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# Diagnosis and Management of Barrett's Esophagus with and Without Dysplasia

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Additional information is available at the end of the chapter

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## 1. Introduction

Barrett's esophagus (BE) is the partial replacement, from the gastro-esophageal junction (GEJ) proximally, of esophageal squamous epithelium with metaplastic columnar epithelium. It develops in patients with gastroesophageal reflux disease (GERD) because of chronic injury and inflammation of the esophageal epithelium. Many other factors have also significance. BE is the only known precursor to esophageal adenocarcinoma (EAC), the incidence of which has been increased faster in Western world in the past four decades [1, 2]. In the United States, the incidence of EAC increased from 3.6 cases per 1,000,000 in 1973 to 25.6 per 1,000,000 in 2006 [1]. Since EAC is frequently detected at an advanced stage, the prognosis remains poor. The 5-year survival rate of patients with locally advanced EAC undergoing curative resection is around 15–20% [3]. So detection at an early stage of neoplastic progression may be important in improving survival. The risk of developing EAC is 30–40-fold higher in patients with BE compared with the general population [4, 5]. The development of EAC in BE has been shown to occur through a multistep process of increasing grades of epithelial dysplasia, from no dysplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally EAC [6]. In two studies of 136 and 170 patients with nondysplastic Barrett's esophagus (NDBE), followed for approximately 4 years, the rate of progression to EAC was 0.5% per patient-year [7, 8]. The risk additionally increases if Barrett's dysplasia is present. The annual incidence of EAC in patients with LGD and HGD is about 1.7% and 6.6% respectively [9]. In another study of 75 BE patients with HGD, 16% developed EAC over a mean follow-up period of 7.3 years [10]. In last years, there are many new data for the pathogenesis and the natural history of BE, which raise many points regarding surveillance of BE and risk stratification for EAC, and current role

of anti-reflux therapy. Many enhanced imaging technologies and new endoscopic modalities for detection or management of any grade dysplasia and early cancer have been developed.

## 2. Definitions and diagnosis of BE

### 2.1. Definitions of BE

There is universal agreement that the underlying component of the definitions of Barrett's esophagus is the partial replacement, from the GEJ proximally, of esophageal squamous epithelium with metaplastic columnar epithelium. A mosaic of several histologic types of columnar metaplasia can be seen on biopsies from BE, including cardia type metaplasia, gastric fundus type metaplasia and specialized intestinal metaplasia (IM) type, containing goblet cells. The term BE is currently confusing because of varying definitions used for the diagnosis of BE [11, 12]. There is a lack of consensus among various professional organizations whether goblet metaplasia should be a requirement for the diagnosis of BE. According to the British Society of Gastroenterology (BSG), BE represents an endoscopically apparent area of columnar mucosa proximal to the GEJ, proven on histologic examination [13]. The American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) recommend documentation of IM for the diagnosis of BE [14, 15]. Several arguments can be made in favor of requiring IM for the diagnosis of BE. This definition is related with the concept of more malignant potential of IM compared to the risk of neoplastic progression in patients with metaplastic nongoblet columnar epithelium [14]. Some studies have also suggest that a diagnosis of BE may have a negative impact on overall quality of life of the patients. Patients with BE tend to overestimate their risk of EAC, and this leads to higher utilization of healthcare resources. A diagnosis of BE can result in higher health insurance premium and difficulty in obtaining health insurance [16, 17]. The varying definitions of BE lead to difficulties in the interpretation of know ledges for BE, because of the selection and follow-up of different cohorts of cases [12]. The "only IM type" definition of BE dominates the literature, but in many publications the diagnosis is made on the basis of varying endoscopic criteria unsupported by histopathology or on the presence of any type of columnar metaplasia. In 2006 the definition of BE was considered by the Global Evidence-Based Consensus Workshop on the Definition and Classification of Reflux Disease (the Montréal workshop) [18]. The experts reached consensus that the label BE should be used when any type of columnar metaplasia (CM) is confirmed by histology, with description of presence or absence of IM. There are different evidence -based considerations which support this non-restrictive definition of BE. The density of goblet cells in any segment of CM is dependent on a variety of factors, such as patient age, length of the columnar-lined segment, and number or location in which biopsies are obtained [19-22]. The most endoscopists in routine practice do not take enough biopsies to screen adequately for IM so many patients are being incorrectly assigned to diagnosis "not BE" on the basis of a technically inadequate diagnostic process. The analysis of 1646 biopsies from 125 consecutive patients with suspected endoscopic CM showed that goblet cells were identified in 68% of patients when a mean of 8 biopsies were obtained but only in 34.7%, when a mean of 4 biopsies were evaluated [22]. The goblet cell density is greater near the proximal

neo-squamocolumnar compared to the distal area of CM [21]. The findings that the nongoblet columnar epithelium possess "intestinal" features and exhibit molecular and genetic abnormalities similar to those seen in BE with IM are other data supporting the use of non-restrictive definition of BE [23, 24]. The immunohistochemical study of the expression of different markers of intestinal differentiation as DAS-1, villin, and CDX-2 showed reactivity in both types of metaplastic (goblet and nongoblet) epithelium [23]. Abnormal DNA has been found recently to be present to similar degrees in esophageal CM of all types, making the malignant potential of "negative for IM-type" BE also probable [24]. In confirmation of Montreal definition of BE are the data that dysplasia and cancer may arise in nongoblet CM [25, 26]. It was found that there is no statistical difference in the risk of dysplasia or EAC in patients either without ( $n= 322$ ) or with ( $n= 612$ ) IM in index biopsies from metaplastic CM [25]. In another study endoscopic surveillance (median follow-up of 12 years) of patients with BE according "any metaplasia" was evaluated. It was reported that EAC developed in the 399 patients in whom IM was not found, at a rate that did not differ significantly from the 379 patients in whom IM had been demonstrated [26].

All these data confirm that the more correct definition of BE is that of Montreal definition.

## 2.2. Diagnosis of BE

BE is diagnosed by both endoscopy and histology. On endoscopy, it is suspected by the presence of "tongues" as extensions of salmon-colored mucosa above the GEJ. According to Montreal classification endoscopically suspected esophageal metaplasia (ESEM) describes the endoscopic findings consistent with BE that await histological evaluation [18]. The term BE should not be used before histological confirmation. Multiple, closely spaced biopsies are necessary to characterize ESEM. Standard protocol includes four quadrant biopsies performed at every 1 or 2 cm intervals from the proximal GEJ extending to the squamocolumnar junction. It was decided that all types of histologically proven oesophageal CM, including gastric or specialized IM should be included in the diagnosis of BE. The presence or absence of dysplasia should be evaluated. Morphologically, dysplasia is defined as "unequivocal neoplastic epithelium confined to the basement membrane, classified as LGD and HGD. Because of significant interobserver variations, the diagnosis of dysplasia should be confirmed by at least one additional pathologist, preferably one who is an expert in gastrointestinal (GI) pathology.

### 2.2.1. Endoscopy in BE

Endoscopy is the only practical option for the routine diagnosis and surveillance of esophageal CM. The first steps of endoscopic assessment are the recognition of BE and the grading of it's extent. BE has been divided into long-segment (>3 cm), short-segment (1-3 cm), and ultra-short-segment (< 1cm) categories [27]. The first systematic and standardized method for description of the extent of BE, which was carried out by the International Working Group for the Classification of Oesophagitis (IWGCO), resulted in the Prague C & M Criteria [28]. They were developed on the base of interpretations of purpose-recorded and standardized endoscopic video recordings. The C-value describes the length of circumferential metaplasia, whilst the M (for maximum) value describes the most upper point of any tongue of metaplasia. These

values are referenced to the position of the GEJ and are given in centimeters. The validation of the Prague C&M Criteria showed good inter-observer agreement on the position of the GEJ and also on C&M-values greater than 1 cm. The agreement on presence of metaplastic segments less than 1 cm in length was unacceptably poor. A second, independent validation study of the Prague Criteria was done in several Asian countries [29]. It confirmed the data of the IWGCO and showed that the endoscopist can use the criteria successfully also in regions with a low prevalence of BE.

The most misdiagnoses of BE are related with the endoscopic features in patients with a hiatus hernia. This is due to failure to spend enough time in observing the region of the diaphragmatic hiatus and the upper end of the gastric mucosal folds at a relatively low level of distension [12]. Accurate location of the GEJ is of diagnostic importance, since mucosa of columnar appearance above this level has to be concluded to be metaplastic. The histological examination cannot reliably differentiate between metaplastic esophageal mucosa and the mucosa of the extreme upper stomach. Correct interpretation of biopsies around the GEJ depends on the accuracy of their location by endoscopy. Current guidelines recommend use of the Seattle protocol as the primary approach to assessment of the mucosa in BE with and without dysplasia [14, 15]. It was found that the protocol, with biopsies from all visible abnormalities and random four-quadrant biopsies every 1cm starting from the top of the gastric folds up to the GEJ, is superior to random biopsies or 2-cm biopsies in detecting early cancers arising in BE with HGD. In a study of 45 patients with BE with HGD, the 2-cm protocol (four-quadrant biopsies every 2 cm) missed 50% of cancers that were detected by a 1-cm protocol in Barrett's segments of 2 cm or more length without visible lesions [30]. In last years, with the improvement of image resolution of endoscopes, there is convincing evidence that guided biopsy is more sensitive for detection of dysplasia and EAC than blind biopsies [31-33].

The significant increase in image resolution by high-resolution endoscopy and high definition monitors (HDTV) is the most important recent improvement in endoscopic imaging in general, and particularly with regard to detection of early neoplastic lesions [34].

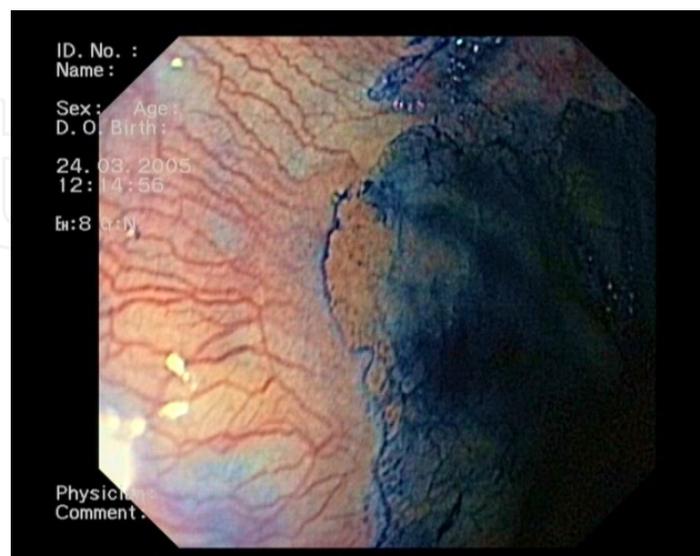
These require updating to place greater emphasis on visually guided biopsy with a high-resolution endoscopic system [12]. Given that general endoscopists are currently inadequately skilled and equipped for recognition of mucosal areas of concern, it is probably best that blind biopsies are also taken at least for the present [12]. Many imaging modalities as chromoendoscopy/magnifying chromoendoscopy, narrow band imaging (NBI) with/without magnification, autofluorescence imaging (AFI), and confocal microendoscopy can improve identification of abnormal areas and their targeting biopsy, and finally increase identifying HGD and early neoplasia [32, 34, 35].

*Chromoendoscopy* involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy [36]. Methylene blue chromoendoscopy (MBC) has been reported to improve the detection of dysplasia in BE [37]. However, other authors found that MBC may be less effective in detecting dysplasia and also labor-intensive, and operator-dependent [38-41]. A meta-analysis of nine studies showed that staining with methylene blue did not significantly increase the detection of specialized IM and dysplasia compared with random biopsies [41]. In addition, methylene blue has been shown

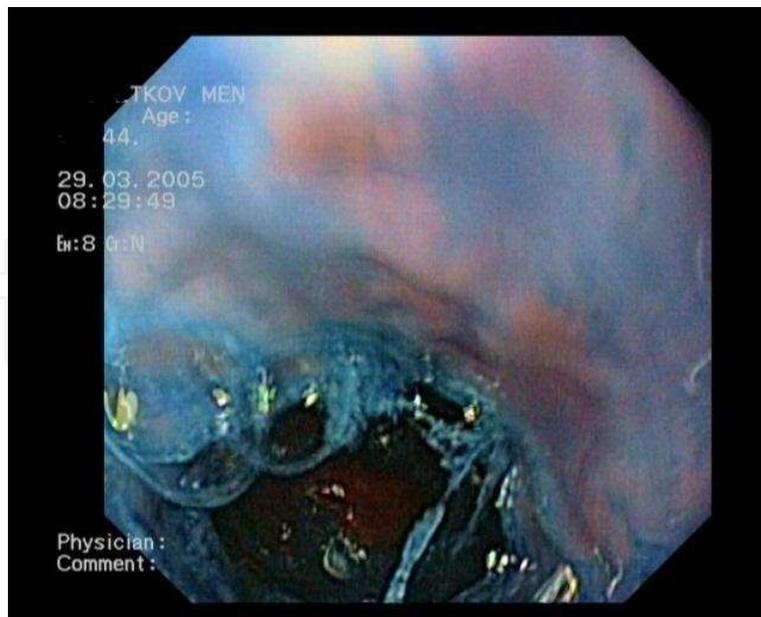
to induce cellular DNA damage when is photoexcited by endoscopic light and therefore it may be potentially carcinogenic [42]. It has been demonstrated that combination of chromoendoscopy with magnifying endoscopy improves the inspection of the mucosal surface pattern and may differentiate HGD from NDBE [43]. Our experience shows that magnifying chromoendoscopy with methylene blue and indigo carmine is helpful for more correct distinguishing between the focal metaplastic as well as dysplastic epithelial lesions in patients with BE [44]. It also increased the diagnostic rate of islands with Barrett's IM or dysplasia after endoscopic therapy (figure 1, 2, 3). *NBI* is a high-resolution endoscopic technique that enhances the fine structure of the mucosal surface. The improved imaging of mucosal patterns is resulted from the relatively high-intensity of blue light in *NBI* which reveals superficial structures because of its shallow penetration depth. In addition, absorption of blue light by hemoglobin enables detailed inspection of the microvasculature [45]. Using high-resolution endoscopy and *NBI*, the same authors have proposed a classification of mucosal surface characteristics of BE, which may be useful in the characterization of dysplastic and nondysplastic tissues. In their study of 200 mucosal areas in 63 patients with Barrett's, a regular mucosal and vascular patterns, and flat mucosa (i.e. without any villi or pits) were significantly associated with IM, while all areas with HGD exhibited irregular mucosal and irregular vascular patterns, or abnormal blood vessels. *AFI* is based on the tissue autofluorescence in exposition to light of a short wavelength and certain endogenous biological substances (fluorophores). In BE, normal and early neoplastic tissues have different autofluorescence properties [34]. According to our experience, delta-aminolevulinic acid/Protoporphyrin IX (5-ALA/PpIX) is a very good fluorescent marker for dysplasia and tumor detection in esophagus [46, 47]. *AFI* technology has been incorporated into high-resolution endoscopy systems. Using such a system, one study reported that the total number of detected lesions was doubled and one-third of the patients with HGD or early cancer were diagnosed with *AFI* when compared with high-resolution endoscopy alone [48]. The limitation of *AFI* was a relatively high rate of false positive findings. In later study the same authors used a combination of high-resolution white light imaging, *AFI* and *NBI* and they called endoscopic tri-modal imaging (ETMI) [49]. They found that *AFI* increased the sensitivity and *NBI* reduced the false positive rate, thus improving specificity. These findings were confirmed in two multicenter studies [50, 51]. The first study demonstrated that *AFI* increased the sensitivity for detecting early neoplasia in BE from 53% to 90%, and the inspection with *NBI* of suspicious areas reduced the false positive rate from 81% to 26% [50]. The other study, which was a multicenter randomized crossover study, compared ETMI to standard endoscopy in 87 patients referred for early neoplasia [51]. There was a significant increase of the targeted detection of early neoplastic lesions with *AFI* compared with standard video endoscopy. It was summarized that ETMI did not improve the overall detection of early neoplasia. *Confocal Endomicroscopy* derived from laser scanning confocal microscopy and allows subsurface analysis of the intestinal mucosa or *in-vivo* histology during the endoscopic procedure. The potential of this technique is to allow real-time histopathological diagnosis and eventually reducing the need of taking biopsy specimens. In a study of 63 patients using laser confocal microscopy, BE and associated neoplasia could be predicted with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively [52]. But the limitation of this technique is the need of significant operator expertise in the use of the probe and in the interpretation of

the real-time microscopic details. Further studies are needed to elucidate the clinical relevance and cost-effectiveness of in vivo pathology as a decision-making tool during endoscopy. The review on advanced endoscopic imaging in BE by M. Kara, W. Curvers and J. Bergman [34] may have practical importance. The authors summarized that the new endoscopic imaging techniques should be regarded as complementary to each other. High-resolution endoscopy should be the cornerstone and basic equipment for endoscopists who have a high volume of BE patients. On the basis of their own experience, the authors gave recommendations regarding advanced endoscopic imaging of BE. The first and the most important element is the use of a systematic and thorough approach for the initial endoscopic inspection. Targeted biopsy sampling is the main aim of this process. The use of a high-quality endoscope is of great importance in this aspect. Special attention should be given in the area between 12 and 6 o'clock in the endoscopic view, because in this region the neoplastic lesions are found very often. Most endoscopists are not familiar with the endoscopic appearance of early neoplastic lesions in BE and practical knowledge is required. Subtle lesions are generally shown but not necessarily recognized as such by the endoscopists ("the eyes see what the mind knows). Regarding new complementary imaging techniques, no technique improves sensitivity significantly above high-resolution endoscopy in BE surveillance. Autofluorescence imaging may improve targeted lesion detection but it may not improve overall sensitivity. Optical magnification with or without indigo carmine chromoendoscopy or NBI may be useful for precise delineation and characterization of lesions. Other techniques are of even more limited use.

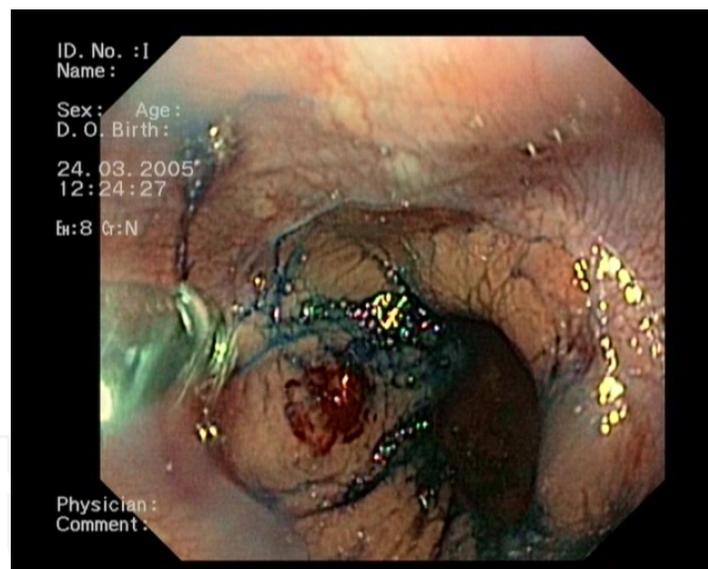
Currently, *endoscopic ultrasonography (EUS)* is used to rule out lymph node metastasis. This method is accepted for the accurate locoregional staging. Its use is recommended in visible lesions and or in suspicion of early EAC. EUS is required in order to differentiate between patients with cancer in BE in whom endoscopic therapy is suitable and those in whom surgical treatment is required [53].



**Figure 1.** Magnifying chromoendoscopy with methylene blue in a BE patient.



**Figure 2.** Magnifying chromoendoscopy with methylene blue after argon plasma coagulation of BE.



**Figure 3.** Magnifying chromoendoscopy with methylene blue after mucosal resection of BE.

### 2.2.2. Histology in BE

The normal squamous epithelium in BE is replaced by a mixture of cell types resembling gastric and or intestinal mucosa. The cardiac type BE contains mucus-secreting columnar cells; the fundic type BE is characterized with the parietal cells and chief cells; and the specialized intestinal epithelium is indicated by the presence of goblet cells. Morphologically, goblet cells can be identified by their large, cytoplasmic vacuole filled with abundant mucin on routine

hematoxylin-eosin stain. The so called 'pseudogoblet cells' represent injured foveolar epithelial cells by concomitant GERD and resemble goblet cells with their abundant accumulation of cytoplasmic mucin [54]. But compared with true goblet cells, the mucin in pseudogoblet cells is neutral and stains slightly eosinophilic on hematoxylin-eosin stain. The biopsies specimens may also show a multilayered epithelium, which is characterized basally located squamous epithelium overlaid by superficial columnar epithelium. It is thought that this epithelium represents an early stage in the development of esophageal CM [55]. The cases with BE also exhibit stromal alterations as duplication and fragmentation of the muscularis mucosae (MM), increase in the number of blood vessels and lymphatics, and changes in the inflammatory cells [56, 57]. As already mentioned, the histological diagnosis of BE cannot be made when the exact site of biopsy is not known. Beside this, the IM of the distal esophagus and upper stomach are histologically indistinguishable. IM in a biopsy taken near the EGJ could be a part of a multifocal atrophic gastritis secondary to *Helicobacter pylori*. The etiology and significance of cardiac IM has become a topic of interest, because of rapidly rising incidence of gastric cardiac adenocarcinoma [58]. One study showed that the dysplasia risk of BE patients is significantly greater than in IM from the cardia, indicating two potentially different clinical processes [59]. Because of the difficulty in determining the precise site of a biopsy specimen in some cases and the inability to distinguish IM of the esophagus from gastric origin (cardiac IM) by routine methods, various immunohistochemical markers have been studied to be useful for this distinction. For example, cytokeratin (CK)7 and CK20 immunohistochemical staining has been used to differentiate IM of the esophagus versus gastric cardia [60]. It was found that Barrett's mucosa displays CK20 expression in the surface epithelium and superficial glands with no staining in the deep glands, but CK7 shows strong diffuse positivity in superficial and deep glands. On the other hand, gastric IM displays focal CK20 staining of both the superficial and deep glands, but only weak and variable CK7 labeling in the deep glands. Our results showed similar results [61]. Unfortunately, other studies have been unable to show the reliability of CK7 and CK20 immunoreactivity in distinguishing short-segment BE from IM in gastric cardia and corpus [62-64].

*Histologic grading of dysplasia* represents the "gold standard" method of estimating cancer risk and surveillance in patients with BE [14, 15]. The decision for subsequent patient management is also based on this evaluation. Clinically relevant diagnostic categories, include negative for dysplasia, indefinite for dysplasia, positive for dysplasia (either LGD or HGD), intramucosal adenocarcinoma (IMC), and invasive adenocarcinoma, which correspond to the Vienna classification of gastrointestinal epithelial neoplasia [65]. The term "dysplasia" is still used more widely than intraepithelial neoplasia [66]. In the 2000 WHO classification the term "dysplasia" was deserted for lesions which are characterized by morphological changes resulting from clonal alterations in genes and which carry a predisposition for progression [67]. But the new 2010 WHO classification brought back the term "dysplasia" officially and concluded that dysplasia is the more appropriate term for morphological changes indicative of precancerous lesions especially in the gastrointestinal tract [68]. Pathologic diagnoses of moderate dysplasia and in situ carcinoma (which is equivalent of HGD) are not recognized in current classification schemes.

Barrett's dysplasia is recognized histologically and graded into LGD or HGD by a combination of architectural and cytologic abnormalities. When no features of dysplasia are found, the diagnosis is negative for dysplasia. When the findings are uncertain, the category indefinite for dysplasia is applied. The grading in BE dysplasia is analogous to that of dysplasia complicating inflammatory bowel disease [69]. *NDBE* shows an absence of atypical cytologic or architectural features characteristic of dysplasia. Regenerating epithelium is characterized with "surface maturation", which included a progressive increase in mucin content and reduction in nuclear/cytoplasmic ratio from the bases of the glands to the mucosal surface. In some cases metaplastic epithelium may also demonstrate slight baseline architectural distortion, such as occasional branching and budding of crypts, atrophy, irregularity. "*Indefinite for dysplasia*" does not represent a discrete biologic entity. Biopsies that are classified in this category showed intact or mild distorted glandular architecture and the cytologic changes are also mild. The uncertainty whether or not dysplasia (generally low-grade) is present is usually due to the effects of active inflammation, erosion, or ulceration. This diagnosis may also be assigned to biopsies in which technical artifacts as thick or overstained sections or with lack of surface epithelium. These cases need rebiopsy after control of inflammation. *LGD* in BE is characterized mainly with cytologic changes. The nuclei are enlarged, elongated, hyperchromatic, and stratified, mostly confined to the basal half of the cell cytoplasm. In *LGD*, the nuclear polarity is preserved as the long axes of the nuclei remain perpendicular to the basement membrane. The cytoplasm is typically mucin-depleted and shows an increased nuclear/cytoplasmic ratio. These changes involve the crypts and there is lack of surface maturation. Glands may also demonstrate slight crowding or other mild architectural abnormalities. *HGD* in BE exhibits a greater degree of cytologic and/or architectural aberration. Characteristic architectural changes include increased budding, branching, and crowding, villiform surface configuration, and the presence of intraluminal bridges or papillae. Cytologic features include marked nuclear pleomorphism, loss of polarity, and full-thickness nuclear stratification. Mitotic figures, especially atypical ones, are often present and may involve the surface epithelium. *IMC* is diagnosed when single or small clusters of malignant cells infiltrate the lamina propria or MM but has not invaded the submucosa. This lesion is associated with a small risk of regional lymph node metastasis and, as such, is staged as T1a [70]. In contrast, *AEC* that invade into the submucosa are considered submucosal invasive carcinoma and the risk of lymph node metastases increases dramatically with depth of invasion. There is significant interobserver variation in the assessment of dysplasia in BE [39, 47, 56, 67-70]. This fact is related to various reasons. The reactive changes, particularly in the setting of active inflammation, overlap with those seen in dysplasia. Given the subtle gradation of changes from baseline atypia to *LGD* to *HGD* consecutively, it is not surprising that there is a variation in the diagnosis of degree of dysplasia. One study reported that the variation was most evident at the low end of the histologic spectrum or in distinguishing *NDBE* from changes that are indefinite for dysplasia or *LGD* [71]. In other study, 65% of 20 general pathologists misdiagnosed a case of *LDG* such as 25% classified it as normal, and the other as either moderate or *HGD* [72]. It was reported that general pathologists had only poor to fair interobserver agreement on the diagnosis of *LGD* [73]. In a study from the Netherlands, 85% of *LHD* cases diagnosed by general pathologists were downgraded to "not dysplasia" on review by expert

pathologists [74]. These results lead to the recommendation that the diagnosis of LGD should be reviewed by an expert of GI pathology. At the other end of the spectrum, the differentiation between HGD and IMC is also difficult [75]. There are no objective criteria to distinguish HGD from IMC because endoscopic biopsies almost never sample the submucosa. The pathologic diagnosis of HGD or EAC shows excellent interobserver agreement among pathologists with extensive experience of BE but it is not so among general pathologists [72, 73]. In practice each biopsy report of HGD should also be review by an expert of GI pathology. Recent studies analyzed the histopathologic criteria in biopsies that appear to help the distinguishing between HGD and EAC, and those who have EAC elsewhere in the metaplastic mucosa [76, 77].

In last years, with the wide use of ablative and nonablative endoscopic therapy for BE with and without dysplasia, the role of histology increased. Because of ablation, patients develop islands of re-epithelialized squamous mucosa as it is called "neosquamous epithelium" (NSE). The last may also develop in patients treated with high-dose proton pump inhibitors (PPIs), but without ablation [78, 79]. The findings of various studies strongly suggest that NSE has no malignant potential and represents a successful outcome of ablation [19, 80]. A problem with NSE is that a residual Barrett's epithelium or dysplasia may persist underneath NSE, because they remain invisible on endoscopy. The prevalence rate of buried Barrett's or buried dysplasia is variable and dependent on the type of ablative therapy. The buried dysplasia is difficult to interpret because the maturation to the mucosal surface cannot be evaluated in the presence of NSE. The biologic potential of buried BE is the subject of many investigations [19, 81, 82]. The available data suggest that residual buried dysplasia, continues to be at risk for malignant progression. In contrast to non-tissue acquiring ablative therapies, endoscopic mucosal resection (EMR) is a modality designed to remove mucosa and superficial submucosal tissue [19]. In this way, it allows more accurate histologic evaluation and grading of dysplasia and determination of location and depth of invasion by adenocarcinoma when present. EMR is a valuable diagnostic tool which allows change of diagnosis of BE dysplasia when compared with mucosal biopsies. One study reported that 37% of cases of BE with dysplasia showed a change of dysplasia grade in pre-EMR biopsies compared with EMR specimens. Of them, 21% of biopsies were with under-reported grade of neoplasia and 16% of biopsies were with over-reported grade [83]. In another study it was found that 24% of cases with HGD in biopsy specimens showed an increase in grade to IMC, and 40% of patients with IMC had their stage increased to submucosal invasive carcinoma by evaluation of EMR specimens [84]. There is also a greatly improved diagnostic agreement between pathologists when evaluating dysplasia in EMR specimens compared with biopsies [85]. This results is related to the larger tissue sampling compared with biopsy specimens and the ability to evaluate mucosal landmarks, such as double muscularis mucosae. Evaluation of depth of invasion in EMR specimens is important because the rate of lymph node metastasis has been shown to correlate with depth of invasion [19, 70]. The evaluations of the presence or absence of lymphovascular invasion and the status of the lateral and deep tissue margins are also of prognostic significance [85-88]. In this aspect, the method of processing EMR specimens and their orientation is very important. In summary, the problems in the diagnosis of dysplasia included difficulties relating to sampling errors, the distinction of reactive changes versus dysplastic ones, differences in observer interpretation of the diagnosis of dysplasia and in the differentiation of HGD from

invasive carcinoma. Requiring confirmation of a diagnosis by a second pathologist is important in taking the decision for management.

The utility of many immunohistochemical and molecular markers has been studied as adjunctive tool for the diagnosis of dysplasia and also for identifying the cases of risk for malignant progression. Unfortunately, only a few markers show such a potential, including studies of DNA ploidy by computerized morphometric analysis, the expression of proliferation antigen Ki-67 (MIB-1) and of tumor suppressor proteins p53 and p16. By flow cytometry, it was found that patients with diploid baseline biopsies showed a significantly lower rate of cancer progression compared with patients with either aneuploidy or an increased 4N fraction (tetraploidy) [89]. Immunohistochemical staining for MIB-1 showed increased expression from normal squamous epithelium to CM to dysplasia and to invasive carcinoma [90, 91]. There are also alterations in the pattern of localization of staining. In NDBE the expression of MIB-1 is limited to the bases of the crypts, whereas in dysplasia it extends upward the mucosal surface. A recent study suggests that the combined use of MIB-1 and p53 staining reduces variations in the diagnosis of BE dysplasia [91]. Immunostaining for p53 has been widely studied, but the results have been controversial [19, 91, 92]. The frequency of positive immunostaining for p53 has been shown to correlate with higher grades of dysplasia, and, in some cases, is associated with an increased risk of cancer. Allelic loss of p16 (p16 LOH), which results in block of cell cycle in the G1-S phase and provides survival advantage of the cells, is common in EAC and appears to be an early event in the BE-dysplasia-adenocarcinoma sequences [94, 95]. It is well-known that the carcinogenesis is a multi-step process that occurs as a result of alterations in many different genes. Because of that, it is clear that there is no single molecular marker that will allow with high sensitivity to predict the neoplastic risk in BE.

### 3. Screening for BE

The most appropriate method for both diagnosis and surveillance of BE is upper GI endoscopy. There are no concrete guidelines for selecting patients who should undergo screening for BE, and this decision is currently made case by case.

The cost-effectiveness of upper GI endoscopy in patients with reflux symptoms, most of whom will never develop cancer is discussed. Approximately 40% of adults in the US experience symptoms of heart burn at least once a month and about 20% report these symptoms once a week [96]. So a large proportion of adult US population would be eligible for screening for BE based on this screening criteria. A study from Sweden estimated that BE was present in 1.6% of the general population [97]. BE patients are usually white, middle-aged males, often overweight [98]. The male-to-female ratio is 2:1 [99]. According to a retrospective study of 2100 patients undergoing upper GI endoscopy, the prevalence is higher among Whites (6.1%) as compared with Hispanics (1.7%) and African Americans (1.6%) [100]. The relationship between BE and gastroesophageal reflux symptoms is well known, but many patients with biopsy-proven BE do not report such symptoms. In one study, BE was identified in 50 of 300 consecutive patients (16.7%) undergoing screening or surveillance colonoscopies who also

received upper GI endoscopy [101]. Among them, 19.8% reported GERD symptoms, whereas 14.9% were asymptomatic and the symptom questionnaires were unable to predict the presence of BE. It has been shown that 40% of patients with EAC also do not report heartburn or regurgitation [102]. By the other hand, even when BE is diagnosed, a vast majority of these patients will not develop EAC during their lifetime [10]. Studies have shown that the overall mortality rate in patients with BE is closely similar to that of the general population and EAC mortality is an uncommon cause of death in these patients [103, 104]. The most patients with BE die due to causes other than EAC. From this point of view, the current position of the AGA is that inadequate evidence exists to endorse endoscopic screening for BE based solely on the presence of GERD symptoms [14]. The decision regarding screening should be individualized after discussion about the benefits and limitations of screening with the patient. Other professional organizations also do not recommend routine screening for BE [13, 15, 105, 106]. The American Society of Gastrointestinal Endoscopy (ASGE) guidelines proposed that an initial screening endoscopy is appropriate in select patients with frequent, chronic, long-standing GERD (>5 years), who are white, males, aged >50 years, and those with nocturnal heart burn. No further screening is needed if the initial endoscopy is negative for BE [106]. Although the upper GI endoscopy with biopsy is the gold standard for the diagnosis of BE, other endoscopic and non-endoscopic alternative methods of the screening for BE are studied. One of them is capsule endoscopy, which is less invasive and offers increased acceptability of screening [107]. One study, using this technique for identifying BE, showed 67% sensitivity and 84% specificity [108]. A recent meta-analysis of nine studies including 618 patients, demonstrated pooled 77% sensitivity and 86% specificity for diagnosis of BE. When IM is used as the reference standard, the reported sensitivity and specificity are 78% and 73% respectively [109]. It was concluded that capsule endoscopy of esophagus has a moderate sensitivity and specificity for the diagnosis of BE in patients with GERD. The EGD remains the modality of choice for evaluation of suspected BE. Capsule sponge esophageal cytology appears to be one relatively low-cost, non-endoscopic screening method for BE which is not yet fully validated and not generally available [110-112]. A cytology sponge is compressed and encased in a gelatin capsule attached to a string. The capsule, but not the end of the string is swallowed. After a few minutes in the stomach, the liberated sponge is dragged back up the esophagus. The presence of BE is based on the expression of trefoil factor 3, which is a specific marker for esophageal CM. A pilot study in 96 controls and 36 BE patients found this test to have a sensitivity of 78% and a specificity of 94% for presence of BE [110].

According to the current data, there are no evidence that routine screening for BE will increase the rate of diagnosed cases of BE with or without dysplasia, or EAC.

#### **4. Surveillance of patients with BE**

Surveillance endoscopy is intended to detect neoplastic progression at an early stage and prevent cancer-related death. As pointed above, the histologic diagnosis and grading of dysplasia represents the "gold standard" method of assessing neoplastic risk in patients with BE. Despite limitations of the scientific evidence, several professional societies offer guide-

lines for endoscopic surveillance of patients with BE. Because the risk of EAC increases as NDBE progresses in a sequential manner to LGD and HGD, the frequency of surveillance is based on the grade of dysplasia. The recommendations of ACG, ASGE and AGA are very similar [13, 14, 106, 113]. Surveillance upper GI endoscopy should include 4 quadrant biopsies from every 1-2 cm of Barrett's mucosa and separate biopsies of areas of mucosal abnormalities if present. In cases with NDBE or LGD 2-cm protocol is recommended but for patients with HGD the 1-cm protocol is needed. MRE for all mucosal nodules or irregularities is recommended. When NDBE is found on biopsy, periodic endoscopic surveillance to rule out progression of disease is advocated. Current surveillance guidelines recommend 2 follow-up endoscopies with biopsy within 1 year of the diagnosis of BE and follow-up every 3 to 5 years thereafter. Surveillance endoscopy is also the mainstay of management for BE with LGD. The diagnosis of LGD has to be confirmed by an expert GI pathologist. If LGD is confirmed, an upper endoscopy should be repeated 6 months later to rule out a higher grade of dysplasia. If repeat biopsies show LGD as the worst histologic grade, annual follow-up endoscopies with biopsy are recommended thereafter as long as dysplasia persists. If regression is noted, surveillance every 3 to 5 years is recommended as with NDBE. For patients with HGD, the recommendations include expert confirmation of HGD and repeat endoscopy with biopsies within 3 months to exclude carcinoma. Patients should be counseled regarding their therapeutic options including continued 3 months surveillance, esophagectomy, or ablative therapies.

The effectiveness of surveillance of patients with BE is also discussed. By one hand, it has been demonstrated that patients with surveillance-detected EAC are diagnosed at an earlier stage and have a better prognosis than those who present with symptomatic tumours [114, 115]. These data support the effectiveness of endoscopic biopsy surveillance for early detection of EAC. However, there are no prospective data showing survival advantage with surveillance. As noted above, the majority of patients diagnosed with EAC have not a prior diagnosis of BE. A study reported that only 3.9% of the patients had a BE diagnosed before their EAC [116]. A review of reports on mortality in BE patients undergoing surveillance found that their risk of malignant progression is low and most of them die of other causes, especially cardiovascular, without development of HGD or EAC [117]. This undermines the cost-effectiveness of BE surveillance and supports the search for valid risk stratification tools to identify the minority of patients that are likely to benefit from surveillance. The majority of patients with LGD regressed and had a cancer incidence similar to all BE patients [9]. HGD is highly heterogeneous with regard to progression to EAC and rates of progression vary substantially in different studies. The reported 5-year cumulative incidences of EAC range from less than 10% to 59% [10, 89]. It may be concluded that even if current surveillance techniques are effective, they are unlikely to substantially impact the population's mortality from EAC and better methods are needed to identify at risk patients [116].

## 5. Therapy of BE

The management of patients with BE includes following major aims: treatment of the associated GERD, endoscopic surveillance to detect HGD or EAC, and treatment of dysplasia or IMC, as well as prevention of cancer.

### 5.1. Antireflux therapy

If one goal of this treatment is the control of GERD symptoms and heal esophagitis, another should be the regression of BE, and prevention of progression to EAC.

*Lifestyle modifications* can help control symptoms only in some patients with BE by increasing esophageal acid clearance and decreasing the incidence of reflux events [118]. *Acid suppressing medication* are the standard therapy for GERD in BE patients. Antisecretory treatment by PPIs or histamine-2 receptor antagonists (H2RAs) are usually used to decrease esophageal acid exposure, symptom relief, and to heal esophagitis. More complete esophagitis healing and heartburn relief is observed with PPIs versus H2RAs and occurs nearly twice as fast [119]. In addition, antisecretory effect of H2RAs failed to heal esophagitis in a high proportion of BE patients [12, 120]. Twice-daily standard dose of PPIs has been usually recommended for BE patients. A large meta-analysis of 136 randomized, controlled trials included 35978 patients with reflux esophagitis showed that taking twice-daily standard dose of PPIs showed modest benefit [121]. Once-daily standard dose PPIs fails to heal esophagitis or control reflux-induced symptoms in BE patients [12]. Esophageal pH monitoring studies have shown that many BE patients treated with once-daily PPIs in the morning still have high levels of esophageal acid exposure, especially at night [122]. A second dose, preferably before dinner, has been usually effective, given that BE patients have increased nocturnal esophageal acid exposure. Further increasing of PPIs dose is sometimes needed. The same authors showed that high-dose PPIs (esomeprazole 40 mg twice daily) for 6 months achieved higher levels of gastric acid suppression and control of oesophageal acid reflux and symptoms. When comparing GERD patients with and without BE, the BE group are characterized with abnormal oesophageal motility, reduced lower oesophageal sphincter pressures, more severe and prolonged pathological supine oesophageal reflux, as well as greater hiatal hernia size [123]. Patients with BE also have significant nocturnal gastric acid breakthrough. In patients with BE, oesophageal acid exposure is often difficult to control with commonly used dosages of PPIs [124, 125]. The underlying high levels of acid reflux may require greater levels of acid suppression. However, whether acid secretion is increased in BE is controversial [126, 127]. In 30–62% of BE patients on different PPIs have demonstrated abnormal oesophageal pH profiles, despite adequate control of reflux symptoms [123, 128, 129]. Esomeprazole up to three times daily decreases this value to 16% [130]. In one recent trial an adequate control of intra-oesophageal acidity in 97% (14/15) of patients with primarily short-segment BE treated by Omeprazole-sodium bicarbonate twice daily was demonstrated [131]. In addition a 100% control of nocturnal oesophageal reflux assessed as 48 h supine intra-oesophageal pH was found. These results demonstrated excellent suppression of daytime and nocturnal oesophageal pH.

Several observational and prospective studies have assessed *regression of BE* in response to antisecretory therapy with conflicting results. At this time there is no evidence that H2RAs or PPIs can completely reverse this condition. Acid suppression with H2RAs has not been associated with significant regression of BE [132]. There are reports high-dose PPIs may decrease the length of BE, but not in all studies [133-135]. The incidence of complete regression in response to PPIs depends of length of Barrett's segment. It has been reported as approximately 2.4% in long-segment BE and 7.1% in short-segment BE [136, 137]. A small number of

prospective studies showed that normalization of acid exposure leads to regression of BE, but other not confirmed these results [132]. It is discussed that control of pH alone may not be sufficient to cause significant regression. About half of patients on PPIs therapy demonstrated partial regression of BE. Development of new squamous islands or increasing number and size of islands within the metaplastic segment were observed [134, 135]. In one long-term endoscopic cohort study 188 BE patients treated with PPIs for 1 to 13 years were prospectively followed (mean follow-up 5 years). During the study period, no decrease in the length of BE was noted, but 48% of the patients developed squamous islands in the BE segments. The squamous islands development correlated with the duration of PPIs therapy but not with the PPIs dose [134]. The data suggest that very long PPI therapy is associated with a minor reduction of extent of metaplasia, but with appearance of more squamous islands. These changes are most unlikely to be associated with any useful reduction of cancer risk. Other authors discussed that chronic PPIs use can increase the risk of EAC or gastric cancer [138]. From other point of view, the increased incidence of these cancers might have been related to the original condition for which PPIs was prescribed rather than the PPI itself [135].

Some studies suggest that acid reflux plays a key role in the *progression* to dysplasia and EAC. There is indirect evidence that acid exposure increases proliferation and decrease apoptosis in BE [139]. Acid exposure may induce DNA double-strand break (DSB), increase reactive oxygen species (ROS), and activate mitogen-activated protein (MAP) kinase pathways in BE, suggesting its potential role in carcinogenesis [135]. Treatment with high-dose PPI was associated with a reduction in epithelial cell proliferation, as measured by proliferating cell nuclear antigen Ki67, in both the crypt and glands and the luminal surface cells [140]. The reduction of inflammation might have resulted from anti-inflammatory effects which may be exerted by PPIs independently of acid inhibition [141]. Another study showed that high-dose PPI (esomeprazole 40 mg twice daily) for 6 months significantly decreased inflammation and epithelial proliferation, but without reversal of aberrant DNA methylation compared with the doses of PPIs before entering the study [142]. However, the clinical significance of the protective benefit of antisecretory therapy is not clear yet. Some data showed a persistence of mucosal markers for mucosal injury during partial control of esophageal acid exposure. The lack of detectable effect on risk for EAC from routine PPI therapy could be due to under-treatment. It has been proposed that twice-daily PPI, given at a dose to "normalize" levels of acid reflux, might reduce EAC risk [143]. This is an optimistic speculation, in light of the negative data for a cancer-protective effect of antireflux surgery [144, 145]. In addition, the study of [142] demonstrated that twice-daily PPIs therapy has no impact on mucosal markers of injury. Despite all, some observational studies showed that acid suppression with PPIs reduce the risk for development of dysplasia in patients with BE and therefore potentially reduce the risk of developing cancer [146-149]. These studies were uncontrolled and retrospective, and information on the effectiveness of the control of oesophageal acid exposure was not available because no pH monitoring was included. When compared with H2RAs, PPIs therapy has been shown to be more efficacious in preventing the progression of BE to both dysplasia and EAC [146, 149]. In one of these observational studies on 236 BE patients, the incidence of any grade dysplasia was significantly lower amongst patients receiving PPIs compared with those not treated by PPIs or treated by H2RAs [146]. A longer duration of PPIs use was associated with

less frequent occurrence of dysplasia. Other authors demonstrated a lower incidence amongst patients being prescribed versus not being prescribed a PPI (7.4% versus 14.1%) [150]. These data suggested that initiating PPI therapy soon after the diagnosis of BE may prevent this progression [148, 150]. In summary, acid suppressing therapy, especially by PPIs, is effective to treat GERD symptoms, heal reflux esophagitis and prevent related complications as it is for patients without BE. Evidence on the chemopreventive effect of PPIs for BE is indirect and not confirmed by a long-term prospective controlled data [14, 151]. The risks /benefit ratio of long-term PPIs therapy should be assessed and discussed carefully with BE patients in the context of their overall health status and medication use. In addition there is no evidence that higher than standard doses of PPIs are needed to reduce the cancer risk.

It has been discussed that *antireflux surgery* using fundoplication eliminates acid reflux and provides better control of GERD than PPIs in BE patients [132]. This effect is not different than those of PPIs. Optimal candidates for antireflux surgery include those who lack major comorbidities and demonstrate incomplete response to PPIs therapy [15]. Antireflux surgery should depend on patient preference and the severity of reflux symptoms despite PPIs therapy, but not for definitive management of Barrett's metaplasia. The concept that adequate reflux control following antireflux surgery is necessary to reduce the rate of progression of BE is supported by some studies [152, 153]. They suggest progression is significantly more likely to occur with a failed fundoplication and persistent reflux. The hypothesis that antireflux surgery could reduce the risk for development of EAC by transforming a highly aggressive esophageal luminal environment is not confirmed in the clinical practice. There are no data that antireflux surgery has detectable effect on adenocarcinoma risk. The incidence of EAC in the 14 102 patients having antireflux surgery in Sweden from 1965 to 2005 was evaluated and compared to controls [154]. Authors concluded that antireflux surgery cannot be able to prevent the development of esophageal or cardia adenocarcinoma. One randomized prospective trial compares antireflux surgery (n=58) and PPIs (n=43) in patients with BE [155]. No significant difference between the two groups was found with respect to preventing progression to dysplasia and adenocarcinoma. Given current knowledge, there are no confirming data that antireflux surgery is more effective than acid suppressing therapy for the prevention of HGD or cancer in BE. Because of that antireflux surgery does not abolish the need for surveillance [132, 151].

## 5.2. Chemoprevention therapy

Except of antireflux medication and surgery, non-steroid anti-inflammatory drugs (NSAIDs) and acetyl-salicylic acid (ASA) as well as other drugs have been evaluated to be able to prevent cancer development in BE patients. It is well known that chronic inflammation has been associated with neoplasia formation in many organs, as well as esophagus. Chronic inflammation is characterised by production of cyclooxygenase (COX) and prostaglandins. COX-2 enzyme participates in several important tissue processes, for example cell proliferation, migration, apoptosis and angiogenesis. Overexpression of COX-2 has been found in patients with reflux esophagitis, BE, dysplasia, and EAC. NSAIDs and ASA as inhibitors of COX-1 and COX-2 enzymes attenuate cell growth and proliferation, inhibits angiogenesis, and restores

apoptosis [156]. In addition to these findings, epidemiological studies suggest that ASA and other NSAID use may protect against cancers of several sites, especially colorectal cancer. Various studies suggest that NSAIDs and ASA use may reduce the risk of EAC but the other studies do not confirm these results [156-159]. Patients with exposure to NSAIDs or ASA had a 55% reduction of development of EAC [160-162]. A systematic review of 9 studies and meta-analysis assessed more than 1800 patients has been showed that NSAIDs or ASA had a 33% odds reduction of development of cancer [163]. Any use of ASA or NSAIDs was associated with a 43% reduced risk of cancer. Frequent use of ASA or NSAIDs decreased cancer risk with 46%, but intermittent use was associated with 18% risk reduction. Both ASA and NSAIDs use was associated separately with reduced risk of cancer. The associations were seen for both EAC and squamous cell carcinoma. In a recent study from Netherlands, 570 BE patients were prospectively followed for a median of 4.5 years. Use of NSAIDs (median duration 2 months) was associated with 53% lower risk of progression to HGD/EAC [164]. A cohort of 350 Barrett's patients from 20770 persons was followed up (median 65.5 months) [165]. The data showed that current NSAID and ASA users had 68% reduced risk of EAC, the past use decreased the risk with 30% compared with never-users of NSAIDs. The 5-year incidence of EAC was observed in 6.6% versus 14.3% in current versus never-users. It is discussed that NSAIDs and ASA may protect against EAC by reducing the risk of development of BE or by preventing progression from BE to EAC [132]. In a retrospective study, NSAIDs use was not found to be higher in BE patients when compare to EAC. However, ASA and NSAID use was lower in both of these groups compared with controls [161]. If there is a true protective effect of NSAIDs, this study suggests it may occur prior to the development of BE. A recent retrospective large population-based case-control study failed to find any benefit of aspirin use [157]. This study collected information of intake for ASA and NSAIDs during the past 5 years and other exposures from 285 patients with NDBE, 108 patients with dysplastic BE, and two separate control groups, including 313 endoscopy patients with acute inflammatory changes ('inflammation controls') and 644 population controls. Use of ASA was not associated with NDBE when compared with population or inflammation controls, but significant risk reductions for users of NSAIDs were found when compared with population controls. No dose-response effects were observed. These data showed little consistent evidence of an inverse association between use of ASA or NSAIDs and risk of BE. Authors concluded that the question of whether or not these medications prevent the onset of BE remains open. PPIs are usual concomitant medication in NSAID or ASA users with GERD. From this point of view, one study evaluated patients who take prescribed NSAIDs/ASA as well as PPIs. A decreased risk of EAC was demonstrated [161]. This protective effect may be due to the combination of each medication. On the other hand, the concomitant use of PPI in BE patients, should decrease the risk of serious GI complications associated with NSAIDs or ASA [151]. COX-2 inhibitors may be of benefit because of more specific inhibition of COX-2 receptors and fewer side effects on GI tract. In a multicenter, randomized trial of celecoxib versus placebo in 222 patients with BE and LGD or HGD, at 48 week follow up, no significant difference was observed in dysplasia or cancer between the groups [166]. Authors suggest that celecoxib does not prevents progression of BE, although further studies are needed. However the majority of these studies are associations and observations, because there are significant barriers in conducting a large clinical trial

evaluating NSAIDs/ASA as potential chemoprotective agents [132]. Current evidence shows that NSAIDs may reduce the risk of EAC. Despite of this, most experts agree it is not clear that potential benefit outweighs the GI risks of this group of medication. On the other hand, there is also evidence that cardiovascular deaths became more common than deaths from EAC among BE patients. Because of that it is appropriate to screen these patients for cardiovascular risk. In addition, the proportion of cases that take low dose aspirin or statins for cardiovascular risk factors or events will be increase in the near future.

Possible chemopreventive properties of *statins* have been also suggested in some recent study [12, 135, 161]. Statins can increase apoptosis and inhibit proliferation in Barrett's epithelial cells because of reduction of serum-stimulated Ras activity, and inhibition of activation of extracellular signal-regulated kinase (ERK), and protein kinase B (Akt) [167, 168]. A case-control study of 12000 BE patients showed that statin use was associated with a reduction in EAC risk [161]. The risk reduction was higher in cases with longer duration of statin use. The Dutch data also confirmed that long-term use of statins (median duration of 5 years) led to 54% reduction in the risk of malignant progression of BE [164]. In addition a combination of NSAIDs and statins decreased this risk to 78%. Finally, the chemoprevention of BE is likely to remain an active area of research. There is a need of new evidence on the possible chemopreventive effects of novel options in prospective, randomized studies. Although, the positive results from chemopreventive studies will not change recommendations for endoscopic surveillance in the near future [12].

According to all current data, in the last version of AGA guidelines for the management of BE, AGA's experts strongly recommend: 1) Elimination of esophageal acid exposure by PPIs more than once daily. Esophageal pH monitoring is needed to define PPI dosing. Antireflux surgery is also recommended as a method to control esophageal acid exposure; 2) Screening of BE patients to assess cardiovascular risk and prescribe an ASA therapy is indicated. On the other hand using ASA solely to prevent EAC in the absence of other cardiovascular indications is not recommended [151].

### 5.3. Endoscopic treatment of BE

In recent years, endoscopic techniques used to eradicate BE with presence or absence of dysplasia or IMC include endoscopic resection and/ or ablations. The most commonly used technologies currently are EMR and RFA, applied alone or in combination. Evidence for their efficacy has emerged rapidly over the past decade [151, 169-171]. The goal of endoscopic eradication therapy (EET) for BE patients, especially those with HGD or IMC is to completely eliminate all dysplastic and non-dysplastic Barrett's epithelium to get a complete reversion to normal squamous epithelium without islands of buried IM.

#### 5.3.1. Non ablative modalities (endoscopic resection-EMR)

EMR has been provided both a diagnostic/ staging and therapeutic tool for Barrett's neoplasia. At now, EMR should be performed in BE patients who have dysplasia as macroscopically visible mucosal irregularities to determine the T stage of the neoplasia (151, 169-175). A large

number of different techniques with or without suction or submucosal injection that raise the lesions can be used. EMR can be performed by the lift and snare technique, cap-assisted endoscopic resection, multiband mucosectomy, and Euroligator technique [169, 170, 172-175]. Endoscopic submucosal dissection (ESD) is also used. No data confirmed that one of these endoscopic techniques has proven to be superior to another. In a prospective randomized trial, both "cap-and-snare" and "band-and-snare" technique can provide adequate depth and histological staging and have similar safety profiles [176, 177]. Studies have demonstrated that EMR is safe and effective for the treatment of superficial lesions for successful eradication of BE with varied degree of dysplasia and IMC [169, 178, 179]. Five-year follow-up data for 231 BE patients with IMC demonstrated a 95.7% complete response rate [180]. Focal EMR is associated with high recurrence rate up to 47%, and increased with longer observation times, may be due to multifocal synchronous lesions previously missed by biopsy, as well as the metachronous development of new lesions [169-172, 181-184]. Recent data suggests that the presence of submucosal invasion of occult adenocarcinoma in the setting of HGD was 6.7% - 12%, which was much lower than previously reported [171, 185]. One small, prospective study demonstrated an eradication rate of focal HGD or IMC more than 90% for small (< 2 cm) or low-risk lesions at a mean of 12 months follow-up [179]. On the opposite, a remission rate of only 59% and recurrence rates of 11% to 14% were observed for larger lesions (> 2 cm). Therefore, EMR has been accepted method for BE with small and/or raised lesions of HGD or IMC [172]. Independently of endoscopic techniques, the most common complications of EMR are bleeding and esophageal stricture formation, but most of them can be treated successfully by endoscopy [186-199]. Perforation has been reported in 1-2.6% of the patients, but seems to decrease with more experience. Despite known efficacy and a relatively good safety profile for small segments of neoplasia and raised lesions, the potential role of EMR in longer segments of BE remains limited because of several factors: piecemeal resections are needed a long time to complete; repeat sessions are often necessary; the risk of possible bleeding and perforation can be increased. EMR for long-segment BE appears to be associated with a relatively high stricture rates of 26% to 37% [196, 198]. *Complete Barrett's eradication EMR (CBE-EMR)* with aim to reduce the potential risk of synchronous or metachronous lesion has been performed in select centers. This more aggressive method is also known as circumferential EMR, stepwise radical endoscopic resection (SRER), and wide area EMR. All of these techniques have proven to eradicate all Barrett's epithelium curatively and give possibility for a more accurate pathology result when compared to pre-EMR biopsy results [169, 170]. Complete eradication rate has observed from 76% to 100%, and recurrence of malignancy in up to 11%, without association with BE tissue recurrence [189, 196, 198, 200-202]. Only in one study recurrence rate of 36.5% was reported [196]. Short-term follow-up shows that CBE-EMR is effective in eradication of all BE and also eliminated the genetic alterations that are associated with early neoplasia [189, 202]. In a retrospective study recurrence of HGD or IMC was observed in 9% of patients and 15% had recurrent IM after a median follow-up of 23 months [197]. A multi-center European cohort study on 169 patients with BE and HGD or IMC treated by CBE-EMR showed a remission of neoplasia in 97.5%, and complete elimination of Barrett's metaplasia in 85% after 27 months of follow-up [200]. The recurrence rate for metachronous lesions was 1.8%. Complete eradication of HGD and/or IMC was observed in 100% at 11-month follow-up, while

complete eradication of LGD and metaplasia was demonstrated in 89% [189]. In retrospective study of 41 patients with HGD or IMC on BE, a regression to normal squamous epithelium was found in 75% at a mean follow-up of 31 months [196]. The number increased to 90% in patients after repeat session of EMR after recurrence of metaplasia or carcinoma. A remission to normal squamous epithelium was recently observed in 96% with HGD and/or IMC at a median of 17 months after stepwise EMR [198]. These data demonstrated the efficacy of EMR for Barrett's dysplasia and IMC. On the other hand CBE-EMR seems to be associated with more complications [186-200]. Rates of bleeding and perforation in large EMRs increased up to 19% and 11% respectively, and appear to be higher than those for ablative modalities [195, 198]. A high stricture rate is the main limitation of CBE-EMR. In 34 patients, treated by SRER with median of two therapeutic sessions dysphagia occurred in 56%, necessitating dilations or stent placement [197]. Another prospective trial reported a stenosis rate of 26% after 88 SRER procedures [189]. A recent multicentre randomised study reported a stenosis rate of 88 % of cases [203]. Development of stenosis is highly dependent on the circumferential extent of the resection. Resections limited to 50% of the circumference rarely cause a significant stenosis. Risk of stricture formation is higher when more than three-quarters of the circumference of the mucosa is resected [204]. Because of that Japanese Society for Gastrointestinal Endoscopy (JSGE) recommended using of EMR only for HGD lesions, involving less than one-third of the circumference of the esophageal wall [179]. Regarding length of BE, recent observational studies reported good results when segments of BE more than 2 cm or flat mucosal lesions can be resected by CBE\_EMR [170, 172, 178]. SRER is mostly limited to a 5-cm Barrett's segment [189]. The most important risk factors for recurrent disease after EMR without total eradication are following: piecemeal resection, long segment BE, no ablative therapy of the remaining BE after complete removal of HGD/IMC, and multifocal disease [170]. The main indications for curative endoscopic resection of early EAC included lesions limited to the mucosa, limited in size to 2 cm, well-to-moderately differentiated, no pathological lymph nodes, and no lymphovascular infiltration in the endoscopic resection specimen [187-190, 205, 206]. In *ESD*, a viscous fluid into the submucosal space is injected to provide a cushion under the lesion, followed by deeper resections into larger areas of submucosa using a special cutting device (knives and snare) [174]. *ESD* has been used successfully for the treatment of large (> 1.5 cm) tumors of upper GI tract [207, 208]. No recurrence of EAC was observed in patients with BE [208]. One potential barrier to this approach is reflux-induced submucosal fibrosis in the distal esophagus [207]. Because of that stricture formation was observed in nearly half of cases [132]. The role of this method in long-segment BE with HGD is still limited, and is generally not widely recommended at this time [171, 172, 178].

Regarding all current data, EMR remains one of the preferred first-line endoscopic treatment for selected patients with early HGD and/or IMC because of its diagnostic/staging value and its established therapeutic role. EMR is characterized with high eradication rate of Barrett's dysplasia, but also with high rate of complications and recurrence. Because of that additional ablation is used to reach complete eliminate all dysplastic and non-dysplastic Barrett's epithelium, as well as complete reversion to normal squamous epithelium.

### 5.3.2. Endoscopic ablative therapies

Endoscopic ablative modalities used to eradicate BE include thermal energy application, argon plasma coagulation (APC), photodynamic therapy (PDT), radiofrequency ablation (RFA), and cryotherapy. In these modalities ablated epithelium is replaced by a neosquamous epithelium. Ablative therapies have an increasing role in the management of BE. In general, they are well tolerated. There are two major limitations related to ablative methods. First there is no possibility for histologic examination. The second problem is associated with the squamous overgrowth and risk of development of EAC beneath regenerated squamous epithelium after ablation, which may be due on the progression of buried Barrett's metaplasia or dysplasia [209]. Most of thermal energy application methods, as well as APC are unsuitable to treat BE with HGD or IMC alone. Despite that, they can be useful as an adjunct to EMR in the treatment of selected BE patients. Our data on 50 BE patients with LGD, treated by APC plus PPIs showed that de novo Barrett's metaplasia was observed in 23 patients, with islands of LGD in 12 cases at 10 years follow up. All of them were treated successfully by new endoscopy. No progression to HGD or EAC was found [210, 211]. No serious adverse events or strictures were observed.

For a long time of period PDT was the primary option for ablative therapy of early Barrett's cancer and HGD, as well as additional treatment to EMR [170, 171]. The principle of PDT based on light-sensitizing reaction which produces oxygen radicals and destroys targeted cells by inducing of cellular apoptosis. Porfimer sodium and 5-aminolevulinic acid (5-ALA) have been used for the relatively selective destruction of malignant and pre-malignant tissue. Several studies have demonstrated the efficacy of PDT in eradicating BE with dysplasia and IMC. Results of the major PDT studies have shown eradication rates of IM, LGD and HGD in a range of 44%-56%, 79%-100%, and 75%-100% respectively and suggest that PDT is an effective treatment modality for eradication of BE with HGD and IMC [212-218]. A retrospective study on 103 patients with LGD, HGD, and IMC, treated by porfimer PDT reported success rates of 92.9%, 77.5%, and 44.4% for each respective group after a mean follow-up of 50 months [215]. The initial response after 5-ALA PDT in patients with Barrett's dysplasia or early EAC has been range between 67% and 100% with a relatively high recurrence rate (30%) [216, 219]. Other study in which 5-ALA PDT was used after EMR, showed that it did not prevent recurrent disease, particularly when there were positive margins in the EMR specimen [220]. In a prospective study, 66 patients with HGD or IMC on BE after 5-ALA PDT were followed-up for a median of 37 months [216]. Complete response was observed in 97% of HGD group and 100% of IMC group. Disease-free survival of HGD patients was 89%, and 68% in IMC cases. The 5-year survival was 97% for HGD and 80% for IMC. There were no deaths related to Barrett's neoplasia. In a multicenter, randomized controlled trial, the long-term outcomes of porfimer sodium PDT plus twice-daily Omeprazole 20 mg (n = 138) versus PPI only (n=70) were evaluated [221, 222]. At 24 months, 77% of PDT+PPI treated patients had remission of Barrett's dysplasia versus 39% in the PPI group. At 5 years, there was no residual dysplasia in 59% of PDT-treated patients versus 14% of PPI group. Complete neosquamous mucosa was found in 52% of the patients in the PDT group but only in 7% in the control group. In addition, the cancer progression was prevented in 29% in PDT group v/s 15% in the PPI group. These data confirmed that PDT is an effective procedure for the eradication of BE with HGD and

early EAC, but there are no randomized, controlled prospective trials which compared PDT and surgery. In Mayo study of BE patients with HGD who received PDT ( $n=129$ ) or esophagectomy ( $n=70$ ), retrospective data were analysed [223]. No significant differences in mortality or long-term survival between different treatment groups were found. Overall mortality in the PDT group was 9% and in the surgery group was 8.5% over a median follow-up period of 59 months for the PDT group and 61 months for the surgery group. Although initial and long-term success for neoplasia eradication, several limitations for using of PDT as a primary choice for treatment of Barrett's neoplasia exist. The additional time required for the administration of the photosensitizers 2–3 days prior to endoscopic therapy, and the high price of PDT procedure are also pitfalls. The most important adverse effects are photosensitization, stricture formation, and the issue of buried glands that harbored neoplastic potential and decreased efficacy when compared with newer modalities [209, 212, 215, 223]. Post-procedure skin sunburn was reported in two-thirds of the patients [170, 172]. Other important side effects are acute chest pain, nausea and odynophagia. Symptomatic esophageal stricture formation was reported in average 30% of patients, and increased from 18% with one PDT session to 50% with two treatment sessions [215]. These strictures necessitate multiple endoscopic dilations and even esophageal stenting [169]. The significant risk factors associated with post-PDT stricture development include performance of EMR before PDT, history of prior esophageal stricture, and the number of photodynamic sessions (more than one in a single procedure) [223]. Adenocarcinoma arising from sub-squamous Barrett's esophagus glands after PDT was reported [209, 215]. However, the clinical significance of sub-squamous Barrett's glands is not fully defined. If PDT has been capable to effectively ablate lesions greater than 2mm in depth is discussed [224]. For this reason regular follow-up endoscopies with biopsies are very important. In one study including 349 patients with dysplasia or IMC were treated by EMR (80%) or PDT [225]. Only 13 patients were treated with a combination therapy of ER and PDT. Complete response was achieved in 96.6% of patients with endoscopic therapy. At 5-year follow up survival was 84% and there were no cancer-related deaths. Metachronous lesions occurred in 21.5% of the patients. After re-treatment, the long-term eradication was 95%. Other studies have shown similar success between EMR alone and EMR plus ablation therapy combining the diagnostic accuracy and therapeutic resection of EMR with adjuvant ablation to some degree [226, 227]. On the base of current data on efficacy and safety of PDT, this ablative modality remains an effective treatment for BE with HGD and IMC. There is a need to improve photosensitiser agents, dosimetry, and light parameters which should help minimize the associated complications. On the other hand the PDT use decrease in clinical practice in recent years. PDT was been replaced by newer ablative modalities with less risk of procedural complications as RFA and cryoablation.

*RFA* is one of the newer endoscopic treatment modalities. The ablation process includes direct thermal energy with the electrodes embedded in either the circumferential or focal device. The effect of RFA has been well studied in several trials in BE patients with or without dysplasia and IMC [228]. The safety and efficacy of RFA were first assessed on BE patients without dysplasia in the Ablation of intestinal metaplasia (AIM) study [217]. This multicenter trial showed a 70% complete remission of BE after circumferential RFA at 1 year follow-up. Stricture formation or buried BE was no found among 4306 biopsy specimens evaluated. The AIM-II

trial (n=70) demonstrated complete eradication in 98% of patients treated with an additional mean of 1.5 circumferential RFA followed by 1.9 focal ablation procedures at 2.5-year follow-up [218]. Five-year outcomes from the AIM-II trial (n=50) showed complete remission in 92% of the patients [229]. Four (8%) patients had NDBE and were all re-treated successfully with focal ablation. In addition, no strictures, perforations, buried glands, dysplasia, or serious adverse events were reported. The results of these large clinical studies proved that NDBE can regress in response to RFA. The use of RFA for BE with dysplasia has also been evaluated in several additional studies and RFA has been shown to be efficacious. One study included 63 patients with LGD (n = 39) and HGD (n = 24) treated by circumferential or focal RFA [230]. At a median follow-up of 24 months, 79% and 89% of patients achieved complete remission of IM and dysplasia, respectively. Patients with LGD had a higher rate of response than patients with HGD for both eradication of IM (87% vs 67%) and dysplasia (95% vs 79%). In a multicenter randomized sham-controlled trial 127 BE patients with dysplasia (64 LGD and 63 HGD) received RFA (mean of 3.5 procedures/patient) or a sham procedure, as well as esomeprazole 40 mg twice daily [231]. At 12-month follow-up complete eradication of LGD occurred in 90.5% in the ablation group v/s 23% in controls, and 81% vs 19% for HGD and controls respectively. Complete eradication of IM was observed in 77% v/s 2% for RFA and control group respectively. There was less disease progression in patients in the ablation group (3.6% vs 16.3%) and fewer cancers developed (1.2% vs 9.3%). The rate of esophageal stricture in the RFA group was 6%. All patients were successfully treated with endoscopic dilation (mean 2.6 sessions). This stricture rate is markedly lower than that reported for EMR. These data demonstrated a significant advantage for RFA in treatment of BE with HGD. In addition, after 3 years followed up, 98% eradication of dysplasia and 91% eradication of metaplasia were found. Although RFA appeared to be efficacious in clinical trials for both dysplastic and NDBE, it was unclear whether the results would be reproducible in community practice [172]. Regarding this, in one study were investigated 142 BE patients with HGD after circumferential RFA from 16 separate academic and community centers [232]. At 1 year follow-up, complete remission of HGD was observed in 90%, complete regression of LGD was found in 80%, and 54% of patients achieved complete eradication of BE. Only one stricture was observed as adverse event. The data of a multicenter practice registry from 4 community-based gastroenterology practices were also evaluated [233]. A total of 429 patients with confirmed IM with or without dysplasia were treated with circumferential RFA. Complete eradication of BE or regression of dysplasia were achieved in 72% and 89% of patients, respectively, at a median follow-up of 9 months (338 patients with  $\geq 1$  biopsy session after the initial treatment), as well as in 77% and 100%, respectively, with a median follow-up of 20 months (137 patients with  $\geq 1$  biopsy session  $\geq 1$  year after the initial treatment). No serious adverse events were reported, although esophageal strictures were observed in 2% (successfully treated by endoscopy). The observed safety and efficacy outcomes associated with RFA in this community practice study appeared to be comparable with those reported in clinical trials, supporting its wider applicability in community practice.

Several smaller trials have shown the possibility of combination of EMR of visible lesions with subsequent RFA for the treatment patients with dysplastic BE or EAC. The results of these studies showed that eradication rate of IM, any dysplasia, including also HGD was in

46%-100%, and 71%-100% respectively. [230, 232, 234-240]. In one study 44 patients with LGD, HGD, or IMC treated with RFA (31 patients had prior EMR for visible lesions before RFA) were evaluated [237]. Complete eradication of all dysplasia and IM was achieved in 98%. Post-ablation complications (all with prior EMR) included mucosal laceration and transient dysphagia ( $n = 3$ ), and esophageal stricture ( $n = 4$ ), which responded to endoscopic dilatation. No dysplasia recurred after a 21-months follow-up period. A more recent multicenter European trial reported results of 24 patients with BE and HGD or IMC who were treated with EMR for visible lesions and then serial RFA were applied [238]. The complete eradication rates of neoplasia, including those with EAC and IM were 100% and 95% respectively, after 22-months follow-up. No major adverse effects were observed. Regarding patients with BE segments >10 cm, one study reported complete response rates of 83% and 79 % for neoplasia and IM, respectively after focal EMR followed by RFA [241]. Both of these trials demonstrate neoplasia-free outcomes in their follow-up periods of 22 and 9 months, respectively. In a randomized control trial, CBE-EMR followed by serial focal EMR was compared with the focal EMR followed by RFA in BE up to 5 cm containing HGD or EAC [203]. Complete remission rates were similar between two groups (100% for CBE-EMR v/s 96% for EMR/RFA group). The most finding of this study is that CBE-EMR group showed higher rate of stenosis (88 % vs. 14 %). These results confirmed that RFA, applied after focal EMR of visible lesions can be effective therapy for the remaining Barrett's dysplastic epithelium, because RFA has associated with better safety profile. Most procedure-related side effects are mild, including fever, chest pain, superficial mucosal injury (non-transmural lacerations), nausea or sedation-related complications [217]. Esophageal function appears to be well preserved [242]. Stricture formation rate was up to 6%, much lower than the rate associated with EMR [234]. In combination with EMR complications are found more frequently [237, 238]. Nontransmural laceration associated with circumferential RFA following EMR was observed in 7% of patients, which occurred only at the level of the EMR. In contrast, no lacerations or stenosis occurred in patients treated with RFA alone [238]. Buried Barrett's glands have been evaluated in all RFA studies showing positive result in one of 5000 biopsies. Re-EMR specimens after ablation did not show any buried glands [237]. Neo-squamous epithelium on EMR specimens in a group of 22 post-RFA patients with baseline BE with IMC or HGD showed no evidence of persistent genetic abnormalities or buried BE glands [243].

RFA is characterized with very good control of the depth of ablative penetration [224]. Because of that many side effects are reduced. Now, RFA is seem to be the most efficacious modality to treats any stage of BE with a better safety profile than other ablation techniques (PDT) and EMR. RFA is also safely when combined with EMR for visible lesions. This combined endoscopic method is quickly integrated in routine clinical practice. RFA therapy for patients with NDBE and LGD seems to be capable to reverse to normal squamous epithelium for a long time (5 year) after procedure. In addition, RFA treatment reduces progression to EAC in patients with HGD. Because of that RFA has become one of the preferable method for the EET of BE with HGD and/or IMC.

*Cryotherapy* or CryoSpray Ablation therapy (CSA) is a relatively newer non contact ablation modality. Sprayed liquid nitrogen or carbon dioxide is applied onto the Barrett's mucosa,

which produces tissue freeze-thaw cycles. Cryotherapy leads to intracellular disruption or tissue ischemia, with minimal damaging of extracellular matrix and fibrosis formation [169-172]. One prospective open-label cohort trial on 30 patients with BE and HGD or IMC undergoing CSA showed that 27 of the patients (90%) had pathological downgrading post-treatment [244]. Elimination of cancer or downgrading of HGD was achieved in 80% of IMC and 68% of HGD patients at a median of 1 year follow-up. The therapy was well tolerated, but one gastric perforation reported in a patient with Marfan syndrome in whom decompression during therapy was not performed. Of 6 patients who showed a complete response, 3 had recurrence of dysplasia or cancer in the gastric cardia. Recent trials demonstrate initial success with regression of HGD more than 90% for both liquid nitrogen or carbon dioxide cryotherapies [245-247]. A retrospective analysis of 60 patients with HGD treated by CSA (mean of 4 sessions) was done [245]. Complete eradication of HGD was observed in 97% (87% for all dysplasia) at a mean follow-up of 10.5 months. In 57% were found regression to squamous epithelium. Disease progression occurred in 1 patient. Overall, no serious adverse events occurred over the course of 333 sessions, with 3 strictures requiring endoscopic dilation. Other study reported that primary and additional treatment in refractory HGD or EAC with carbon dioxide resulted in a safe and effective ablation in more than 90% of the patients with a mean of six sessions [247]. In a four-center study of 23 patients (17 HGD, 4IMC, 3 early EAC), complete regression to HGD was found in 94% with HGD, and 100% with IMC and EAC [246]. Complete response to IM was observed in 53% with HGD, 75% with IMC, and 67% with cancer. No symptoms were reported in 48% of 323 procedures. Esophageal strictures developed in 3 patients, but all were successfully treated by dilation. In addition to early success with IMC, this therapy has also been considered as a treatment for patients with localized EAC that are not candidates for standard therapies. In a recent study it was demonstrated a 61.2 % complete local response [248]. The safety profile of cryotherapy appears to be good. CSA related adverse events include chest pain, dysphagia, odynophagia, sore throat, stenosis, and rarely perforation [244-246]. The overall incidence of stricture formation was 8 %. This rate is lower than the reported rates for EMR and PDT.

In summary, cryotherapy has become now as a potential alternative to the other endoscopic ablative modalities. According to present data, cryotherapy appears to be safe, well tolerated, and capable to ablate IM, dysplasia and early EAC. On the other hand, there is no evidence that cryotherapy leads to sustained reversion to normal squamous epithelium. The efficacy of this ablation method is lower when compared with RFA or PDT. There are no randomized trials comparing CSA with other endoscopic or nonendoscopic modalities. Further studies are needed also to assess long-term efficacy of cryotherapy, as well as its real clinical significance.

Two recent studies evaluated the cost-effectiveness of ablative therapy for BE [249, 250]. One of them reported endoscopic ablation with continued surveillance is significantly more cost-effective than surveillance only [249]. A separate cost-effective analysis concluded that endoscopic ablation could be the preferred strategy for management of BE with HGD [250]. If ablation permanently eradicates  $\geq 28\%$  of LGD or 40% of NDBE, endoscopic ablation would be preferred to surveillance alone.

#### 5.4. Surgical treatment

Until the past decade, esophagectomy for BE with HGD and IMC had been the traditional standard, because of the high rate of suspected risk of occult invasive carcinoma or recurrence [132, 184, 185, 251-253]. Surgery ensures accurate staging and adequate therapy including negative margins and lymph nodes extraction. Complete resection of the entire Barrett's segment is done in cases of unsuspected multifocal disease and to minimize the risk of metachronous lesion development in residual Barrett's [254]. Some studies reported significant morbidity and mortality associated with esophagectomy, with overall morbidity rates as high as 50% and mortality as high as 10% [255]. The immediate postoperative complications include pulmonary events, hemorrhage, anastomotic leak, infections, postoperative arrhythmias and heart failure, and nerve palsy [132, 224]. The long-term complications are dysphagia, weight loss, GERD, esophageal strictures, cough and dumping which may impair health-related quality of life [256]. Reported mortality rates for esophagectomy usually were based on outcomes after surgery for cancer and not HGD. It is well known that patients with cancers are older, more morbid, and have more comorbidities than patients with HGD alone [257]. On the other hands the results from high-volume centers with greater surgical expertise have shown better outcomes [224]. The mortality rate from esophagectomy for cancer of 2%–3% was reported [258, 259]. In a Dutch study, based on the number of esophagectomies a year, hospitals were classified as low-volume centers (<10 resections a year), medium-volume centers (11–20 resections a year) and high-volume centers (>50 resections a year). Hospital mortality at these centers was 12.1%, 7.5% and 4.9%, respectively [260]. In another study a mortality rate of 1% after esophagectomy for HGD was found. Others data also confirmed that surgical resection of patients with HGD is associated with operative mortality of 0-2% and overall 5-year survival of 83%-88% (91% for HGD without invasion and 68% for those with invasion), and 10-year survival of 86% [261-264]. This result showed that regarding HGD and surgical experience, esophagectomy is a lower-risk surgery [257]. Recurrence rates of BE or EAC after esophagectomy have been assessed in a limited number of trials. In one study on BE patients with HGD or EAC, the 2-year surveillance of 85% was reported [175]. The cure rate for dysplasia or localized EAC was reported to be lower than 78% in another study [265]. These data raise questions about the need for continued endoscopic surveillance following surgical resection. Conventional approaches for esophagectomy are transhiatal and transthoracic resection. A randomized trial comparing of patients undergoing transhiatal esophagectomy (n=106) or transthoracic esophagectomy with lymphadenectomy (n=114) demonstrated a significantly lower rate of postoperative respiratory complications with the transhiatal approach (27% versus 57%), but greater survival was shown for the transthoracic approach at 5 years (39% versus 27%) [266]. One potential limitation of the transhiatal approach is the inability to retrieve lymph nodes required for nodal staging [267]. Minimally invasive esophagectomy avoids the thoracotomy and laparotomy has potential advantages over open esophagectomy because of a lower incidence of pulmonary complications, faster postoperative recovery, and decreased length of hospital stay [268, 269]. However, lymph node retrieval is largely inferior to the standards of open surgery. The morbidity and mortality of minimally invasive esophagectomy is not proven to be lower when compared with open esophagectomy at experienced centers [270]. Recommendations favoring minimally invasive esophagectomy over open esophagec-

tomy cannot be made due to a lack of randomized trials comparing the two approaches. In patients with few comorbidities and an otherwise long life expectancy, a vagal-sparing esophagectomy can be considered to improve outcomes and quality of life. It was demonstrated lower infectious, respiratory, and anastomotic complications in patients with HGD or IMC undergoing this procedure compared with transhiatal esophagectomy. Quality of life advantages were also demonstrated because of the reduction of postvagotomy dumping and diarrhea, as well as a shorter hospital stay [271]. However, lymphadenectomy is not performed with this procedure. Regarding early cancer (IMC), esophagectomy with therapeutic lymphadenectomy is today reserved for more selected cases with evidence of submucosal invasion, lymph node metastasis, or unsuccessful endoscopic therapy, National Comprehensive Cancer Network (NCCN) recommended all modalities –EMR or ablation or esophagectomy [272], but European Society for Medical Oncology (ESMO) [273] pointed that surgery is the treatment of choice in early cancer. On the contrary, esophagectomy can be discussed in patients with high-risk features of HGD or IMC [274]. A patient's age, comorbidities, and willingness to undergo surgery should also be taken into account. According to the current AGA's guidelines for BE management "Esophagectomy in patients with HGD is an alternative; however, current evidence suggests that there is less morbidity with ablative therapy" The experts also enhance that patients with HGD or IMC "should be referred for evaluation by surgical centers that specialize in the treatment of foregut cancers and HGD" [151].

There are no prospective head-to-head randomized trials to compare EET versus surgery. However, when compared with esophagectomy, EET is less invasive, associated with low morbidity and mortality, and is more cost-effective in treating all types of BE. The reported outcomes of EET are superior to those of esophagectomy. Endoscopic procedures related mortality versus death from postoperative complications was 0% v/s 2.1% and the percent of patients free of carcinoma after EET v/s free of carcinoma after esophagectomy was 88% v/s 86% [191, 275]. Recurrence rates of EAC after EET were 12% and all were cured by further endoscopic therapy. In a long-term follow-up of 132 patients treated with EMR and 46 who underwent surgery, there was no difference in the 5-year survival rate between the surgically or endoscopically treated groups [276].

Now, EET with EMR, RFA or PDT is became a first chois of treatment for BE patients with confirmed HGD [151,169-172]. The key point to successful EET is appropriate selection of each patients. EET is also associated with complete reversion to normal squamous epithelium in NDBE or LGD. Despite that, there is no evidence EET is more cost-effective to reduce cancer risk than long-term endoscopic surveillance [14, 151, 234]. Regardless EET can be used for select BE patients with LGD who have high risk for progression to HGD and EAC [151].

## 6. Conclusions

All types of histologically proven esophageal columnar metaplasia, including gastric or specialized intestinal metaplasia should be included in the diagnosis of BE. But various definitions of BE still exist. Diagnosis and grading of dysplasia rely on careful endoscopic and

histological examinations in a Barrett's segment, confirmed by expert. There is different management strategy in BE with or without LGD and HGD because of the different prognostic profiles between them. There are no evidence regarding outcome of endoscopic surveillance but all professional organizations recommend this approach for all types of BE. When BE without evidence of dysplasia or cancer is found on biopsy, the management focuses on reflux control and risk of cancer development (periodic endoscopic surveillance, PPIs or fundoplication, and ASA for cardiovascular risk/disease). Patients with LGD might be managed similar to NDBE. Antireflux therapy (medical or surgical) and endoscopic surveillance to exclude HGD missed on prior biopsy or progression to EAC are recommended. There is a greater discrepancy regarding the management of BE with HGD. The options for management of these patients include intensive surveillance until EAC, EET with EMR, RFA, or PDT, and surgery. The EET and surveillance are both equal recommended as a first choice of treatment for patients with confirmed HGD on BE. An individualized approach based on risk stratification and patient preference is also recommended, especially for LGD or HGD.

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