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ABSTRACT

Barrett's esophagus (BE) represents a special clinical entity, which may have reduced symptoms, but an increased potential for malignant degeneration. The factors that lead to the appearance of Barrett's esophagus are multiple, the most important being gastro-esophageal reflux, as well as smoking and obesity. BE occurs as a result of damage of the esophageal mucosa, caused by acid/basic gastroesophageal reflux and resulting in the transformation of the epithelium from squamous to intestinal type. The diagnosis of BE is primarily based on endoscopic examination. This method has not only a diagnostic role, but also a therapeutic one through the minimally invasive resection of the mucosa with suspicious dysplastic lesions, thus reducing the risk of esophageal adenocarcinoma. Conservative therapeutic methods by administering chemoprotective agents (proton pump inhibitors, statins, etc.) are also useful. Surgical treatment of Barrett's esophagus aims to both resect areas of high-grade esophageal dysplasia/adenocarcinoma and reduce the degree of gastroesophageal reflux through various surgical procedures. As a conclusion, the potential for malignant degeneration of BE should not be neglected, the form of treatment largely depending on the patient's age and comorbidities.

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Introduction

Barrett's esophagus (BE) is a condition primarily caused by gastroesophageal reflux, which can occur with or without symptoms. This disease leads to the transformation of the epithelium from squamous to intestinal type, which can be a precursor state of esophageal adenocarcinoma. Determining the exact onset and incidence in the general population can be difficult. Consequently, focusing on the prevalence and early diagnosis of BE becomes essential, as it provides important insights into the subsequent therapeutic management of the disease [1,2].

An evolutionary complication of this disease is represented by malignant transformation, BE being considered a premalignant condition [3]. Early diagnosis is an essential element in order to obtain good survival rates in the case of esophageal adenocarcinoma [4]. Esophagogastroduodenoscopy (EGD) with biopsy is the standard of care in both the therapeutic management and surveillance of BE. Other endoscopic procedures are able to quantify and treat the early stages of the disease, while surgical procedures are reserved for refractory cases or advanced stages [5].

The present study is a review of the articles published on the BE topic in WOS, PubMed, Scopus and Google Scholar databases, with the aim of presenting the new diagnostic methods, their effectiveness, as well as the most appropriate treatments depending on the stage (early or advanced) of the disease at the time of diagnosis.

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Discussions

Epidemiology

The cause of Barrett's esophagus (BE) is primarily represented by gastroesophageal reflux, which can be symptomatic or even asymptomatic, making it impossible to know the exact moment of onset of the disease as well as its incidence in the general population. Starting from these observations, it is therefore more useful to determine the prevalence of the disease, which is conditioned by the availability of endoscopy. This is the main diagnostic method at present, being less accessible in developing or isolated areas. However, in areas that have access to complex investigations such as endoscopic procedures, a slight increase in the prevalence of BE was observed. As a result of the existence of a close link between the etiologic factors and the onset of the disease, the prevalence of BE is strongly related to the prevalence of gastroesophageal reflux disease, which reaches high levels in North America, Europe, and South Asia [6,7].

Recent studies have attempted to determine the prevalence of BE in the general population of Northern Europe. Thus, 3,000 inhabitants of the northern part of Sweden were questioned regarding possible digestive symptoms, approximately 1,568 of them having varying degrees of heartburn. Then 1,000 patients were enrolled and were investigated by upper digestive endoscopy. BE was detected in 1.6% of cases based on biopsy results [8]. Lower prevalence rates (1.3%) were found in southern Italy, in a rural area, in a population with similar digestive symptoms [9]. Compared to European data, a tertiary center in the USA found a prevalence of 6.8% in patients undergoing endoscopy as a screening method.

The results of studies on populations from the Asian continent show an average prevalence of about 1.3%. Large geographic variations were observed, from 4.15% in Central and South Asia to 0.91% in the Eastern region, mainly influenced by access to advanced medical services [10]. Data for Latin America is currently limited. A single study was reported on a group of 104 patients (who were investigated by digestive endoscopy for upper digestive manifestations), and which showed a prevalence of 3.8% of BE [11]. The Middle East and Africa are geographic areas where epidemiological data related to intestinal metaplasia of the esophagus have not been measured, excepting Lebanon and Saudi Arabia where rates of 0.2 and 0.3%, respectively, have been identified [12,13].

Regarding risk factors in the development of BE, the most important is repetitive gastric reflux into the esophagus. Thus, GERD is particularly associated with intestinal metaplasia in the lower third of the esophagus, extending more than 3 cm from the esophagogastric junction [14]. This observation led to the conclusion that BE has a polygenic and hereditary character, as shown by the high prevalence of the disease in some families [15]. The gender distribution of the population observed a 2-fold higher risk in men than in women, increasing with age [16]. In multicultural countries living in the same geographic area, the Caucasian population has been identified as being at risk of developing BE, followed by Hispanic, Asian, and African American populations, respectively [17].

Another predisposing factor in the development of BE is obesity. A body mass index of more than 30 predisposes to BE, especially if the distribution of adipose tissue is intra-abdominal or central. The consequences are due to the reduced ability of the lower esophageal sphincter to perform its normal constrictive function, as well as due to the pro-inflammatory status present in obesity [18-20].

Exposure to cigarette smoke appears to be a risk factor in the development of BE. The higher the dose of exposure to tobacco, the higher the risk of BE. Patients with a smoking index of less than 15 packs/year resulted in a rare occurrence of BE compared to those with a smoking index between 15-30 or more than 45 packs/year. It is assumed that the effect would be secondary to the relaxation of the lower esophageal sphincter, as a result of the action of tobacco/nicotine [21]

Pathophysiology

BE occurs as a result of mucosal damage caused by acid/base gastroesophageal reflux, resulting in the transformation of squamous epithelium into intestinal-type epithelium. Two theories have been put forward to explain this phenomenon of metaplasia: the repair mechanism after a caustic type injury [22-24] and/or the action of locally released cytokines [25-27]. All this causes the stem cells to change their normal phenotypic expression, and to subsequently induce the change/metaplasia of the esophageal mucosa [28].

Bile acids lead to the release of proinflammatory cytokines such as IL1b, IL6, IL8, TNF-a [30,31], PGE2 [32], and COX2 [33], which activate NF-kB, preventing cell apoptosis and stimulating the proliferation of epithelial cells, thereby protecting them from harmful effects [28]. If the injury persists, multiple changes in DNA and genomic instability occur, leading to dysplasia.

The most important role in the development of BE is considered to be the reflux of bile acids, in combination with the local decrease in pH, which increases their solubility [29]. Subsequently, local and intracellular changes are induced (including large mitochondrial release), the large amounts of free oxygen radicals leading to further changes in the genetic material [28]. Bile acids lead to the release of pro-inflammatory cytokines such as IL1b, IL6, IL8, TNF-α [30,31], PGE2 [32] and COX2 [33], which activate NF-kB, preventing cell apoptosis and stimulating epithelial cell proliferation (which thus are no longer protected from local or cellular harmful effects) [28]. If the lesion persists, multiple DNA changes and genomic instability occur, ultimately leading to dysplasia.

Due to persistent bile reflux, the CDX2 factor is activated, a marker of differentiation to intestinal-type cells [34], secondary to the activation of the NF-kb pathway with the decrease of the effect of the NOTCH pathway, which is responsible for maintaining the differentiation of stem cells to squamous cells. This has been demonstrated by examining cells in which the NOTCH pathway is inhibited, leading to changes in specific surface markers of squamous epithelium and the presence of markers such as KRT8, KRT18, KRT20, MUC5B and MUC 17, which are specific to columnar epithelium [35,36].

The healing of squamous epithelium is based on the proliferation of cells from the periphery of the ulceration. If the aggression persists, there is a selection of cells that are resistant to the aggressive action of digestive juices (mucus-secreting cells, cardiac cells), leading to the ascension of intestinal-type epithelium with the formation of gland-like structures similar to BE. Epithelial ascent has been experimentally confirmed in mice with esophago-gastric anastomosis. Two weeks after the operation, ulceration was observed in the distal esophagus near the anastomosis, which was epithelialized in the distal margin with immature glands and with a histopathological appearance similar to the jejunum. Surface marker examination shows increased expression of CDX2, villin, CD10, and MUC2 (with increased specificity for intestinal tissue), as well as the absence of expression of MUC5AC and MUC6 (specific to gastric tissue) [23].

Diagnosis

The diagnosis of BE is primarily based on endoscopic examination, able not only to detect neoplastic lesions but also to treat suspected dysplastic lesions by minimally invasive methods (thus reducing the risk of esophageal adenocarcinoma) [37-39]. The appearance of symptoms such as dysphagia, dyspnea or of paraneoplastic condition can be a sign of advanced and/or aggressive disease [40].

A high-quality endoscopic examination can facilitate early diagnosis and minimally invasive treatment for incipient stages. The first step involves identifying esophageal landmarks to investigate tissue alterations, followed by thorough mucosal cleansing using a gentle water jet to avoid any mucosal damage. Subsequently, the endoscopist carefully inspects every centimeter of the lower esophagus [41]. The Seattle protocol standardized the biopsy approach, remaining the standard of care [42]. Accordingly, any ulcerated areas, nodules, or erythema must be biopsied and collected in separate containers. Additionally, any other lesions should be endoscopically resected.

Numerous imaging methods have been investigated for diagnosing esophageal diseases. These include classic or virtual chromoendoscopy, confocal laser endomicroscopy, volumetric laser endoscopy, etc., systems which can be assisted by artificial intelligence, enhancing thus examination sensitivity and specificity (with an increased predictive value for diagnosing dysplasia in the form of intestinal metaplasia) [43].

The most widely used diagnostic method is High-Definition White Light Endoscopy (HD-WLE), demonstrating superiority in detecting dysplasia compared to simple white light endoscopy [44], thus serving as the diagnostic standard for Barrett's esophagus [37].

Virtual chromoendoscopy or dye-based chromo-endoscopy is the most promising diagnostic method for BE, enhancing the detection of early-stage neoplasia. A meta-analysis considering 14 studies showed an increase of up to 34% in the diagnostic rate, especially for dysplasia [45]. Chromoendoscopy employs acetic acid, methylene blue, or indigo carmine to better visualize mucosal vascularity and neoplastic differences. These agents are often applied directly to the mucosal surface through the working channel. Acetic acid causes whitening of dysplastic mucosa, showing a sensitivity of 96.6% and a specificity of 84.6% [46].

Methylene blue can be used for diagnosing BE, being absorbed by colonic and intestinal mucosa, unlike the squamous esophageal epithelium that remains uncolored. In the case of BE, characteristic dark blue spots appear, indicating metaplasia. A meta-analysis considering 9 studies and around 450 patients concluded that there is no difference in BE detection rates when using WLE with random biopsies compared to methylene blue chromo-endoscopy [47], probably due to specific sensitivities (of 65%) and specificities (of 96%) [46]. Similar results were obtained when indigo carmine was used as a coloring agent [37].

Virtual chromoendoscopy achieves similar images to classic chromoendoscopy by employing blue/red/green color filters. Within this technology, narrow-band imaging is utilized on a large scale, being based on the tissue's light absorption capacity (a short wavelength being associated with a shallower penetration). The consequence is a good image of the vascular pattern and mucosal surface. The wavelength typically ranges between 400 and 540 nm [48]. The advantages of this technology include cost-effectiveness, no extension of the procedure, and reduced associated risks [37]. Compared to HD-WLE, the dysplasia detection rate was higher, with a reduced need for biopsies to detect the BE [49]. No other differences were observed compared to classic chromoendoscopy [50].

Regarding BE diagnosis, other methods such as Optical Coherence Tomography (OCT), Confocal Laser Endomicroscopy (CLE), and Autofluorescence Imaging (AI) could be also considered, but they are not widely accessible due to the high costs of the examination or research results that are still ongoing [51].

CLE operates on the same principle as an optical microscope, highlighting various cell types using a gray background. The limitations of this technology in BE are its high cost, the need for contrast agents, and a limited capacity to examine the mucosa [51]. However, it can increase the dysplasia detection rate, although it does not seem to have statistical significance. Connecting to an artificial intelligence system might improve the feasibility of these cumulative characteristics [50].

OCT employs near-infrared light to create cross-sectional images with remarkable resolution. This allows scanning the last 6 cm of the esophagus in almost 90 seconds, obtaining a resolution of 10 mm and a depth of 3 mm [50]. Laser technology can not only detect suspicious lesions, but also increase the positive biopsy rate in the diagnosis of BE. Still, interpreting the resulting images is challenging, and adapting an artificial intelligence system could enhance the feasibility of such a setup [42].

Autofluorescence imaging utilizes the ability of different tissue structures to absorb specific wavelengths based on biochemical characteristics, metabolic activity, blood flow, and cellular density. This allows differentiation between normal tissue and inflammation or modified tissue through metaplasia/dysplasia. However, the efficiency of this system is limited, as it often produces many false-positive results [52-54], but with high equipment costs and prolonged examination times [37].

Artificial Intelligence (AI) systems could assist endoscopists in increasing BE detection rates. ARGOS is a project developed by gastroenterology reference centers in the Netherlands that helps develop artificial intelligence to better recognize suspicious esophageal dysplasia lesions. By exposing static endoscopic images to an AI, they achieved an accuracy of 92%, with a sensitivity of 95% and specificity of 85% [55]. A more advanced system can be used by employing deep learning, which can analyze recorded videos and provide real-time analysis of endoscopic images. An American group developed a neural network based on a convolutional algorithm, achieving a BE detection rate of 93.75% with a sensitivity of 95.6% and specificity of 91.8% [56].

Other methods of diagnosis and screening for BE include cytosponge, esophageal endoscopic capsule, oral microbiome analysis, and liquid biopsy. Cytosponge is a gelatin-coated mesh attached to a thread that is orally administered [57]. Once in the stomach, the capsule is digested and releases a 3cm-diameter sphere, and by passing through the esophagus, it can collect cells from the esophageal level and trefoil factor 3 (a surface protein found on small intestine cells) that are subsequently examined [58]. The results of this method are acceptable with a sensitivity of 73.3% and a specificity of 93.8% [59] compared to the standard diagnostic method (that is upper gastrointestinal endoscopy with biopsy examination). Due to the acceptable sensitivity and specificity that can be improved by simultaneous measurement of other markers (TFPI2, TWIST1), low production costs and ease of use, it makes this method a screening tool, thus reducing the costs of detecting BE by 27-29 % [60]. The disadvantages of this method are represented by sore throats, potential esophageal bleeding that can occur in 16.7% of patients, but without requiring specialized therapeutic intervention. [57].

Esophageal endoscopic capsule (ECE) is a non-invasive method that allows visualization of the esophagus through cameras without being able to collect biopsy specimens. The sensitivity and specificity of this method were around 80%, based on a sample of 618 patients, but compared to the classic examination, it did not prove to be cheaper [58].

Liquid biopsy involves identifying small fragments of specific genetic material (RNA) in peripheral blood related to a specific type of cell. In the case of BE patients, circulating miRNA 95-3p, 136-5p, 194-5p, and -451a were identified, with a sensitivity of 78% and a specificity of 86% [60,61]. However, these data were obtained on small patient samples, necessitating evaluation of this method on a larger number of candidates.

Analysis of volatile gasses exhaled by patients is another method that could be considered for BE diagnosis. Through spectrophotometric analysis of emitted substances, a sensitivity of 82% and a specificity of 80% were obtained, with an accuracy of 81% [62]. The only drawback is the lack of testing on large patient cohorts, as with liquid biopsy.

Treatment

In the natural evolution of Barrett's esophagus (BE), malignant transformation can occur, leading to the development of esophageal adenocarcinoma. The role of treatment is to remove the dysplastic area through endoscopic or surgical methods or to reduce the risk of BE and its consequences through chemoprotective treatment.

Chemoprotective treatment

Proton pump inhibitors (PPIs) have the property of increasing intragastric pH, modulating the release of proinflammatory cytokines, reducing mucosal aggression, and the onset of carcinogenesis [63-65]. Long-term administration to patients with gastroesophageal reflux disease has led to a decrease in the length of affected mucosa and the appearance of islands of squamous epithelial tissue within the metaplasia zone [66,67], but achieving complete regression was rare [66]. An analysis of 2813 cases of BE where PPIs were administered showed a 71% decrease in the risk of BE and esophageal adenocarcinoma (EAC) [68-70], with a correlation between the dose and the total duration of treatment. Administration for over 2 years resulted in a lower rate of metaplasia compared to a shorter duration, but without statistical significance. An esomeprazole dose of 80mg led to lower rates of BE/adenocarcinoma-related mortality compared to a lower dose, with better results when combined with Aspirin [71]. These results were obtained in a predominantly white male population, which could pose disadvantages in a heterogeneous population [72]. An adverse reaction to prolonged PPI use is the increased levels of gastrin, which could theoretically enhance the survival capacity of metaplastic cells and facilitate carcinogenesis. A study on 1440 patients demonstrated an increased risk of developing EAC in patients with BE [73]. Similar results were obtained by a research team in the UK [74]. A subsequent meta-analysis that included patients from these two studies showed results leaning towards a chemopreventive effect of PPIs, but they were not statistically significant [75]. Other negative effects of prolonged NSAID administration include increased rates of gastric ulcers and an increased risk of bleeding, especially in patients over 70 years of age [76], along with nephrotoxicity and an increased overall cardiovascular risk in selective COX2 cases [77-79].

Statins have an immunomodulatory, antiangiogenic, anti-inflammatory and antiproliferative effect through the influence on the mevalonate pathway [80]. The administration of simvastatin, lovastatin, and pravastatin reduced the number of cancer cells by over 30% and inhibited their proliferation. In the case of BE patients, there was a reduction in the risk of EAC development by up to 35% compared to those not taking statins [81,82]. The data obtained for patients already diagnosed with BE and starting statin treatment are favorable, with a reduction in the risk of EAC development by up to 40%. The effect of this class of drugs is related to the duration of administration and the daily dose, being a protective factor in the development of BE in patients with GERD and EAC in the presence of intestinal metaplasia in the esophagus [72].

Metformin is an antidiabetic agent that increases tissue sensitivity to insulin by increasing glucose utilization in the periphery [83]. A decrease in cancer rates has been observed in diabetic patients treated with metformin, highlighting the inhibition of the mTOR pathway by reducing protein synthesis and cell proliferation. Regarding BE and EAC, a decrease in the risk of occurrence by up to 24% has been identified [72]. However, the influence of metformin on the progression of BE to EAC has not been demonstrated [84] and therefore chemoprotective treatment with statins for BE is not recommended at present.

Other chemoprotective agents in the case of BE and its progression to EAC include ursodeoxycholic acid, which can prevent DNA damage and NF-kB activation [85], with questionable results in small patient groups [86]. Folate through p53 protein mediation, vitamin D, green tea through its increased phenol component, curcumin, and zinc are also mentioned. All of them have a theoretical influence on apoptosis and proliferation processes, but without favorable results in large patient cohorts [72].

Endoscopic Treatment

Endoscopic treatment is initially indicated for patients with mucosal irregularities associated with BE. It is necessary to perform either an endoscopic mucosal resection or endoscopic submucosal dissection, removing tissue with malignant transformation potential and providing tissue material that can be analyzed. However, this approach requires extensive specialist training and is associated with high costs due to the required equipment [87,88].

Endoscopic mucosal resection is an endoscopic technique involving the injection of a saline solution into the submucosa, causing the submucosa to separate from the muscular layer. The endoscopist can then pull the lesion of interest or create a pseudopolyp using a vacuum system, which can be ligated and resected at the base. This method is effective in terms of resection, allowing complete removal of the metaplastic tissue, especially when combined with radiofrequency ablation. Complete resection rates reach around 80% of patients [89]. Negative effects of this technique may include strictures, stenoses (in less than 10% of cases), perforations, and bleeding [87].

Endoscopic submucosal dissection utilizes a knife attached to the endoscope, allowing dissection within the submucosa. The first step in excising a nodule or ulcerated area that may contain metaplastic tissue is marking it using an argon-plasma coagulation system. Subsequently, a substance that can mobilize the deep layers is injected into the submucosa, and using the knife, circumferential resection is performed. Saline solution is reinjected under the lesion to mobilize it, and with the progressive advancement of the knife, submucosal dissection is performed, achieving the removal of the suspect lesion [90]. In the hands of a skilled endoscopist, a complete en bloc resection can be more frequently achieved with this method compared to the previous one. An analysis of these two methods performed on patients with EAC localized at the mucosal level showed that submucosal dissection achieved en bloc resection rates of 97.1% compared to mucosal resection, which does not exceed 50%. However, it has a higher risk of perforations and requires longer procedure times [91].

Endoscopic ablation of suspicious areas leads to increased rates of complete resection due to necrosis of the metaplastic or dysplastic tissue, allowing normal epithelization in association with acid suppression treatment [92]. The most commonly used methods include cryotherapy, photodynamic therapy (PDT), and radiofrequency ablation (RFA).

Photodynamic therapy is an endoscopic ablation method based on the property of light (at a specific wavelength) to destroy sensitized cells through a substance that alters their biochemical properties. The most used substance for BE is porfimer sodium, which has the ability to concentrate in large quantities in the mucosa and submucosa of patients with intestinal metaplasia. Administration is done orally 48 hours before the procedure without significant adverse reactions [93]. Another substance that can be used in ablative treatment with light energy is aminolaevulinic acid, which can be administered orally, with better specificity for the mucosa, potentially sparing the submucosa and reducing the risk of complications in case of substantial mucosal involvement [94]. The main drawback of using this substance is hepatotoxicity, neuropathy, and sudden death due to arrhythmias [95]. The effectiveness of ablative treatment using light energy achieves complete resection rates of 52%, compared to proton pump inhibitor treatment, which does not exceed 7% [96]. Esophageal strictures occur at higher rates in these patients, ranging from 36% to 69% of cases due to photosensitization reactions [97], and the costs associated with this therapy are five times higher than radiofrequency ablation [98].

Radiofrequency ablation uses high-frequency wave energy directed towards the mucosal area of interest. After introducing the endoscope, the esophageal mucosa is cleaned with a water jet, excess mucus is removed, and the esophagogastric junction, lower and upper limits of the metaplastic mucosa area are identified. Subsequently, the esophageal diameter is measured using a balloon, measuring from 6 cm above the metaplasia zone and based on all this data, the appropriate catheter is used, followed by the administration of the radiation dose. The benefits and adverse reactions of this method have been extensively studied, being the most efficient ablative method in the treatment of BE, achieving a complete resection rate of 77.4% in cases, but without differentiation regarding high-grade dysplasia or low-grade dysplasia [99]. At 5 years, the disease recurrence rate is high, over 30%, but in 69% of cases, a second complete resection was achieved [100]. Adverse reactions associated with this method include strictures in 5.6% to 11.8% of cases, as well as bleeding and perforation. The incidence of these correlates with the total length of the metaplastic zone [101].

Cryotherapy ablation is another minimally invasive method which uses a cold liquid that causes tissue necrosis by developing ice crystals within the cytoplasm and at the membrane level, followed by local vascular thrombosis. Subsequently, an immune response is initiated, targeting the damaged cells and forces them into apoptosis. Liquid nitrogen and liquid carbon dioxide are used to achieve low temperatures, the nitrogen being the most studied. Regarding the complete resection rate of this method, it reaches an average value of 53.7%, while the recurrence rate of BE is 12.7% [102]. Given these results, the method can be used in cases where radiofrequency ablation was not effective. The occurrence rate of strictures is up to 3%, and regarding the occurrence of post-interventional chest pain, it does not exceed 2%, with no other adverse reactions [103].

Surgical Treatment

The surgical treatment within Barrett's Esophagus aims to reduce the degree of gastroesophageal reflux for cases refractory to medical treatment and to resect areas with a high degree of dysplasia/esophageal adenocarcinoma (EAC), for which distal esophagectomy is performed [104-106].

Antireflux Surgery

Antireflux surgery aims to reduce the reflux rate in the esophagus in cases where treatment with proton pump inhibitors (PPIs) is ineffective or the patients' symptoms persist under this treatment [104]. Nissen fundoplication, which can be performed through both a classic and laparoscopic approach, is even after the age of 60 the best and most commonly used anti reflux procedure [107,108]. It restores the function and competence of the lower esophageal sphincter, both in terms of pressure and length (especially the part exposed to positive pressure from the abdominal cavity), the geometry of the esophagogastric junction, and the diaphragmatic hiatus [104]. Unlike medical treatment, which only suppresses acid secretion, surgical antireflux treatment protects the esophageal mucosa by forming a mechanical barrier, preventing long-term medication use, the progression of BE, and the onset of EAC. The decision to perform surgical intervention must take into account not only the aforementioned advantages but also the anesthetic-surgical risks, the benefits for young patients, and the associated costs [109].

Regarding the disease remission rate after fundoplication, a slight increase is observed in patient groups with a length of affected mucosa less than 3 cm and a major increase in those with a length of affected tissue over 3 cm [110,111]. A decrease in the rates of EAC occurrence has also been observed in patients with a history of BE who underwent surgical antireflux treatment, a fact confirmed by a meta-analysis, with a neoplasia occurrence rate of 2.8 compared to patients treated with PPIs, where 6.3% of patients developed such a BE complication, but without statistical significance [112,113].

Surgical resection treatment of BE is still reserved for cases with high-grade dysplasia, in which over 41% of cases are positive for EAC on resection specimens [114]. With the widespread introduction of endoscopy as a monitoring method for patients, the detection rate of high-grade dysplasia has decreased due to minimally invasive therapeutic interventions and early detection [115]. However, the morbidity and mortality associated with esophagectomy globally reach around 2.5%, with different data for patients with adenocarcinoma compared to those with squamous cell cancer, as the former have a poor metabolic status due to oral feeding incapacity, neoadjuvant radiotherapy, and chemotherapy [116-118]. As a consequence of these effects, the risk of post-procedural adverse reactions reaches 28.1%, with occurrences of stenosis, bleeding, perforation, anterior chest pain, and associated mortality reaching 1.2% [119]. In addition, reintervention, prolonged hospitalization, or endoscopic intervention is necessary to resolve various inconveniences.

The benefit of esophagectomy is significant as it eliminates the risk of dysplasia and neoplasia and even in cases where lymph nodes are involved, the 5-year survival rates reaching 88% [120]. The indications for esophagectomy in BE with a high level of dysplasia are relative and depend on the disease itself, the patient's characteristics, the chosen technique, or the center where it is performed. Thus, in cases where a patient has an area of metaplastic mucosa over 8 cm with nodular dysplasia, endoscopic treatment often fails to eliminate it, necessitating surgical intervention. Alongside this indication, persistent, recurrent, or progressive disease under minimally invasive treatment represents relative indications for distal esophagectomy [115]. Complications associated with endoscopic treatment or its failure can represent indications for esophagectomy. The main adverse reaction of endoscopic procedures it is represented by stenosis of the esophagus and can be resolved through progressive dilatation or resection of the altered mucosa, but it may necessitate a surgical approach as repeated attempts at dilatation or resection can increase the risk of esophageal perforation [121]. Factors related to the patient that weigh in the decision to perform esophagectomy include persistent dysphagia due to structures resistant to treatment. This can lead the specialist to decide on surgical intervention since the quality of life for these patients is not optimal [122]. This decision can be made in young patients with a long-life expectancy and few comorbidities and in cases where patients do not have access to specialized institutions for long-term follow-up, thus eliminating the risk of neoplasia development [123].

The endoscopic approach compared to the surgical one has been extensively studied for BE with high-grade dysplasia. In most cases, patients referred for endoscopic treatment have a higher comorbidity index, a shorter length of the metaplastic mucosa, unlike patients treated by surgical methods. Furthermore, the detection rate on resection specimens of esophageal adenocarcinoma secondary to dysplasia is higher in the case of esophagectomy, but the perioperative mortality risks are higher [124,125].

Conclusions

Barrett's esophagus represents a critical clinical entity necessitating a multifaceted approach for therapeutic management. The diagnostic and treatment tools for BE comprises a diverse array of options, ranging from medical therapies based on the PPI, statins or NASAID’s, to endoscopic interventions and surgical procedures.

Endoscopic approaches, such as endoscopic mucosal resection and submucosal dissection, have revolutionized the management of BE by allowing precise resection of metaplastic tissue associated with good rates of complete resections. Ablative techniques, including radiofrequency ablation and cryotherapy, demonstrate promising outcomes in eliminating dysplastic cells and reducing the risk of disease progression but with high costs. Antireflux surgical procedures, especially Nissen fundoplication, have proven to be highly effective in managing patients with persistent reflux symptoms or inadequate response to proton pump inhibitors. On the other hand, resection procedures like esophagectomy are reserved for cases with high-grade dysplasia or adenocarcinoma, effectively mitigating the risk of neoplastic transformation. Each treatment modality addresses specific aspects of the disease, aiming to mitigate the risk of esophageal adenocarcinoma (EAC) and improve patients' overall quality of life.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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