Dysplastic barrett's esophagus: Surveillance, treatment and follow-up – A systematic horizontal review

https://doi.org/10.56238/globalhealthprespesc-020

Stephanie Assunção Valini
Highest level of education: Completed high school
Academic Institution: Undergraduate student of the medical course
of the Faculty of Medicine of ABC

Ethel Zimberg Chehter
Highest level of education: Doctorate in medicine - Gastroenterology by the Faculty of Medicine university of São Paulo
Academic institution: ABC Medical School

ABSTRACT

INTRODUCTION: Gastroesophageal reflux disease (GERD) is important due to its recurrence, being the main reason for consultations and with prevalence higher than 25% in Asia and Southeast Europe. The most feared complication of GERD is esophageal adenocarcinoma (ECA), preceded by Barrett's esophagus (EB), defined as the replacement of the stratified squamous epithelium with an abnormal columnar epithelium with intestinal characteristics. The epidemiology still remains unknown due to the low specificity of the symptoms and the lack of consensus on the endoscopic characteristics for its diagnosis. In the dysplastic forms of EB with more chance of progression to ACE, there are few studies and better conducts in relation to dysplastic EB. OBJECTIVE: to clarify controversies about the conduct of dysplastic EB. METHOD: horizontal review, PRISMA method through electronic search in PubMed, between 2018 and 2022, with descriptors: "Barrett's Esophagus" and "Surveillance AND dysplasia AND esophagus" for all age groups. Inclusion: articles in English, with compatible titles and abstracts. We obtained 620 results and after selection 17 articles were included. RESULTS: 13 articles indicate the Seattle Protocol for diagnosis and surveillance; 5, anti-reflux therapy before endoscopy and 12, confirmation of dysplasia by a specialized pathologist. Follow-up low-grade dysplasia (GBD): radiofrequency ablation therapy (ART) and surveillance are feasible in 13 articles, with ART preferred in 8 and surveillance in 4. High-grade dysplasia (DAG) follow-up: endoscopic therapies recommended in 12 articles. Follow-up after dysplastic eradication: periodic and continuous endoscopic surveillance indicated in 9 articles and treatment with proton pump inhibitors in 2 articles. DISCUSSION: Although the Seattle Protocol is recommended for surveillance, it covers a small part of the esophageal mucosa, besides being time-consuming and having low adherence. Controversies persist about the management of BPD, but, in general, ablation is recommended to the detriment of surveillance. There is consensus on endoscopic ablation therapy until complete eradication of DAG. Esophagectomy is not recommended. After eradication, continuous surveillance and proton pump inhibitors. CONCLUSION: Disagreements persist due to discrepancies between studies, especially in low-grade dysplastic EB.

Keywords: Barrett's Esophagus, Gastrointestinal Endoscopy, Follow-up Care.

LIST OF ABBREVIATIONS AND ACRONYMS

GERD: gastroesophageal reflux disease
ACE: esophageal adenocarcinoma
EB: Barrett's esophagus
DBG: low-grade dysplasia
DAG: high-grade dysplasia
ART: radiofrequency ablation therapy
TEE: endoscopic eradication therapy
AGA: American Gastroenterological Association
ACG: American College of Gastroenterology

ESGE: European Society of Gastrointestinal Endoscopy
BSG: British Society of Gastroenterology
ASGE: American Society of Gastrointestinal Endoscopy

1 INTRODUCTION

Gastroesophageal reflux is a physiological mechanism, in which gastric contents move spontaneously toward the esophagus.[1] However, this condition becomes pathological when it manifests itself with uncomfortable symptoms or complications in order to configure gastroesophageal reflux disease (GERD).[2]

In large part, the importance of this pathology is due to its recurrence. In the United States, it is the main reason for outpatient visits, accounting for about 4% of visits in primary care3, while globally, it is estimated that the prevalence is higher than 25% in South Asia, Southeast Europe and less than 10% in Southeast Asia, Canada and France.[1]

The pathogenesis of GERD is complex and multifactorial, but in general, it involves the imbalance between aggressor and defensive factors to the esophagus. Defensive factors involve gastric acidity, the volume of gastric acid secreted and the elimination of duodenal contents, since constipation can lead to gastric stasis. Defensive factors involve the anti-reflux barrier, acid clearance in the esophagus and mucosal resistance to recurrent chemical aggressions4.

The anti-reflux barrier depends on the proper functioning of the lower esophageal sphincter (LES) and the crural diaphragm4 in order to prevent the passage of gastric contents to the esophagus. However, relaxations of the LES, therefore, openings of this barrier, may occur routinely associated or not with swallowing. When they are not associated with swallowing, they are considered as transient relaxations that last longer periods than those induced by swallowing, causing up to 90% of reflux events in healthy individuals or those with GERD.[5] In addition, after these events, it is known that acid clearance begins with peristalsis, which assists in the mechanical return of the refluxed structures to their physiological direction. Together, the additional tamponade from saliva swallowing also helps in this clearance, neutralizing the esophageal pH 4,3 ·

Likewise, factors that lead to increased intragastric pressure such as obesity, pregnancy and relaxation of the stomach after increased gastric volume have a clear relationship with the pathophysiology of the disease. This is true because the reflux of gastric contents from the stomach to the esophagus is determined by the pressure gradient between the abdomen and the chest, so the increase in intra-abdominal pressure increases the tension in the anti-reflux barrier, impairing one of the main protective factors of the esophagus.[5.6]

As for the clinic, GERD classically manifests itself with symptoms of heartburn and regurgitation, which are usually referred to by patients as a burning sensation in the retrosternal region, which radiates to the neck, throat and occasionally to the back. These symptoms occur in the

postprandial period and are usually more pronounced after fatty or spicy meals and after alcohol intake. [2.7.] Other symptoms may include nausea, dyspepsia, sore throat, epigastric pain, and a feeling of bloating.[7]

In addition, it is possible that GERD manifests with atypical symptoms, so it should be considered as a differential diagnosis in cases where other diagnoses have already been excluded by a specialist.[8] Thus, even if symptomatic, this disease presents a difficult diagnosis, since it is made through the combination of clinical symptoms, response to acid suppression, esophageal pH monitoring and upper digestive endoscopy, although the latter is not essential for the diagnosis.[8.2]

On the other hand, studies with the European population showed that about 46% of the patients were asymptomatic, a fact that poses a problem, since the diagnosis can be made only when the complications of GERD are already installed, since the course of the disease had minimal or absent symptoms.[2]

It is known that the most feared of these complications, adenocarcinoma of the esophagus (ACE), is preceded by an intestinal metaplasia of the esophagus called Barrett's esophagus (EB).[9] By definition, metaplasia is a reversible alteration, in which a differentiated cell type is replaced by another differentiated cell type of the same lineage and which is often better able to withstand the adverse environment to which the epithelium is being exposed.[10] Thus, EB occurs when the stratified squamous epithelium, which normally lines the distal esophagus, is replaced by an abnormal columnar epithelium, which has intestinal characteristics.[11.12]

This substitution makes the affected site more predisposed to malignancy with such intensity that patients with EB have 55 times more risk of developing ACE.[11] In this situation, the prognosis tends to be poor with 5 years of survival estimated in 10 to 15% of cases.[13th]

Thus, EB is a serious public health problem, especially when considering current epidemiological data. Globally, its prevalence has increased dramatically in recent decades with an estimated range of 0.7 to 5.6%, whereas currently the estimated annual incidence in the general population is 1 to 2%.[13] Corroborating this worldwide increase, the prevalence of this disease has also increased among the Asian population, even though EB predominantly affects white men between 40 and 60 years of age.[14.15]

Despite these data, the epidemiology remains largely unknown mainly because many individuals with EB are asymptomatic or manifest insensitive and non-specific symptoms generally similar to those related to GERD. However, not every individual who develops EB necessarily needs to have had GERD beforehand.[16] Consequently, for this reason, these patients are not correctly diagnosed.[17th]

Considering the low specificity and low sensitivity of the symptoms, for the diagnosis it is important to consider the risk factors to which this patient was exposed during his life. Thus, because

it is a multifactorial disease related to GERD, we should consider similar risk factors. Therefore, obesity, alcohol consumption and smoking are characteristics that should be alerted to the health professional as possible triggers for the progression of the disease.[11th]

However, to be confirmed, the diagnosis of EB requires complementary tests. Among them, the main one is endoscopy with confirmation by biopsy.[18.19]

However, in addition to the clinical factor, the lack of a consensus on the endoscopic characteristics for the definition of the diagnosis poses another challenge for the accurate diagnosis of patients. Although the Prague classification of 2006 has improved the assertiveness of the diagnosis, renowned societies around the world continue to follow their own criteria. For example, the American Gastroenterological Association (AGA) defines EB as any extension of intestinal metaplasia, while the British Society (BSG) defines it as any columnar metaplasia lining the distal esophagus with a minimum length of 1 cm. On the other hand, the American College of Gastroenterology (ACG) defines EB as an intestinal metaplasia that lines the distal esophagus with a minimum length of 1 cm.[19,20] Thus, to elucidate such controversies, the criteria recommended by each guideline for the definition of the diagnosis of EB are shown in Table 1.

Table 1 - Criteria accepted by each guideline for the definition of the diagnosis of Barrett's Esophagus.

GUIDELINE	EXTENSION CRITERIA	HISTOLOGICAL CRITERIA
AGA	Any extension	Intestinal metaplasia
Australian Society	Any extension	Intestinal metaplasia
Japanese Society	Any extension	Columnar metaplasia with or without intestinal metaplasia
ACG	Minimum 1cm extension	Intestinal metaplasia
ESGE	Minimum 1cm extension	Intestinal metaplasia
BSG	Minimum 1cm extension	Columnar metaplasia
Asia-Pacific Consensus	Minimum 1cm extension	Columnar metaplasia
ASGE	Does not define extension criteria	Intestinal metaplasia

Source: Marquis of Sá et. al,202019; Koike et. al., 202220

Likewise, regarding treatment and follow-up, there is no agreement between the recommendations of world-renowned societies. Therefore, more studies are needed to validate the best approaches for these patients until a consensus is reached.[18th]

It is also important to note that Barrett's Esophagus can present itself in multiple ways according to its evolution and severity. Therefore, it can manifest itself in a non-dysplastic form or in

a dysplastic form. Among these presentations, dysplasias are the most serious, because before the neoplastic cells become malignant, some of the same genetic and epigenetic changes that confer malignancy can cause the dysplasias.[15th]

As a rule, a dysplasia can be seen as the expression of a disordered growth, and according to the degree of histological abnormalities can be classified as low-grade or high-grade dysplasia.[15.21.] Also, there may be cases in which dysplasia is classified as undefined, and approximately 4.3 to 8.4% of EB biopsies are diagnosed as undefined.[22nd]

The study of dysplastic forms of EB is important, since it is estimated that the progression of these forms to esophageal adenocarcinoma is greater than in non-dysplastic forms. While the risk of progression from non-dysplastic EB to ACE is estimated at 0.3%, the risk of progression from low-grade dysplasia (DBG) to ACE is estimated to be 0.5% per year and 6.6% per year in the case of high-grade dysplasia.[22nd]

In view of this, it is essential that guidelines are established for early detection, treatment and follow-up of these dysplasias in order to improve patient survival and prevent deaths from esophageal cancer.[12] However, just as there is no consensus on these guidelines for EB in general, there are also no well-defined guidelines when it comes to dysplastic EB.[19th]

Considering this panorama, research that deepens the clarification of the best conducts in the face of dysplastic EB becomes important in order to direct medical practice according to the most recent evidence.

2 OBJECTIVE

The objective of this research is to elucidate the controversies related to the management of dysplastic EB through the analysis of the consensus and divergences of the guidelines recommended by the most influential world organizations in this subject to direct medical conduct according to the most current scientific evidence.

3 METHOD

This systematic review was carried out according to the *Checklist* PRISM.

3.1 RESEARCH IN THE LITERATURE

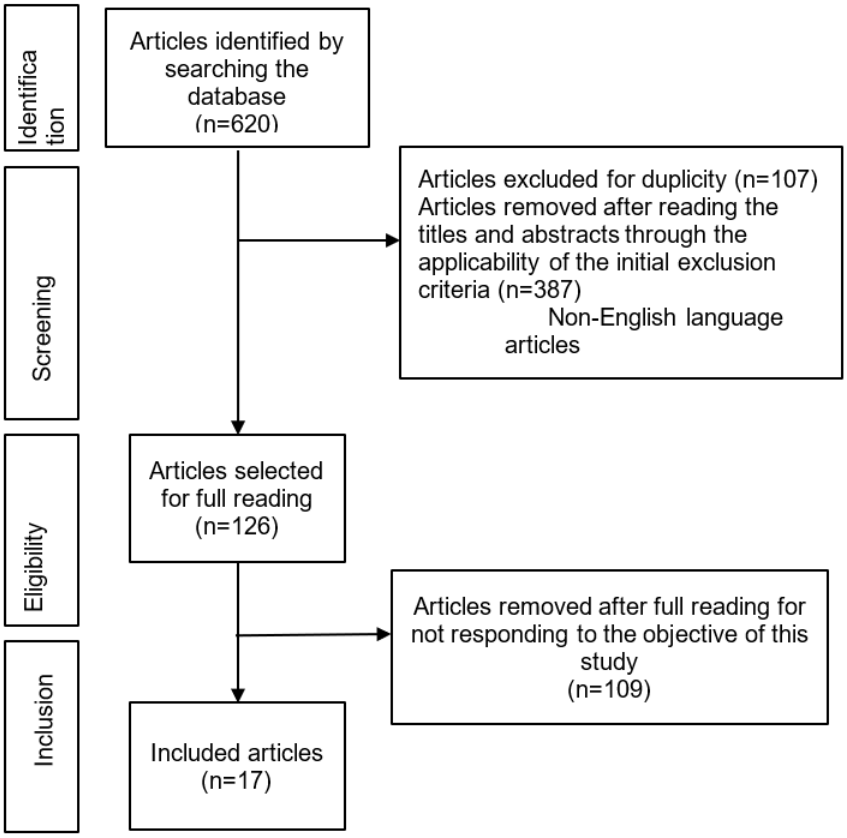
An advanced electronic search was conducted in the PubMed database for systematic reviews published between 2018 and 2022 using initially the descriptors "Barrett's Esophagus" and later using the descriptors "Surveillance AND dysplasia AND esophagus" in all age groups. This search was conducted between September and November 2022; articles eligible up to this period were considered for inclusion.

3.2 DATA SELECTION AND EXTRACTION

Two independent reviewers identified studies for inclusion and analyzed the selected articles and discrepancies were resolved by discussion. The selection process of this study is illustrated in Figure 1.

First, the titles and abstracts were revised to include only articles published in the last 5 years and to exclude manuscripts that were published in non-English journals, any study model that did not stand as a review and that did not address the surveillance of dysplastic lesions. The remaining full articles were evaluated for eligibility and excluded if they did not fit the questions to be answered by this research.

Figure 1 - Selection process according to the *PRISMA* checklist.



4 RESULT

The results found in the studies included in this systematic review are shown in Table 2.

Table 2 - Studies included in this systematic review.

1st AUTHOR (YEAR)	DIAGNOSIS OF DYSPLASTIC LESIONS	LOW-GRADE DYSPLASIA	HIGH-GRADE DYSPLASIA	SURVEILLANCE AFTER ERADICATION
Nabeeha Mohy-ud-din, MD (2019)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - Surveillance biopsies should only be obtained after resolution of active esophageal inflammation or in cases of esophagitis previously treated with anti-reflux therapy. - There is a direct relationship between the time interval between endoscopic examinations for surveillance and the detection of dysplasia.	- 1st line: ablation therapy - 2nd line: annual surveillance from 4-quadrant biopsies with 1 cm intervals. If two consecutive tests are negative for dysplasia, surveillance should be performed from 4-quadrant biopsies with 2 cm intervals at intervals of 3 to 5 years.	- 1st line: TAR every 2-3 months	- Complete eradication of intestinal metaplasia and dysplasia is confirmed after two negative biopsies. - Typically, ART sessions are repeated every 2-3 months until complete eradication. - After eradication, patients should follow a regular surveillance schedule. - There is no evidence to support stopping surveillance.
Michelle Clermont (2018)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - Recommended use of a high-quality endoscopic technique with white light.	- 1st line: TAR - 2nd line: surveillance from 4-quadrant biopsies with 1 cm intervals.	- 1st line: endoscopic ablative therapy.	- does not address surveillance after eradication.
Prateek Sharma (2019)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology.	- Endoscopic therapy and continuous surveillance are reasonable options for management. - 1st line: periodic surveillance in the range of 6 to 12 months. - Patients with confirmed DBG should repeat endoscopic examination with high-definition white light in 3 to 6 months to rule out visible lesion that should	- 1st line: endoscopic therapy.	- After DBG eradication, the ACG recommends surveillance in 1 and 3 years. - After the eradication of DAG, the ACG recommends surveillance every 3 months during the first year, every 6 months during the second year, and annually from the third year. - Evaluations should be made from high-definition white-light endoscopy and should

		receive immediate resection. - Esophagectomy not recommended.		include careful inspection of the neosquamous mucosa and retroflex inspection of the gastric cardia.
Vedha Sanghi (2019)	- Use of the Seattle Protocol recommended. - Confirmation of dysplasia by a pathologist who specializes in gastrointestinal pathology is recommended.	- This study does not draw its own conclusions about DBG.	- This study does not draw its own conclusions about DAG	- Discontinuing the investigation is not recommended even after multiple negative tests.
M Harrison (2018)	- The use of the Seattle Protocol is recommended.	- Radiofrequency ablation therapy and surveillance are possible treatment alternatives for DBG.	- doesn't address DAG.	- does not address surveillance after eradication.
John J. McGoran (2020)	- The use of the Seattle protocol is recommended. - At least one minute should be used for inspection of each centimeter of Barrett's mucosa, focusing on the right wall and proximal segment.	- Endoscopic eradication therapy and surveillance are viable treatment options. - In the face of any abnormality seen on surveillance examination, endoscopic mucosal resection should be performed. - On occasions when GBD is detected without the presence of injury, a careful multidisciplinary discussion on the merits and risks of the intervention is recommended.	- Endoscopic eradication therapy (TEE) is more cost-effective and eliminates the need for esophagectomy. - TEE is recommended at 3-month intervals until complete eradication of intestinal metaplasia.	- ART is effective for treating residual intestinal metaplasia and should begin 2 to 3 months after focal mucosal resection and performed every 3 months until no areas of EB are identified. - After eradication, endoscopic surveillance should be done. - Endoscopic surveillance should be done 1 to 3 years after endoscopic eradication therapy for DBG. - Endoscopic surveillance should be done 3.6 and 12 months later after endoscopic eradication therapy for DAG. - New lesions should be submitted to endoscopic resection and ablation of the columnar mucosa.
Kevin Kyung Ho Choi (2022)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - In the West, endoscopic surveillance every 2 to 5 years is recommended for EB patients for early detection of	- Surveillance program in a health center specialized in EB. - Endoscopic eradication therapy may be offered as a treatment. - The benefit of ART is related to aggressive protocols - In patients under	- Refer patient to a referral center in EB to repeat endoscopy in 4 weeks. - All visible lesions should be treated with endoscopic mucosal eradication, followed by sequential sessions	- does not address surveillance after eradication.

	adenocarcinoma.	surveillance by specialists, any progression to AGD or cancer can be detected early. - Adverse events following radiofrequency ablation therapy occur in about 10% of cases, but are rarely severe.	of radiofrequency ablation therapy until complete eradication of metaplasia. - DAG without visible lesions can be treated only with radiofrequency ablation therapy. - Surgery should not be offered.	
Tomoyuki Koike (2022)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - In the West, endoscopic surveillance every 2 to 5 years is recommended in EB patients for early detection of adenocarcinoma. - Recommended Seattle protocol. - In Japan, surveillance methods for EB have not been established and targeted biopsies only on suspicious lesions are commonly done.	- does not address DBG	- doesn't address DAG.	- does not address surveillance after eradication.
Jia Di (2020)	- It does not draw its own conclusions about the diagnosis.	- Recommended surveillance with an interval of 6 months.	- Endoscopic ablation resection recommended.	- does not address surveillance after eradication.
Fouad Otaki (2018)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - In the West, endoscopic surveillance every 2 to 5 years is recommended for EB patients for early detection of adenocarcinoma.	- It doesn't draw its own conclusions about DBG.	- Endoscopic surveillance is only recommended when there is AGD in patients with limited life expectancy and should be discontinued when life expectancy is less than 5 years.	- does not address surveillance after eradication.
Spyridon Michopoulos (2018)	- The investigation of EB in the general population is not cost-effective. - Screening of target populations recommended, but this approach has a low level of scientific evidence.	- When histology is undefined for dysplasia, the GCA recommends intense anti-reflux therapy with double-dose proton pump inhibitors to minimize inflammation and repeat endoscopy	- There is less discrepancy among pathologists as to histological diagnosis. - Confirmation of DAG by a second pathologist specializing in DAG is required.	- does not address surveillance after eradication.

		according to the Seattle protocol. - If after the second endoscopy, the degree of dysplasia remains the same, most guidelines advocate performing a new endoscopy in 6 months, reevaluation of the biopsies by a pathologist specializing in EB pathology. - Follow-up with biopsies every 1 cm once a year. - There is a great discrepancy among pathologists regarding the definition of DBG.	- Visible lesions should be resected with endoscopic mucosal resection. - Flat lesions with no visible abnormalities should be treated with ablative methods, usually radiofrequency ablation therapy is the method of choice. - Other ablative methods such as cryoablation or coagulation with hybrid argon plasma are less evaluated, but may play an important role in the future. - If after radiofrequency ablation therapy EB lesions remain, the use of argon plasma coagulation may be considered. - It is still debatable whether endoscopic submucosal resection is preferable in cases of large lesions.	
Aamir N. Dam (2020)	- Diagnostic confirmation required by a pathologist specialized in gastrointestinal pathology. - Endoscopic surveillance should use high-definition white light. - Any abnormality found in the mucosa should be submitted to endoscopic mucosal resection. - If no abnormalities are visualized, surveillance should be performed according to the Seattle protocol.	- 1st line: TEE - Surveillance is an acceptable option.	- 1st line: TEE.	- Follow-up after eradication consists of the collection of biopsies of 4 quadrants every 1 c along the original dysplastic segment and gastric cardia. - Most recurrences are detected in the distal 2cm of the esophagus. - Recurrences are treated similarly to initial treatment involving mucosal resection and ablative modalities. - Anti-reflux therapy may be associated for symptom control.
Inês Marques de Sá (2020)	- High-quality endoscopy recommended.	- The surveillance interval differs between guidelines in that they are based on	- For AGD without visible lesion, most guidelines recommend repeat	- Recommended surveillance after endoscopic treatment.

		expert opinion and the low quality of scientific evidence.	high-quality endoscopy to look for abnormalities. - If no visible lesions are found, ablation therapy is proposed by all guidelines except ESGE which proposes repeating the Seattle protocol and repeating endoscopy in 3 months and, if DAG is confirmed, ablation is recommended.	
Andrew M. Bellizzi (2018)	- The use of the Seattle Protocol is recommended - Recommended high-quality endoscopy	- This study does not draw its own conclusions about DBG.	- This study does not draw its own conclusions about DAG.	- Patients should be kept under surveillance after endoscopic eradication of EB.
Tavankit Singh, MD (2019)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - Patient education is essential before surveillance.	- Surveillance with random biopsies of 4 quadrants every 1 cm if history and biopsy of any mucosal irregularity. - Patients with DBG who do not undergo eradication therapy should undergo endoscopy every 6-12 months.	- It is critical that maximum acid suppression is performed with a proton pump inhibitor twice daily and a histamine-2 blocker at night. - The current treatment of choice is endoscopic mucosal resection of elevated lesions for patients without severe comorbidities, followed by radiofrequency ablation of the entire affected segment. Alternatively, surveillance every 3 months can be done.	- After eradication, continued surveillance and prolonged treatment with PPIs are required. - Surveillance endoscopy involves 4-quadrant biopsies taken every 1 cm of the entire length of the segment where EB was seen prior to ablation. - The time of surveillance interval depends on the degree of pre-ablation dysplasia. - DBG: surveillance every 6 months in the first year after ablation and annually after this period if there is no recurrence. - DAG: surveillance every 3 months in the first year, 6 months in the second year and annually from the third year.
Francesco Maione (2022)	- Required use of high-quality technique for diagnostic confirmation.	- There is currently no consensus on the management of DBG. - Ablation methods are the most commonly used for flat dysplastic EB. - Endoscopic surveillance is	- It doesn't address DAG surveillance.	- does not address surveillance after eradication.

		recommended in patients not undergoing endoscopic treatment.		
Ishaan Maitra (2020)	- The gold standard method for screening is visual inspection and biopsies of mucosal irregularities according to the Seattle Protocol. - EB should be considered if a paceintis with GERD has risk factors such as advanced age, male gender, long-term history of reflux, increased frequency of esophagitis symptoms, anterior hiatal hernia, esophageal stenosis, or esophageal ulcers. - Endoscopy should be performed in patients with controlled reflux symptoms for better diagnostic accuracy. - Findings such as inflammation and ulceration considered undefined for dysplasia may be results of erosive esophagitis. Because of this, acid suppression should be offered and a new endoscopy should be performed in 6 months.	- If a histological finding of AGD is found, a new endoscopy should be performed in 6 months. - In case of diagnostic confirmation, it should be discussed which is the best treatment to follow: endoscopic surveillance (every 6 months for 2 years and then annually) or eradication therapy. - The absolute benefit of eradication therapy is not certain as the rate of progression from DBG to ACE is low. - Among the eradication therapies, the most used is radiofrequency ablation therapy. - Initial ablation has been shown to be more cost-effective than intensive surveillance.	- The ideal is to refer the patient to a specialized center in EB for endoscopic mucosal resection and eradication therapy.	- Continued vigilance recommended. - There are no long-term data on the recurrence of intestinal metaplasia or dysplastic changes in the squamous epithelium.

5 DISCUSSION

5.1 SURVEILLANCE OF DYSPLASTIC LESIONS IN BARRETT'S ESOPHAGUS

As for the definition, all current guidelines agree that for Barrett's esophagus to be characterized, there must be the presence of columnar mucosa in the esophagus instead of the squamous epithelium.[18,23] However, there is no consensus regarding the extent of this alteration for the diagnosis to be made accurately. The BSG, ACG and ESGE consider that it is necessary to have at least 1 cm of columnar mucosa extension above the proximal gastric fold, while the Japanese Society, the AGA and the Australian guideline have not determined minimum length for this definition. Finally, the ASGE does not cite criteria for the extent of the change.[18.24]

Based on these considerations based on metaplastic extension, the Prague criteria were created in order to standardize the endoscopic report of the extent of esophageal epithelial metaplasia from the

circumferential extension and maximum extension visualized.[18,23,25,26] In this analysis, at least one minute should be used for the inspection of each centimeter of Barrett's mucosa, with a particular focus on the right wall and proximal segment.[24th]

These definitions are important, because from the moment that the metaplastic cell development changes, becoming a dysplasia, this should be identified early from the routine surveillance to which these patients diagnosed with EB must be submitted.

Thus, the main function of any surveillance program is the early detection of dysplasia so that treatment is properly implemented.[23,24,25,26,27] Currently, the guidelines recommend that surveillance be performed through endoscopic examinations performed in certain periods of time. Such a disposition is important, because there is a direct relationship between the period of the examination and the detection of dysplasia, so that a complete evaluation of the mucosa and regular evaluation of the mucosa is essential for effective surveillance.[24.27]

To optimize this evaluation, all guidelines recommend the use of the Seattle Protocol, which consists of the biopsy of four quadrants obtained every 2 cm for patients without dysplasia and every 1 cm for patients with previous dysplasia. [24,25,30,31]

However, this protocol has some challenges. One is that surveillance from random biopsies shows only a small proportion of the mucosa of Barrett's Esophagus. In addition, it is a tedious and time-consuming protocol, which hinders the adherence of patients, especially those who have longer segments affected and that, therefore, the risk of progression to other prevalent cancers is higher. Thus, it has been shown that low adherence is associated with lower rates of dysplasia detection.[32nd]

Importantly, surveillance biopsies should only be obtained after resolution of an active esophageal inflammation or in cases of esophagitis previously treated with anti-reflux therapy. This is recommended because inflammation can cause the pathologist to confuse regenerative changes with the dysplasia itself, leading to misdiagnosis.[20,23,26,27,33]

Another consensus among international guidelines is that any visible dysplastic lesion, whether low-grade or high-grade, should be diagnosed by at least two pathologists, one of whom should be a specialist in gastrointestinal pathology and use a high-quality endoscopic technique to confirm the diagnosis.[13,18,20,26,27,31,33,34] This recommendation was established in order to minimize the chances of misdiagnosis, since low-grade dysplasia can often be confused with non-dysplastic EB even among experienced pathologists.[27.35]

Still, for diagnostic confirmation, the British Society of Gastroenterology (BSG), the European Society of Gastrointestinal Endoscopy (ESGE) and the Australian guideline recommend repeating the same endoscopic evaluation at 6 months.[18,23,28,30]

In particular, the American societies of the American Gastroenterological Association (AGA), the American Society of Gastrointestinal Endoscopy (ASGE), and the American College of

Gastroenterology (ACG) recommend, in addition to the consensus criteria, the use of proton pump inhibitors before the second endoscopy, with performance recommended in the interval of 8-12 weeks by AGA.[19.25]

5.2 LOW-GRADE DYSPLASIA

As for low-grade dysplasia (GBD), there are still some controversies among the guidelines regarding its approach. However, two treatments can be used for this: radiofrequency ablation therapy and endoscopic surveillance.

But first of all, it is important to emphasize that to allow informed decision-making between the doctor and the patient, before choosing the approach to this disease, patients should be informed about the risks of developing cancer in the absence of endoscopic therapy and these risks after its realization. In addition, they should be clarified about the benefits and limitations of each choice, as well as the importance of adherence to the chosen treatment.[13,25,30]

Radiofrequency ablation therapy involves the delivery of high-frequency currents to the tissue so that the heat generated results in the denaturation of the proteins and therefore in local cell death.[27] This technique stands as one of the main treatments, as it has been shown to have better effects in reducing the progression to high-grade dysplasia and has led to the eradication of intestinal dysplasia and metaplasia in a significant number of patients.[27] For these reasons, all guidelines recommend ablation over surveillance, with the exception of the AGA, the Australian guideline, and the Asia-Pacific Consensus.[19,23,28]

The randomized "SURF" study compared the efficacy of radiofrequency ablation therapy with that of endoscopic surveillance in 136 patients with DBG previously confirmed by three pathologists. As a result, this research showed that ablation decreased the risks of progression to high-grade dysplasia (DAG) and adenocarcinoma of the esophagus (ACE) by 25%, while surveillance decreased the risks by only 8.8% in the control arm over a 3-year follow-up period.[23,24,25,33,34] Similarly, the prospective randomized trial "*AIM DYSPLASIA*" demonstrated that ablation was associated with a higher rate of DBG eradication, as well as a decreased risk of progression from DBG to DAG/ACE. Therefore, the risk of progression was assessed at only 5% for follow-up with ablation at 14% with surveillance over the 12-month period.[25,33]

Based on such evidence, the ACG, the British Society of Gastroenterology (BSG), the European Society of Gastrointestinal Endoscopy (ESGE), the American Society of Gastrointestinal Endoscopy (ASGE) recommend ablation therapy for confirmed cases of DBG. However, the annual surveillance recommended by the ACG and ASGE and the surveillance every 6 months recommended by the BSG would only be an alternative management for those patients in whom the risks may be greater than the benefits.[26,27,30,35]

Despite all recommendations indicating ablative therapy as the best option, it is known that there are complications associated with it. Among them, post-procedural stenosis occurs in about 6% of cases is the most common and, together, the risk of neoplasia is not negligible after endoscopic ablation therapy, and there may be relapses.[19] Despite this, the ablation technique is the most recommended because there is a scarcity of studies comparing ablative techniques and in view of this, the current literature indicates that the risks of stenosis and other complications associated with endoscopy ablation therapy are lower.[19] Therefore, these other techniques may play an additional role in the future, namely argon plasma coagulation, cryoablation, cryotherapy, and photodynamic therapy.[19.35]

On the other hand, surveillance still remains an acceptable first-line management in some of the international guidelines. In 2019, with the aim of guiding AGA members, an expert review was commissioned, which demonstrated that both endoscopic therapy and surveillance are equally effective options for the management of patients with confirmed DBG.[13] In these patients, however, in order to rule out the presence of a visible lesion that may harbor malignancy and therefore justify an endoscopic resection, a new examination of 3 to 6 months should be performed with endoscopy with high-definition white light and, preferably, by optical chromoendoscopy using the Seattle Protocol before proceeding with the surveillance protocols.[13,24,29,33]

In view of any visible abnormality found in the endoscopic surveillance examination, endoscopic mucosal resection (REM) should be performed, since this alteration suggests a higher probability of neoplastic development.[13,24,24] A study by Peters et.al. demonstrated that the histological evaluation from the MSC led to a 49% change in the diagnosis of these evaluated lesions and alteration of the treatment plan in 30% of the cases.[24.29]

However, a major impasse for the consensus regarding the surveillance interval and the biopsy protocol of DBG is that, in most cases, these approaches are based only on the opinion of specialists, on the lack of well-defined criteria to title a professional as a specialist, on the reliability of their histological interpretation and on the low quality of scientific evidence. Therefore, such parameters continue to differ slightly between international guidelines.[19,32,35]

Therefore, the AGA recommends periodic surveillance in the range of 6 to 12 months as the first line of treatment.[13,30,31] On the other hand, the interval of only 6 months is recommended by the Australian guideline and the Asia-Pacific Consensus and supported by the study by Jia et. al.[28.30]

In this situation, surveillance would consist of an annual endoscopic examination following the Seattle protocol. If two consecutive examinations are negative for dysplasia, the regimen made for Non-Dysplastic Barrett's Esophagus should be resumed, that is, biopsies in 4 quadrants with intervals of 2 cm [25,27,30,34] and, if no dysplasia is found, surveillance should continue to be done with endoscopic examinations at intervals of 3 to 5 years.[27,30] The negative point is that, because it requires a long period of time, this biopsy protocol may be impaired by the low adherence of the patient over the years.[20.23]

5.3 HIGH-GRADE DYSPLASIA

When it comes to high-grade dysplastic lesions, all guidelines recommend endoscopic ablation therapy as a good approach option to be performed in sessions every 2-3 months until complete eradication of the change is achieved.[18,19,23,26,27,31] Despite the lack of a consensus, this eradication is generally defined as the endoscopic remission of all metaplasias and dysplasias after two negative biopsies obtained in 4 quadrants with 1cm intervals.[27] However, even in those who do not achieve complete eradication of Barrett's mucosa, the overall 5-year survival rate is good and appears to be approximately 90%.[33rd]

Demonstrating the efficacy of ablation in the scientific literature, the study by Shaheen et. al. demonstrated that patients with AGD were randomized to receive radiofrequency ablation or a sham procedure. As a result, 81% of those treated with ablation achieved complete eradication of dysplasia compared to the 19% who achieved the same outcome with the sham procedure. Similarly, eradication of intestinal metaplasia was achieved in 77% of patients with ablation versus 2% of patients with dummy therapy. Finally, 3-year follow-up results from the same cohort showed a complete eradication of dysplasia in 98% and intestinal metaplasia in 91%.[34th]

In particular, for patients with confirmed high-grade flat dysplasia, the AGA recommends in its latest 2019 update, ordering a new examination in 6-8 weeks with high-definition, white-light endoscopy to rule out visible lesions amenable to resection. This would be important because in the presence of visible lesions, resection would precede ablation, aiming at the best staging, as well as the complete eradication of the segment.[13,27,31,33,34] Thus, in these cases, an additional advantage of endoscopic resection is the availability of large tissue samples, leading consequently to better conditions for pathological evaluation and staging.[35th]

Regarding the choice of resection technique, endoscopic resection remains the preferred method according to all guidelines, although recent Japanese studies have shown fewer local recurrences for squamous cell carcinomas when endoscopic submucosal dissection was applied.[35th]

Therefore, surveillance is restricted to patients with AGD who have limited life expectancy and such follow-up should be discontinued in cases where this expectation is less than 5 years.[32,34] In this context, before the initiation of ablative therapy, AGA, ASGE, GCA and ESGE recommend surveillance every 3 months.[28.34]

Therefore, current evidence shows that it is possible both to eradicate intestinal dysplasia and metaplasia and to regress the levels of progression to adenocarcinoma[25,27] without the need for esophagectomy13,24,34. However, the main reason that esophagectomy is not the most recommended option is the scarcity of evidence of high quality of survival and recurrences after surgery, since most studies are retrospective and with small numbers.[33rd]

However, the risk of developing stenosis in about 5.6% of patients undergoing treatment by ablation or endoscopic resection recommended for AGD is still a challenge for these approaches. Thus, in an attempt to minimize these outcomes, it is recommended that patients should receive high-dose proton pump therapy to mitigate stenosis formation, following evidence of its use in reflux esophagitis.[24,33] Other serious adverse events of these endoscopic managements include bleeding in 1% and perforation rate in 0.6%. Post-procedure chest pain in the absence of these serious complications can occur from 1.5% to 5.4%.[33]

5.4 CONTINUITY OF SURVEILLANCE AFTER ERADICATION OF THE LESION

There is no evidence to support discontinuation of surveillance even after multiple negative endoscopy in both DBG and DAG cases. However, a recent study found that recurrence of metaplasias and dysplasias are uncommon. Thus, more studies are needed to determine the best surveillance strategies in patients for eradication.[24,27,30] Currently, in the same way as surveillance in cases of dysplasia, follow-up after eradication consists of the collection of biopsies of 4 quadrants every 1 cm along the original dysplastic segment and gastric cardia, and most recurrences were detected in the distal 2 cm of the esophagus.[29th]

The interval between biopsies depends on the degree of dysplasia before eradication of the lesion. The ACG and the UK's national Halo registry recommend that surveillance be done in the first and third year after eradication for DBG.[13,29,30,34] On the other hand, Singh's study et. al. states that surveillance after the eradication of DBG should be every 6 months in the first year and annually from the second year if there is no recurrence.

For cases of eradicated SAD, the ACG, ASGE and the Australian guideline recommend surveillance every 3 months during the first year, every 6 months during the second year and annually from the third year, while the ESGE recommends surveillance every 3 months during the first year and annually from the second year.[13,19,24,30,34] The UK National Halo Registry and the AGA recommend surveillance at 3 months, 6 months and 1 year after eradication.[13,24,30,34] By contrast, the Asia-Pacific Consensus does not state any recommendation in this regard.

Such evaluations for surveillance should be made from endoscopy with high-definition white light and should include careful inspection of the neosquamous mucosa and gastric cardia, as well as should follow the Seattle Protocol with the collection of biopsies of 4 quadrants every 1cm.[13.29]

In this context, a prospective cohort supported the findings of the prospective study *"AIM DYSPLASIA"* showing recurrences of Barrett's Esophagus and dysplasia respectively in 5.2 and 1.8 per 100 person-years, with most recurrences occurring in the first two years.[24] Therefore, this would be a finding that could justify the higher frequency of surveillance biopsies in the first years after the complete eradication of metaplasia and dysplasia.

In addition to prolonged follow-up with surveillance, treatment with proton pump inhibitors is recommended, mainly by the ASGE, ACG and AGA guidelines.[19,34]

If there are recurrences, it is recommended that they be treated similarly to initial treatment protocols involving mucosal resection and ablative modalities.[24,29] Together, anti-reflux therapy is recommended to achieve symptom control and absence of erosive esophagitis.[29th]

6 LIMITATIONS OF THE STUDY

For the construction of this systematic review, the selection of articles, data extraction and evaluation of the quality of information were performed by only two investigators, a fact that may be a source of bias for this study.

7 CONCLUSION

This review synthesizes more recent surveillance and treatment data of dysplastic Barrett's esophagus, concluding that there is considerable consensus among international guidelines in order to optimize good medical practice regarding the diagnosis, treatment, follow-up and stratification of this pathology.

However, there are still disagreements to be clarified. One reason for such discrepancies is based on the precariousness of scientific evidence and clinical studies that compare the approaches to dysplastic EB, especially when it comes to low-grade dysplasia.

REFERENCES

Feldman M, Friedman LS, Brandt LJ, Chung RT, Rubin DT, Wilcox CM. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11o ed. Philadelphia: Elsevier; 2021. p.670.

Richter JE, Rubenstein JH. Presentation and Epidemiology of Gastroesophageal Reflux Disease. Gastroenterology. Janeiro de 2018;154(2):267–76.

Chen J, Brady P. Gastroesophageal reflux disease: Pathophysiology, diagnosis, and treatment. Gastroenterology Nursing. Janeiro de 2019;42(1):20–8.

Kahrilas PJ. GERD pathogenesis, pathophysiology, and clinical manifestations. Cleveland Clinic Journal of Medicine. Novembro de 2003;70 (Suppl 5):S4-19.

Tack J, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. Gastroenterology. Janeiro de 2018;154(2):277–88.

Chang P, Friedenberg F. Obesity and GERD. Gastroenterol Clin North Am. Março de 2014;43(1):161–73.

Young A, Kumar MA, Thota PN. GERD: A practical approach. Cleve Clin J Med. abril de 2020;87(4):223–30.

Cesario S, Scida S, Miraglia C, Barchi A, Nouvenne A, Leandro G, et al. Diagnosis of GERD in typical and atypical manifestations. Acta Biomed. Dezembro de 2018; 89, (8-S): 33-39.

Qumseya BJ, Qumsiyeh Y, Ponniah SA, Estores D, Yang D, Johnson-Mann CN, et al. Barrett's esophagus after sleeve gastrectomy: a systematic review and meta-analysis. Gastrointest Endosc. fevereiro de 2021;93(2):343-352.e2.

Kumar V, Abbas AK, Aster JC. Robbins & Cotran Patologia - Bases Patológicas das Doenças. 9o ed. Elsevier; 2016. Capítulo 2, Respostas Celulares ao Estresse e às Agressões Tóxicas: Adaptação, Lesão e Morte, p. 87-89.

Thrift AP. Barrett's Esophagus and Esophageal Adenocarcinoma: How Common Are They Really? Digestive Diseases and Sciences. 18 de agosto de 2018;63(8):1988–96.

Clarrett DM, Hachem C. Gastroesophageal Reflux Disease (GERD). Mo Med. 2018 May-Jun;115(3):214-218.

Sharma P, Shaheen NJ, Katzka D, Bergman JJGHM. AGA Clinical Practice Update on Endoscopic Treatment of Barrett's Esophagus With Dysplasia and/or Early Cancer: Expert Review. Gastroenterology. fevereiro de 2020;158(3):760–9.

Turner JR. O Trato Gastrointestinal. Em: Kumar V, Abbas AK, Aster JC. Robbins & Cotran Patologia - Bases Patológicas das Doenças. 9o ed. Elsevier; 2016. p. 1373.

Spechler SJ, Souza RF. Barrett Esophagus. Em: Feldman M, Friedman LS, Brandt LJ, Chung RT, Rubin DT, Wilcox CM. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11o ed. Philadelphia: Elsevier; 2021. p.691-694.

Hamel C, Ahmadzai N, Beck A, Thuku M, Skidmore B, Pussegoda K, et al. Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with

chronic gastroesophageal reflux disease with or without other risk factors: two systematic reviews and one overview of reviews to inform a guideline of the Canadian Task Force on Preventive Health Care (CTFPHC). Syst Rev. 29 de dezembro de 2020;9(1):20.

Cook MB, Thrift AP. Epidemiology of Barrett's Esophagus and Esophageal Adenocarcinoma. Gastrointest Endosc Clin N Am. Janeiro de 2021;31(1):1–26.

Clermont M, Falk GW. Clinical Guidelines Update on the Diagnosis and Management of Barrett's Esophagus. Dig Dis Sci. 18 de agosto de 2018;63(8):2122–8.

Marques de Sá I, Pereira AD, Sharma P, Dinis-Ribeiro M. Systematic review of the published guidelines on Barrett's esophagus: should we stress the consensus or the differences? Diseases of the Esophagus. 30 de novembro de 2020; doaa115.

Koike T, Saito M, Ohara Y, Hatta W, Masamune A. Current status of surveillance for Barrett's esophagus in Japan and the West. DEN Open. 13 de abril de 2022;2(1).

Kumar V, Abbas AK, Aster JC. Robbins & Cotran Patologia - Bases Patológicas das Doenças. 9o ed. Elsevier; 2016. Capítulo 7. Neoplasia. p. 483-484.

Krishnamoorthi R, Mohan BP, Jayaraj M, Wang KK, Katzka DA, Ross A, et al. Risk of progression in Barrett's esophagus indefinite for dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. janeiro de 2020;91(1):3-10.e3.

Maitra I, Date RS, Martin FL. Towards screening Barrett's oesophagus: current guidelines, imaging modalities and future developments. Clin J Gastroenterol. 3 de outubro de 2020;13(5):635–49.

McGoran JJ, Ragunath K. Endoscopic management of Barrett's esophagus: Western perspective of current status and future prospects. Digestive Endoscopy. 16 de julho de 2021;33(5):720–9.

Harrison M, Allen JE, Gorrepati VS, López-Jamar JME, Sharma P. Management of Barrett's esophagus with low-grade dysplasia. Diseases of the Esophagus. 1o de abril de 2018;31(4).

Maione F, Chini A, Maione R, Manigrasso M, Marello A, Cassese G, et al. Endoscopic Diagnosis and Management of Barrett's Esophagus with Low-Grade Dysplasia. Diagnostics. 23 de maio de 2022;12(5):1295.

Mohy-ud-din N, Krill TS, Shah AR, Chatila AT, Singh S, Bilal M, et al. Barrett's esophagus: What do we need to know? Disease-a-Month. janeiro de 2020;66(1):100850.

Di J, Sharma N, Pérez LKM, Zhang J, Ho K. Surveillance strategy of Barrett's esophagus in the Asian region with particular reference to its locoregional epidemiology. JGH Open. 12 de agosto de 2020;4(4):565–8.

Dam AN, Klapman J. A narrative review of Barrett's esophagus in 2020, molecular and clinical update. Ann Transl Med. setembro de 2020;8(17):1107–1107.

Sanghi V, Thota PN. Barrett's esophagus: novel strategies for screening and surveillance. Ther Adv Chronic Dis. 26 de janeiro de 2019;10:204062231983785.

Bellizzi AM, Hafezi-Bakhtiari S, Westerhoff M, Marginean EC, Riddell RH. Gastrointestinal pathologists' perspective on managing risk in the distal esophagus: convergence on a pragmatic approach. Ann N Y Acad Sci. 11 de dezembro de 2018;1434(1):35–45.

Otaki F, Iyer PG. Point–Counterpoint: Screening and Surveillance for Barrett's Esophagus, Is It Worthwhile? Dig Dis Sci. 30 de agosto de 2018;63(8):2081–93.

Choi KKH, Sanagapalli S. Barrett's esophagus: Review of natural history and comparative efficacy of endoscopic and surgical therapies. World J Gastrointest Oncol. 15 de março de 2022;14(3):568–86.

Singh T, Sanghi V, Thota PN. Current management of Barrett esophagus and esophageal adenocarcinoma. Cleveland Clinic Journal of Medicine. 2019 Nov; 86(11):724–32.

Michopoulos S. Critical appraisal of guidelines for screening and surveillance of Barrett's esophagus. Ann Transl Med. julho de 2018;6(13):259–259.