophagus is a pathological process where the inflammatory milieu created within the esophagus leads to progressive changes over time that can lead eventually to frank malignancy. It is a pre-malignant condition and involves a metaplastic transformation of the distal epithelium of the esophagus. There is a conversion of the normal type of squamous epithelium into the columnar type of epithelium. There are several risk factors associated with this condition and it is typically diagnosed endoscopically. This review article provides a brief overview of this condition.

INTRODUCTION

Over the years, chronic inflammation has been recognized as an underlying key component of many disease states. Barrett's esophagus (BE) is a pathological process where the inflammatory milieu created within the esophagus leads to progressive changes over time that can lead eventually to frank malignancy. It is a pre-malignant condition that is encountered in clinical practice. It involves a metaplastic transformation of the distal aspect of the esophagus which involves the conversion of the normal type of squamous epithelium into the columnar type of epithelium.¹ This is known as intestinal metaplasia as the columnar epithelium is a specialized type since it contains goblet cells.¹ The most commonly known predisposing factor is

gastroesophageal reflux disease (GERD) which can be present in about 20% of adults in developed countries.² Given the risk for progression to malignancy, surveillance programs exist in order to monitor and capture dysplastic changes in high-risk groups.

This condition is named after Norman Rupert Barrett who was a London based surgeon at a hospital called St. Thomas. In 1950, he described ulcerations lined by columnar type epithelium in the distal portion of what we know to be the esophagus. Barrett argued that because the esophagus, by definition, must be lined by squamous epithelium, the ulcerations he described were on a tubular segment of the stomach that was drawn into the thoracic cavity due to a congenitally short esophagus.¹ In 1953, Allison and Johnstone reported 7 patients with reflux esophagitis that demonstrated an esophagus lined by gastric mucosa, thus refuting Barrett's claims. Ultimately, Barrett did accept that the ulcerations were in the esophagus and not the intra-thoracic stomach as he had previously believed. During the 1970s further evidence was presented in support of the esophageal location of the columnar epithelium based on biopsies obtained with the assistance of manometric guidance.³ By the late 1980's the connection between Barrett's esophagus and adenocarcinoma had been recognized by multiple observational studies.³

This review article provides a brief synopsis of the epidemiology, pathogenesis, clinical features, diagnosis, and management.

Definition:

The criteria for diagnosis and thus the definition of Barrett's esophagus differs across the world. In the United States, Barrett's esophagus is described as a metaplastic process resulting in a change of the lining of the distal esophagus from one that is a normal squamous epithelium to a columnar-lined epithelium containing goblet cells.⁴ The definition does require that at least 1 cm of metaplastic columnar epithelium be replacing the lining of the distal esophagus which is normally stratified squamous epithelium.⁴ The segments that are less than 1 cm in length are categorized as specialized intestinal metaplasia (IM) of the esophagogastric junction (SIM-EGJ). These

segments are linked to high interobserver variability and are associated with a very low risk of EAC.⁴ While goblet cells are thought to be the defining characteristic of "intestinal metaplasia," there is disagreement over whether or not this condition should be included in the diagnostic criteria for BE⁵. Contrary to the United States guidelines, the British Society of Gastroenterology states that the presence of cardiac or oxyntocardiac mucosae (which lack goblet cells) as sufficient for establishing the presence of Barrett's esophagus⁶. It is similar to the US school of thought where histological proof of metaplastic esophageal columnar mucosa is necessary for diagnosis. Japan was the first nation to propose that intestinal metaplasia and goblet cells were not necessary for the diagnosis of BE. They frequently use the distal margin of the palisade vessels in the lower esophagus to define the columnar-lined esophagus (CLE), which is equivalent to BE⁵.

Epidemiology:

Barrett's esophagus is being detected more readily in clinical practice given the increased awareness about Barrett's esophagus and the long-term risks associated with it, especially esophageal adenocarcinoma (EAC).⁷ It is reported to be seen in about 2.3% to 8.3% of people with GERD and about 1.2% to 5.6% of those without GERD.⁸ In the United States, it is known to impact about 5% of people overall and about 1% globally.⁸ A meta-analysis of 51 studies on the prevalence of BE in Asian countries found that the pooled prevalence of endoscopic BE was 7.8% and of BE that was histologically confirmed was 1.3%.⁹ Additionally, from 1991 to 2004, there was a trend of increasing prevalence of BE, especially in eastern Asia, with the pooled prevalence of low-grade dysplasia (LGD), high-grade dysplasia (HGD), and adenocarcinoma of the esophagus being 6.9%, 3.0%, and 2.0%, respectively.⁹ A systematic review published in 2020 analyzed 103 on the global prevalence of BE and found that the pooled prevalence of Barrett's esophagus in Western, Eastern, and Latin American countries was 2.30%, 0.59%, and 0.51% respectively.¹⁰ The incidence of not only GERD but Barrett's esophagus and EAC has been increasing over the preceding few decades and is

suggested to be partly due to increased endoscopic procedures being performed likely for GERD.¹¹ Studies have suggested that the absolute risk of having EAC is about 0.1 – 0.5% annually in patients with non-dysplastic BE, for those with LGD, the annual EAC risk has a wide range from 1 to 43% while for HGD the annual risk is much higher at 23 – 60% with about 5% of patients with BE going on to develop cancer.¹¹ Esophageal cancer ¹ is the sixth most common etiology of cancer related mortality and is the eighth ¹⁰ most prevalent malignancy across the globe.¹² Hence the timely recognition of risk factors for BE and endoscopic evaluation with eradication of dysplastic changes is important in the prevention of development of frank EAC. The annual risk for progression of progression to cancer for nondysplastic BE is about 0.2-0.5% per year.¹³ Whereas for ¹⁰ low-grade dysplasia it is 0.7%/year and for high-grade dysplasia, it is about 7% per year.¹³

Pathogenesis and Risk Factors:

There are several well established risk factors linked to the emergence of Barrett's esophagus and it is through recognition of these risk factors that a clinician can identify those patients using their clinical judgment.

Table 1: Established risk factors associated with BE⁴

Chronic (≥ 5 years) GERD symptoms

Advancing age (> 50 years)

Male gender

Caucasian race

Tobacco usage

Central obesity (waist circumference > 102 cm or waist-hip ratio > 0.9)

Family history of BE

GERD is a risk factor that is implicated in the pathogenesis of BE. However, the duration of the GERD carries relevance as it is chronic GERD defined as symptoms of GERD for 5 years or more with frequent weekly symptoms.⁴ A common symptom

associated with GERD is a retrosternal burning sensation termed heartburn which is especially worse after food consumption. Patients may also complain of difficulty with swallowing, a 'lump' like sensation in the throat, nausea, or indigestion. It is important to remember that GERD can also be asymptomatic or present as 'silent reflux' which may present with a chronic cough and repeated throat clearing. Longstanding and untreated acid reflux stimulates acid-related damage to the mucosa of the esophagus due to chronic inflammation. This can be seen initially with the changes of erosive esophagitis due to acid reflux-mediated damage.⁷ This eventually leads to the metaplastic changes known as BE. This specialized intestinal epithelium which contains the columnar and goblet cells is thought to have less susceptibility to acid reflux-related damage.¹⁴ The acid-mediated chronic inflammation leads to ongoing exposure of the esophageal lining to the deleterious effects of cytokines, chemokines, and reactive oxygen species.¹⁵ These mediators of a chronic inflammatory state promote the growth of cells as well as vasculature and stimulate invasion.¹⁵ The exposure to acid leads to caustic injury and oxidative damage to the DNA with decreased growth factor secretion as well.¹⁶ Poor contractility of the esophagus and decreased clearance of acidic and bilious esophageal refluxate are also reported to occur.¹⁶ Acid stimulates the squamous epithelial cells to produce pro-inflammatory cytokines like interleukin 8 and interleukin 1b.¹¹ These cytokines create an inflammatory milieu by attracting the T lymphocytes and neutrophils into the epithelium.¹¹ Bile acid refluxate upregulates an intestinal differentiation factor called CDX2 and MUC2 which is the goblet cell specific gene.¹¹ Bile acids also tend to lead to DNA damage and activation of NF-kB (prevents apoptosis and death of damaged cells).¹⁷⁻¹⁹ Hence it is the prolonged exposure of the distal esophagus to noxious stimuli that causes the alteration of the squamous epithelium typical of the esophagus into the metaplastic intestinal-type columnar epithelium and then eventually the dysplastic type.

Smoking tobacco is linked to the causation of Barrett's esophagus as well as to the formation of adenocarcinoma of the esophagus.¹² The risk increases with an increased number of pack years of smoking and tends to be higher in male smokers as compared

to females.²⁰ It stimulates the formation of ¹ pro-inflammatory cytokines like interleukin (IL)-1, IL-6, and IL-8 as well as tumor necrosis factor- α (TNF- α).²¹ Furthermore, it leads to reduced amount of IL-10, which is a mediator that combats inflammation.²¹ One of the main pathways that leads to the formation of a pro-inflammatory response to smoking is the NF- κ B (Nuclear factor kappa B).²² Smoking tobacco also leads to oxidative damage due to the production of free radicals for example reactive nitrogen and oxygen species.²³ These free radicals cause the stimulation of the NF- κ B pathway and a pro-inflammatory milieu with resultant harm to proteins, lipids and nucleic acids ultimately predisposing to malignant changes.²⁴ Lipid peroxidation generates products that injure the DNA and proteins.²⁵ Another phenomenon that has been described to be caused by smoking is the momentary relaxation of the lower esophageal sphincter (LES).²⁶ An increase in the period of smoking causes a proportional increase in the mean hourly rate of the LES relaxation in asymptomatic smokers as well as smokers with reflux symptoms.²⁶ These transient relaxations of the LES can result in further acid reflux and drive metaplastic changes in the lower esophagus. Through these deleterious processes, tobacco lends itself to promoting the changes necessary for the development of BE. It seems that smoking and GERD work together to raise the ² risk of Barrett's esophagus. The International BEACON (Barrett's Oesophagus and Esophageal Adenocarcinoma Consortium) pooled five population-based case-control studies and found that smokers had a 1.7-fold increased risk of Barrett's esophagus compared to nonsmokers without GERD and a 1.6-fold increased risk compared to nonsmokers with GERD²⁷.

Obesity is linked to the development of Barrett's esophagus utilizing increasing acid-mediated damage as it raises the intra-abdominal pressure.²⁸ By increasing acid reflux, it directly augments the possibility of Barrett's esophagus in a patient with untreated reflux disease. It is also linked to an ongoing state of low levels of inflammation involving the adipocytes resulting in increased levels of C-reactive protein.²⁸ Pro-inflammatory substances such as cytokines are produced by inflammatory cells (T-lymphocytes and macrophages) as well as the adipocytes themselves.²⁹ Interferon-

gamma (INF- γ), IL-1, and IL-17 are generated by the T-lymphocytes and the macrophages generate IL-12 and TNF- α .³⁰ Certain cytokines are speculated to have carcinogenic potential such as insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF- β), and vascular endothelium growth factor.³¹ They are associated with cell proliferation and stimulate angiogenesis hence the potential association with the development of neoplastic changes.³¹ Central obesity in particular is linked to Barrett's esophagus as the visceral fat impacts quantities of insulin-like growth factors.³² To lend further support to this theory, a consistent and strong relationship has been established between obesity and EAC based on several large, population-based studies. Over the last four decades, there has been over an 8-fold rise in the incidence of EAC which has occurred parallel to a global boom in obesity rates.³³ A large study by Hoyo *et al.* to evaluate the link between the risk of EAC and obesity pooled data from 12 population-based studies and included 4000 patients with EAC and 10000 controls.³⁴ They reported a dose-response relationship with the greatest chances of EAC being observed among individuals with the highest body mass index (BMI).³⁴

Some studies have shown that the male gender is linked with a higher prevalence of Barrett's esophagus (about 6.8%) and so is a family history of BE or EAC (about 23%).³⁵ Those over the age of 50 years are also shown to have about 6.1% prevalence of Barrett's esophagus.³⁵ Of all individuals with Barrett's esophagus, it is reported that about 67% are males and 33% are females.^{4,36} The possibility of transformation of Barrett's esophagus into EAC is significantly increased in men as compared to women with an odds ratio of about 2.2.³⁶ This is portrayed in the disproportionate difference in that 89% of EAC is seen in males.^{4,36}

As a result of this gender disparity, BE screening in women is anticipated to have a modest yield in terms of lowering EAC incidence. However, screening women with numerous risk factors for BE and EAC may be justified after discussing the pros and cons with the patient. The Caucasian race is another risk factor associated with the development of BE.⁴ As there is an accumulation of a number of risk factors, the risk of

development of BE further increases as compared to having long-standing GERD alone.⁴

Figure 1: Pathogenesis of Barrett's esophagus

Progression of Barrett's esophagus to Esophageal Adenocarcinoma

Several factors have been studied for their association with higher rates of development from Barrett's esophagus to adenocarcinoma of the esophagus. Studies demonstrate that male gender, older age, a history of smoking, and low-grade dysplasia (also known as low-grade intraepithelial neoplasia) are associated with a higher chance of transformation of Barrett's esophagus to EAC.³⁶ There was also a proportional increase in the risk of development of EAC with a longer length of Barrett's esophagus segment on endoscopic measurement.³⁶ Based on this data, Parasa *et al* devised the Point Progression in Barrett Esophagus (PIB) score which combines data from sex, age, smoking history, presence of low-grade dysplasia, and length of Barrett segment to assess the chances of Barrett's esophagus progressing to EAC.³⁷ Each patient is scored on a range of 0 to 45 based on their risk factors with a higher score being at a higher probability of transforming to cancer. Based on the PIB score patients may be grouped as low risk (score 0-10 with 0.2% annual progression rate), intermediate risk (score 11-20 with 0.5% annual progression rate), or high risk (score > 20 with 1.5% annual progression rate).³⁷

Strategies to prevent progression of Barrett's esophagus to Esophageal Adenocarcinoma

Studies have been undertaken to evaluate the effectiveness of chemo-preventative strategies for limiting the transformation of the dysplastic changes in Barrett's esophagus to adenocarcinoma. The ASPECT trial was a double-blind study that included 2557 patients with Barrett's esophagus randomized into four treatment groups of high dose omeprazole with aspirin, low-dose omeprazole with aspirin, high-dose omeprazole without aspirin, and low-dose omeprazole without aspirin.³⁸ The trial

reported that at 8.9 years of follow-up, the patient group treated with high-dose omeprazole and aspirin had significantly lower rates of EAC, all-cause mortality, and high-grade dysplasia (also known as high-grade intraepithelial neoplasia) when compared to the other treatment groups.³⁸ Additionally, there was no major disparity in the rates of severe adverse events among the groups that received aspirin compared to those that did not use aspirin.³⁸ The study, conducted mainly in a white UK and Canadian population and including only about 500 women, may have limited applicability to more diverse ethnic groups and genders. Complexities arose from unreported over-the-counter use of aspirin and NSAIDs, potentially diluting the treatment effects. The trial lacked the statistical power to reliably assess the combined effects of high-dose PPI and aspirin, and the use of a composite endpoint makes it difficult to discern which specific outcomes were most affected by the treatments. The study didn't specify an optimal duration for chemoprevention, which appears necessary only after many years, questioning its practicality. Despite noting a few serious adverse events, the study did not address long-term risks associated with high-dose PPI use, like kidney disease and bone fractures.

Prolonged use of proton pump inhibitors (PPIs) alters the nature of reflux rather than eliminating it by altering the pH of refluxed material. Under PPI treatment, the usually inactive bile salts become aggressive toward the esophageal mucosa when reflux is alkalinized, increasing the risk of damage to the esophageal lining and potentially exacerbating conditions like Barrett's Esophagus. This highlights a significant limitation of PPI therapy and signifies the necessity for meticulous management and monitoring of patients on long-term PPI therapy, as alkaline reflux can adversely affect disease progression and risk of complications.

Long term use of proton pump inhibitors has been linked to adverse effects such as osteoporosis, renal dysfunction, dementia and risk for infections particularly pneumonias and clostridium difficile infection. However, many of these potential effects are not conclusive as different studies have shown inconsistent results. Given the limitations and potential adverse effects of long-term use of proton pump inhibitors, the

use in clinical practice is based on evidence from the guidelines and discussion with the patient.

⁵ The American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) do advocate the limitation of acid exposure to the esophagus using proton pump inhibitors to decrease the progression of dysplastic changes.^{13,39} The ACG does discourage the routine use of aspirin and other cyclooxygenase inhibitors for chemoprevention in Barrett's esophagus due to the potential of serious adverse effects such as gastrointestinal and cerebral bleeding.¹³

Clinical Features:

The symptomatology of Barrett's esophagus is typically associated with GERD and reflux-associated symptoms and related complications. The change in the lining of the esophagus to intestinal columnar type of metaplasia typical of Barrett's esophagus itself does not lead to symptoms but it is the reflux that does so ⁴⁰. Patients may complain of long-standing retrosternal burning sensation termed heartburn or even dysphagia related to underlying peptic stricture or erosive esophagitis. Barrett's esophagus can often lead to complications such as ulceration and stricture formation which presents as dysphagia and odynophagia while bleeding of the GI tract rarely occurs ⁴¹. In patients with GERD, atypical symptoms such as nausea, hoarseness, wheezing, chest discomfort, and globus sensation may be seen ⁴². In such cases, Barrett's esophagus may be discovered as an incidental finding during an endoscopy performed for other reasons.¹¹

Diagnosis:

Screening:

Screening refers to the evaluation of individuals with GERD for Barrett's esophagus. The gold standard for diagnosis of Barrett's esophagus is *via* direct visualization of the aberrant segment of the esophagus.⁴ This is performed with the use of conventional per-oral endoscopy.⁴ The Prague classification is one of the best-validated methods for

defining BE and involves measuring the maximal and the circumferential extent of the columnar epithelium above the proximal margin of the gastric folds.⁴³ At least 1 cm of columnar mucosa is required for classification as BE and to perform biopsies and it is not recommended to biopsy < 1 cm length of proximal displacement of the Z line from the top of the gastric folds.⁴ This screening criteria improves the specificity of the testing so as to minimize the number of false positive results that would confound diagnosis and therapy down the road. (Figure 2).

Figure 2: Barrett's esophagus and esophageal landmarks

However, conventional endoscopy does have limitations as the routine application in the general population is not cost-effective for screening.⁴⁴ Especially as there is a significant burden of GERD in the overall population and a wide-scale application of screening endoscopies would result in a large health care burden and cost as it would lead to surveillance in many cases as well.⁴ In addition, it is invasive and carries procedure-related and anesthesia-related complications.

Hence as per the latest Barrett's guidelines, it is advised that a single screening endoscopy be implemented for certain high-risk patients.⁴ This includes patients who have symptoms of chronic GERD in addition to ≥ 3 risk factors connected with the formation of BE.³ The factors linked with the progression to BE include age more than 50 years, male gender, Caucasian race, tobacco use, obesity, and those with a strong family history of BE or esophageal adenocarcinoma in a first-degree family member.⁴

A less invasive modality known as unsedated Trans-Nasal Endoscopy (uTNE) can also potentially be employed for screening for BE. The advantages include that it is less expensive and less invasive without anesthesia-related risks.⁴⁵ It has comparable sensitivity and specificity to endoscopy for the diagnosis of BE.⁴⁵ Providers other than physicians can be trained which helps to reduce the cost.⁴⁵ However, it is not readily utilized due to limitations such as discomfort for the patient especially as it is unsedated.⁴

A non-endoscopic technique that is available is the swallowable capsule sponge device and when used in conjunction with a biomarker it is considered an acceptable

substitute for endoscopic evaluation.⁴ These devices are composed of dissolvable gelatin or vegetable capsules that have a spherical sponge made of polyurethane. The sponge is connected to a string that enlarges into a spherical shape once the outer capsule dissolves or they are made of an inflatable silicone balloon. The devices are swallowed in order to obtain esophageal cells which are used for cytology. The cells collected are then analyzed for the presence of certain biomarkers that are seen in IM (trefoil factor 3) or methylated DNA markers associated with BE.⁴

Advantages include being able to be conducted as an outpatient without any sedation or anesthesia and being less expensive than endoscopy. It is minimally invasive and does not require a physician.⁴ Patient discomfort can occur with the swallowing of the device and potential dislodgement can occur in which case the device can be removed endoscopically.⁴

Esophageal video capsule endoscopy is another non-invasive technique that can be well tolerated. However, it has limited diagnostic yield with limited accuracy and low sensitivity as well as specificity hence not recommended for routine use.¹³

Another technique that is being created is a device that evaluates the volatile organic substances that are exhaled by a metal oxide sensor and the assessment is conducted by artificial neural networks.⁴ However, this is not yet available in the United States.

In routine practice, the most utilized modality is high-definition white light endoscopy. A repeat endoscopy is not recommended for screening for BE after an initial negative endoscopic evaluation of BE.⁴ However, if erosive esophagitis is noted on the initial evaluation, then a repeat endoscopy is recommended.⁴ After about 8-12 weeks of treatment with acid suppressive therapy with proton pump inhibitors, an endoscopy should be performed to evaluate for resolution of the esophageal inflammation and assessment of any underlying BE.⁴

Once BE is suspected on endoscopy, a minimum of 8 endoscopic biopsies are recommended. In cases of short segments of 1-2 cm where 8 biopsies are not feasible then **4 biopsies/cm of circumferential columnar mucosa and 1 biopsy per cm of tongues** of suspected Barrett's mucosa is recommended.⁴ For segments longer than 4 cm, the

Seattle protocol is recommended for sampling.⁴ The Seattle protocol involves obtaining 4 quadrant biopsies every 1-2 cm in the columnar lined mucosa and sampling areas of irregular appearing mucosa separately.³⁹ Any dysplasia that is identified on biopsy specimens is mandated to be verified by a second pathologist who has expertise in gastrointestinal pathology.⁴ If there is salmon-colored mucosa that extends ≥ 1 cm above the top of the gastric folds and the biopsies come back negative for intestinal metaplasia, then a repeat endoscopy is advised in 1-2 years.⁴ Figures 3 and 4 show histologic findings of BE on biopsies obtained during endoscopy.

Figure 3: Hematoxylin and eosin stain (magnification 10x) of esophageal biopsy showing squamous epithelium overlying the glands with intestinal metaplasia (arrowhead).

Figure 4: Hematoxylin and eosin stain (magnification 40x) of esophageal biopsy showing columnar epithelium with intestinal metaplasia characterized by barrel shaped goblet cells filled with bluish cytoplasmic hue (mucin-rich).

Surveillance

In contrast to screening, surveillance refers to the periodic evaluation of those with a proven diagnosis of Barrett's esophagus in order to identify malignancy in the esophagus at the earliest. Once the diagnosis of BE is established, a discussion needs to be held with the patient regarding surveillance programs. The rationale for performing endoscopic surveillance is to identify dysplasia or carcinoma at an initial and potentially treatable stage.⁴ Given the need for repeat endoscopic assessments and associated risks as well as the potential detection of dysplastic mucosa in the future and the implications associated with that. The overall patient profile and comorbidities also need to be taken into consideration when implementing surveillance programs.

Endoscopic evaluation with both white light endoscopy, as well as chromoendoscopy, is advised when performing surveillance of BE. Initial assessment of the BE should start with high-definition white light endoscopy which should incorporate a retroflexed view of the cardia. This should be followed by

chromoendoscopy which can be used to augment the efforts to identify dysplastic changes and even carcinoma.⁴ Vital dyes such as acetic acid can be used or through electronic chromoendoscopy. Dye based chromoendoscopy can be performed by applying diluted acetic acid to the BE causing a whitening of the area and neoplastic tissue loses this whitening effect more quickly than non-dysplastic BE.⁴ Electronic chromoendoscopy systems provide an enhanced assessment of the mucosa and the vascular patterns and abnormal mucosa (dysplastic or even harboring carcinoma) will have irregular mucosal or vascular changes with narrow-band imaging. Chromoendoscopy-guided biopsies are not a replacement for standardized biopsies and chromoendoscopy is recommended to be used in combination with high-definition white light-based biopsy protocols.⁴

Other imaging techniques are available to further improve the detection of dysplastic changes and cancer. Confocal laser endomicroscopy involves the intravenous administration of fluorescein and utilizes blue laser light to visualize the esophageal tissue.⁴ This helps to obtain targeted biopsies with real-time high-magnification imaging.

Volumetric laser endomicroscopy uses optical coherence tomography and is a probe-based method that can perform a 6 cm circumferential scan of the esophagus.⁴⁶ It has the ability to visualize the mucosa and submucosa of the esophagus in a 2-dimensional method and to a depth of 3 mm.⁴⁶ There is also work underway on utilizing artificial intelligence as well in the detection of dysplastic BE and detection of carcinoma, utilizing computer-based techniques.³

The surveillance intervals vary depending on the length of the segment, presence and degree of dysplasia and preferences of the patient.⁴

If there is no dysplasia detected and the length of the BE segment is ≥ 3 cm then surveillance is recommended in 3 years and if the segment is < 3 cm then surveillance can be extended up to 5 years.⁴ If the samples are indefinite for dysplasia, then this needs to be verified by a second pathologist who has expertise in the field of gastrointestinal pathology. Once confirmed then high-dose acid suppression therapy

with proton pump inhibitors taken twice daily followed by a repeat endoscopy within 6 months.⁴ If again indefinite then an EGD is recommended in a year. If nondysplastic BE or LGD (low-grade dysplasia) is detected, then surveillance is done accordingly. If LGD is detected, then the risks and benefits of surveillance *vs* treatment must be discussed and accordingly plan of care is decided. If the patient opts for surveillance, then a repeat EGD is recommended at 6 and 12 months from the initial diagnosis followed by annually.⁴

Figure 5: Surveillance for Barrett's esophagus.⁴

Treatment

Non-endoscopic:

The mainstay of non-endoscopic treatment is centered around acid suppression with proton pump inhibitor (PPI) therapy. Once daily PPI therapy is advised in patients that do not have contraindications to their use to prevent ongoing acid-mediated damage to the esophageal mucosa.⁴ The latest guidelines do not make any recommendations for the combination of ASA with PPI to decrease the chances of advancement of BE to HGD or even EAC.⁴

Endoscopic treatment:

Once high-grade dysplasia (HGD) or intramucosal carcinoma (T1a) is detected on biopsies then this needs to be treated and can potentially be done endoscopically. If a patient with LGD also opts for treatment, then they would also be candidates for endoscopic approaches. A risks and benefits discussion needs to be held before embarking on this path as it also lends to future repeat endoscopies and surveillance programs. Endoscopic management is recommended for LGD, HGD, or intramucosal carcinoma (IMC).¹³ The aim of endoscopic treatment is to attain the complete eradication of dysplasia (CED) and IM (CEIM).⁴ It involves endoscopic resection of any visible lesions and is then followed by ablation of the segment. Visible lesions such as

nodules can be removed endoscopically (Figure 6). The resection of visible lesions has both a diagnostic and therapeutic effect.⁴

Figure 6: Barrett's esophagus with a visible nodule seen on endoscopy.

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The modalities of endoscopic resection include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). They are cap-assisted EMR, multiband EMR, and ESD. Both EMR techniques (cap-assisted, multiband) have comparable efficacy and safety.⁴ ESD has a higher risk for complications as compared to EMR given the increased depth of resection.

Radiofrequency ablation (RFA) is the most efficacious and safe eradication technique for ablation and is the preferred one routinely.⁴ RFA uses thermal energy to obliterate the precancerous cells and the treated tissue usually sloughs off over 48-72 hours.¹³ After about 6-8 weeks, this treated area will be replaced by a new, normal esophageal lining.¹³ Once CIEM is attained, then a surveillance program is initiated in which endoscopies are performed at intervals to detect the recurrence of BE.

Figure 7: Surveillance after endoscopic eradication therapy and achieving complete eradication of intestinal metaplasia (CEIM).⁴

Surgical Treatment:

For those with involvement of the submucosa, T1b lesions and beyond surgical treatment are advised. The possibility for lymph node metastasis in T1b disease is significantly higher and hence patients should be referred for surgical consultation for evaluation for esophagectomy.⁴ In cases with T1b lesions that involve the superficial one-third of the submucosa (sm1) and have favorable features such as lesion < 2 cm, well-differentiated and without lymphovascular invasion then endoscopic treatment may be considered in select cases.⁴ However, it should be in conjunction with surgical consultation with a multidisciplinary approach.

Future of Barrett's Esophagus

As research in this area evolves, there are advances in techniques for detection and diagnosis of Barrett's esophagus. More non-invasive markers are being developed for use as alternatives to endoscopy. Another upcoming area that is being studied is the use of artificial intelligence (AI) to evaluate for BE. AI is being used to detect neoplastic lesions with the development of computer aided detection (CADe).⁴⁷ Additionally, it can then also help characterize the neoplastic lesion and hence assist with the diagnosis and further management (referred to as Computer aided diagnosis (CADx)).⁴⁷ It is a powerful tool that has many advantages as it is not subject to fatigue or the observer bias that an endoscopist can encounter.⁴⁷ It can also serve as a quality control mechanism as it can improve the quality of the procedure performed by giving feedback to the endoscopist in real time.⁴⁷ As use of AI is explored further in gastroenterology, it will gain popularity in the near future and may be available widely over time.

CONCLUSION

Barrett's esophagus is a common pathology encountered in clinical practice by both gastroenterologists and general practitioners. It deserves recognition and careful consideration when considering patients who require screening and the implications of the subsequent steps that may arise as a consequence. The early detection of dysplastic changes in BE is paramount so that treatment can be ensured to prevent progression to EAC and drastic surgeries.

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