Diagnosis and management of Barrett’s metaplasia: What’s new?

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Abstract

Barrett’s esophagus (BE) is a complication of gastroesophageal reflux disease, and a premalignant lesion for esophageal adenocarcinoma (EAC). Observational studies suggest that endoscopic surveillance is associated with the detection of dysplasia and EAC at an early stage along with improved survival, but controversies still remain. The management of patients with BE involves endoscopic surveillance, preventive and clinical measures for cancer, and endoscopic and surgical approaches to treatment. Deciding upon the most appropriate treatment is a challenge. This study presents the results and the effectiveness of these practices.

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Key words: Barrett’s esophagus; Intestinal metaplasia; Metaplastic columnar mucosa; Esophageal premalignancy; Esophageal adenocarcinoma

INTRODUCTION

Barrett’s esophagus (BE) is a sequel of longstanding gastroesophageal reflux disease (GERD) and a premalignant lesion of esophageal adenocarcinoma (EAC), a cancer type whose incidence has been rapidly increasing in the Western world[1]. Interpretation of the exploding body of knowledge about BE is impaired by the use of several conflicting definitions[2]. The challenge is to achieve a definition which can be accepted world-wide. The initial informal consensus definition of BE is the partial replacement of normal squamous mucosa that lines the distal esophagus with metaplastic columnar mucosa[3].

BE is judged to develop through the process of metaplasia in which one adult cell type replaces another. The diagnosis of columnar-lined esophagus is typically established at endoscopy, but the final “definitive” diagnosis is confirmed by histological examination of biopsy tissue[4].

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teria, because there are no universally accepted precise and validated landmarks delineating the distal extent of the esophagus. Moreover, there is no method for checking whether gastric-type columnar epithelia found in the distal esophagus are metaplastic[9]. The epithelial type required for BE diagnosis is currently unknown. The divergence between the United States and the British Society guidance is related to intestinalization and the presence of goblet cells[1].

Intestinal-type epithelium can be readily identified by the pathologist and, unlike the gastric-type epithelium, it is clearly abnormal when located in the esophagus[9]. However, there are data suggesting that cardia-type epithelium may not be normal, but rather a metaplastic lining that develops as a consequence of GERD[9]. Recent data suggest that cardia-type epithelium has histochemical and genetic abnormalities similar to those found in specialized intestinal metaplasia (SIM), which may predispose to malignancy, although the magnitude of that risk is not yet clearly defined[3].

Correct interpretation of biopsies at and around the gastroesophageal junction currently depends entirely on the accuracy of the endoscopist in locating biopsies. Some authors agree that the restricted definition of BE must be abandoned and that the importance of finding goblet cells in esophageal columnar metaplasia has been overestimated[2]. In addition, they recognize the malignant potential of “negative for intestinal-type metaplasia” BE biologically plausible. Since any histological type of esophageal columnar metaplasia carries risk for EAC, the diagnosis of BE should no longer require demonstration of intestinal-type metaplasia[2,7].

**NATURAL HISTORY**

In the 1960s, EAC was so rare that authorities questioned its existence. Over the recent decades, a marked change in the epidemiology of esophageal malignancy in North America and Europe has been reported, with an increasing incidence of EAC[8,9]. The reasons for this change are largely unknown, but several lifestyle and dietary risk factors have been proposed, like obesity, smoking and alcohol consumption. To date, relatively few studies have evaluated obesity and other lifestyle risk factors associated with esophageal premalignancy or potential biologic mechanisms underlying these epidemiologic observations[10].

GERD is a key factor for BE development, but other factors may underlie its development, since it only occurs in a minority (10%-15%) of patients with GERD. The key drivers of the development of dysplasia and EAC are still unknown[10,11].

**MANAGEMENT OF BE**

The management of patients with BE involves four major components: treatment of the associated GERD, measures to prevent cancer, endoscopic surveillance to detect dysplasia, and treatment of dysplasia.

The primary goal of antireflux therapy with proton pump inhibitors (PPI) for patients with BE is to control reflux symptoms. In addition, the goal of therapy is to prevent cancer development. Available data suggest, but do not prove, that aggressive antireflux therapy might also prevent cancer in these patients[12].

Observational clinical trials suggest that PPIs can protect patients from developing neoplasia[12,13]. Some prospective clinical studies have shown that PPI therapy is associated with a decrease in proliferation markers, a potentially cancer-protective effect, in biopsy specimens of Barrett’s metaplasia[14,15]. However, prospective clinical studies have yet to prove that PPI therapy can prevent the development of dysplasia and its progression to BE[16].

Most available reports suggest that aspirin and other non-steroidal anti-inflammatory drugs can protect against cancer development in BE, although definitive studies are lacking. A recent technical review by The American Gastroenterology Association has concluded that it is appropriate to consider the prescription of low-dose aspirin for patients with BE who also have risk factors for cardiovascular disease[16].

Antireflux surgery (fundoplication) is another option for controlling GERD in patients with BE, although this does not appear to be more effective at preventing EAC than medical therapy[10].

**Risk factors**

There is a need to identify factors that are able to predict which patients with BE have an increased risk of developing high-grade dysplasia (HGD) and EAC. The risk is predominantly determined by the presence of low-grade dysplasia (LGD), a known duration of BE > 10 years, greater length of BE, and presence of esophagitis[17].

The study of molecular biomarkers of cancer progression could not only allow us to identify the group at high risk of progression of BE to cancer but also potentially to predict the response to endoscopic therapies[18].

**Endoscopic surveillance**

The transition of BE to adenocarcinoma is believed to progress through LGD and HGD, thus justifying endoscopic surveillance for these pre-malignant stages[19].

In the absence of any preventive strategy, regular surveillance to identify early neoplasia is the most pragmatic approach; thus, most international gastroenterological societies advise surveillance programs in patients with BE[18,20]. Intervals of 3-5 years have been suggested for patients who have no dysplasia, 6-12 mo for those who present LGD, and every 3 mo for patients with HGD who receive no invasive therapy[20]. Endoscopic surveillance can detect curable early neoplasia, and asymptomatic cancers discovered during surveillance are less advanced than those found in patients who present with cancer symptoms, such as dysphagia and weight loss[19].

In the absence of mucosal abnormalities, random four quadrant biopsies every 1-2 cm is the standard prac-
tice (Seattle Protocol). Unfortunately, this “blind biopsy protocol” renders visual recognition of areas of dysplasia or early EAC impossible.\textsuperscript{[21,23]} Moreover, dysplasia is an imperfect marker for disease progression of BE to EAC. There are significant variations in interobserver agreement among pathologists, significant sampling errors in obtaining specimens, and the natural history of dysplasia is not linear and predictable for invasive potential.\textsuperscript{[23,24]} The dilemma is identifying BE before the appearance of adenocarcinoma.

On the other hand, the relevance of surveillance programs has been questioned because they have never been shown to have any effect on survival and so are not cost-effective.\textsuperscript{[23]}

In a recent large population-based study, the absolute risk of EAC after a diagnosis of BE was several times lower than the risk reported in previous studies, and this forms the basis for current surveillance guidelines. This study is one of the largest follow-up studies to date on the risk of adenocarcinoma in patients with BE.\textsuperscript{[25]}

As compared with the general population, the relative risk of adenocarcinoma was 11.3 and the absolute annual risk was 0.12%. This is much lower than the assumed risk of 0.5%, the basis of surveillance guidelines, which involved only a few hundred patients, thus increasing the risk of publication bias.\textsuperscript{[23]}

There is a solid evidence that EAC will develop in very few patients with BE.\textsuperscript{[23]} Detection of LGD in the initial endoscopy was associated with an incidence rate of adenocarcinoma of 5.1 cases per 1000 person-year. Risk estimates for patients with HGD were slightly higher.\textsuperscript{[23]}

In contrast, the incidence rate among patients without dysplasia was 1.0 case per 1000 person-year.\textsuperscript{[23]}

The results of this study,\textsuperscript{[23]}

Together with another recent study,\textsuperscript{[26]}

As well as studies of cost-effectiveness and patient quality of life,\textsuperscript{[27,28]}

Suggest that the risk of EAC among patients with BE is so minor that in the absence of dysplasia, routine surveillance of such patients is of doubtful value.\textsuperscript{[25,29]}

Intestinal metaplasia of the gastroesophageal junction is common in the population, but the natural history of this condition remains unclear. Subjects with intestinal metaplasia of the cardia who have distinct demographic and clinical characteristics from BE subjects, do not progress to adenocarcinoma, and may not require surveillance.\textsuperscript{[23,29]}

**Advanced endoscopic imaging techniques**

Wide-field technologies, high resolution and magnification endoscopy, multiple wide-field technologies including narrow-band imaging (NBI) and the Fujinon Intelligent Color Enhancement system, have been developed with the goal of highlighting suspicious gastrointestinal (GI) mucosa.\textsuperscript{[30]}

Better imaging modalities have the potential to improve detection of BE and surveillance for dysplasia and cancer. Many new endoscopic techniques continue to be developed, including magnification endoscopy, chromoendoscopy, and NBI. These techniques aim to achieve the best possible results with visually guided biopsies, to identify LGD and HGD and high risk patients for EAC and to reduce the number of random biopsies.\textsuperscript{[13,32]} However, but none of these techniques is currently routinely used in clinical practice.

The diagnosis of BE with regular endoscopy may not always be accurate, because biopsy of specimens from short segment BE has been shown to identify metaplasia in only 40%-60% of patients. Furthermore, because the distribution of dysplasia and early EAC is uneven and focal, the accurate detection of these conditions using standard biopsy technique is low.\textsuperscript{[33]}

Chromoendoscopy involves the application of chemical agents that highlight various features of the esophageal mucosa in an attempt to improve the detection of abnormalities. Reports on the use of methylene blue, which is absorbed by non-dysplastic intestinal-type epithelium, have reported variable results.\textsuperscript{[34]} A recent meta-analysis compared the detection rates for neoplasia in BE between methylene blue staining and four-quadrant, random biopsies of Barrett’s metaplasia. No significantly higher yield was found for methylene blue over random biopsies in detecting HGD and early cancer.\textsuperscript{[35]} In addition, another report has raised the issue of DNA damage resulting from methylene blue staining and white light illumination.\textsuperscript{[36]} These concerns, along with safety issues, increased cost and procedure time, have prevented the widespread use of vital dye staining chromoendoscopy techniques.

Magnifying endoscopy with indigo carmine and acetic acid instillation has been reported to correctly identify SIM and HGD.\textsuperscript{[37]} Various mucosal pit patterns, such as ridged/villous, circular and irregular/distorted patterns were identified by Sharma et al.\textsuperscript{[38]}. Ridged or villous patterns were associated with intestinal metaplasia, while the irregular or distorted pattern was noted with Barrett’s HGD or superficial adenocarcinoma.

Guerald et al.\textsuperscript{[39]} described four pit patterns using acetic acid and magnification endoscopy (round, reticular, villous and ridged) and found ridged and villous patterns to be associated with intestinal metaplasia. Overall, however, the pit pattern categorization systems have yet to be standardized, and there is high inter-observer variability.

NBI is a new endoscopic diagnostic technique capable of providing virtual chromoendoscopic images using only a single button touch. The technique consists of an electronic endoscope system and a source of light equipped with a narrow band filter, yielding very clear images of microvessels on mucosal surfaces. NBI with magnification could help in assessing the microstructural (pit) and vascular patterns of any suspicious areas detected in BE. Several studies have identified pit patterns and capillary patterns in BE.\textsuperscript{[40-42]} Regular pit patterns include round, linear, tubular/ridged, and villous types. Irregular patterns and absent pit patterns are also reported. Microvascular patterns are classified as either regular or irregular. The sensitivity and specificity of the irregular microvascular and pit patterns for predicting HGD was
as high as 90% and 100% in an observational study. Similarly, the villous, ridged, and absent pit patterns were considered highly suggestive of SIM, while round patterns were associated with columnar lined epithelium.

In a subsequent study by the same research team, a simplified classification system was proposed consisting of four different types of patterns: (1) round pits with regular microvasculature; (2) villous/ridged pits with regular microvasculature; (3) absent pits with regular microvasculature; and (4) distorted pits with irregular microvasculature. Pattern A had positive predictive value (PPV) and negative predictive value (NPV) of 100% and 97%, respectively, for columnar mucosa without intestinal metaplasia. Patterns B and C had a PPV and NPV of 88% and 91%, respectively, for SIM. Pattern D had a PPV and NPV of 81% and 99%, respectively, for HGD.

A prospective controlled trial comparing NBI with standard endoscopy found that NBI detected significantly more patients with dysplasia and higher grades of dysplasia with fewer biopsy samples. A recent meta-analysis confirmed a high diagnostic accuracy of NBI with magnification in diagnosing SIM and dysplasia. However, Kara et al. compared high resolution endoscopy using indigo carmine chromoendoscopy with NBI in 14 patients with Barrett’s HGD and found the same efficacy in both techniques. Similar results were found by Curvers et al. Moreover, poor inter-observer agreements have been reported in some reports.

In a recent study, Silva et al. evaluated the accuracy and inter-observer agreement of different classification systems grading BE using magnification endoscopy and narrow band imaging. They found all systems to have limitations in terms of accuracy for the detection of SIM, identification of dysplastic BE, and inter-observer agreement, regardless of the endoscopist’s expertise. Thus, even when these techniques are used and current classification systems are followed, they cannot as yet replace random biopsies and targeted biopsies of visible lesions.

In conclusion, the main limitations of the NBI system include the learning curve associated with the new technology, the lack of sufficiently validated and standardized classification schemes for the NBI patterns observed in various conditions, and the limited number of randomized controlled trials comparing NBI with conventional white light endoscopy. Thus, additional studies are needed before the system can be incorporated into routine clinical practice. Although initial studies are promising, none of these techniques has yet been shown to provide sufficient additional clinical information (beyond that of high resolution white light endoscopy) to justify its routine application for surveillance purposes. A thorough examination using high resolution white light endoscopy after clearing the mucosa with mucolytics should be the minimum standard to improve detection during Barrett’s surveillance.

There is convincing evidence that biopsy guided by mucosal appearance, observing surface details, using high resolution endoscopes, is now substantially more sensitive for dysplasia and EAC detection than biopsies taken according to the Seattle Protocol.

Finally, maximization of the quality of endoscopic surveillance in BE requires more than enhancements of endoscopic equipment. Unfortunately, general endoscopists are rarely exposed to patients with dysplasia and EAC in training and routine clinical practice.

Overview of new technologies

The last several years have been marked by the emergence of several innovative “optical biopsy” technologies that provide real-time subcellular imaging of GI tract. Although many endoscopic techniques have initially shown high accuracy rates, these technologies are still evolving.

Optical coherence tomography: Optical coherence tomography (OCT) is an endoscopic technique using light waves to generate images. It is an optical signal acquisition and processing method that can capture high-resolution, three-dimensional images within any optical scattering media, such as a biological tissue.

OCT is usually performed by introducing a linear or radial catheter into the accessory channel of a standard endoscope. An increased resolution allows for visualization of microscopic mucosal features such as villi, crypts and glands, but the sampling depth of OCT is limited to 1-2 mm by the scattering of light by tissue and the resolution is not sufficient to visualize some abnormalities.

Adler et al. reported the findings of three-dimensional OCT in BE and in a follow-up after radiofrequency ablation (RFA) looking for residual BE from incomplete ablation and buried BE glands beneath regenerative neosquamous epithelium.

Endocytoscopy: Endocytoscopy is based on the principle of light contact microscopy that allows real-time visualization of the cellular structures of the superficial epithelial layer in a plane parallel to the mucosal surface. Often, the mucosa is treated with a mucolytic such as N-acetylcysteine prior to staining with an absorptive contrast agent such as methylene blue, cresyl violet or toluidine blue.

Confocal laser endomicroscopy: Confocal laser endomicroscopy integrates a confocal laser microscope either in the tip of an endoscope or as a probe that can be passed through the channel of any endoscope. It offers the ability to make a real-time, in vivo histological assessment of GI mucosa.

In order to obtain images, the patient must be given a fluorescent contrast agent, like fluorescein, which optimally highlights the vasculature, lamina propria and intracellular spaces, allowing visualization of vessel patterns and cellular architecture.

Sharma et al., in a recent, international multicenter, prospective, randomized, controlled trial demonstrated significantly improved sensitivity in the detection of...
HGD and early carcinoma in BE with probe-based confocal laser endomicroscopy than with high-definition white-light endoscopy.

The ability to make a real-time histopathological diagnosis is potentially invaluable in enhancing the detection of early neoplasia and facilitating endoscopic invasive therapies. However, widespread application of these technologies is still limited by their high cost and the learning curve associated with the interpretation of the images.\[94\]

**ENDOSCOPIC ERADICATION THERAPY**

**Non-dysplastic Barrett esophagus and LGD**

Several reports have established that endoscopic ablative therapies can eradicate non-dysplastic and low-grade dysplastic Barrett’s epithelium in the short-term for the majority of patients. It is not clear whether the potential benefit of ablation in reducing the small risk of cancer in this group warrants the risks and substantial expense of the ablative procedures.\[8\]. A recent meta-analysis demonstrated that ablation significantly reduces the risk for cancer in patients with non-dysplastic BE and LGD.\[8\]

Fleischer et al.\[51\] proposed RFA as a safe, efficient and cost-effective method that should be considered in the management of patients with non-dysplastic or low-grade dysplastic BE, because it achieves complete response in all patients, eliminates all risk of developing cancer, with rare advent effects and less expense than surveillance in terms of absolute costs.\[81\]. These authors reported complete response by intestinal metaplasia in 92% at 5-year follow-up. Biopsy depth was adequate to detect recurrence, and all failures (4/4, 100%) were converted to complete response with single session focal RFA.\[82\]

However, in a recent Editorial, Spechler suggested that routine ablation of BE would not be an appropriate choice at this time and recommend a randomized, controlled trial to establish the cost, the risks and benefits of RFA for patients with BE.\[83\]

An ideal management paradigm for a non-dysplastic population in the future might be to risk stratify patients by assaying for a genotype associated with propensity for neoplastic progression, and then eradicate the non-dysplastic BE in those patients at highest risk, with surveillance or no action in those patients at lower or zero risk.

**HGD**

Deciding upon the most appropriate treatment in a patient with BE and HGD is currently more difficult than in any time in the history of the disease. Until recently, surgical resection was the undisputed treatment of choice for localized esophageal cancer with or without regional lymph node metastases. This paradigm is currently challenged by interventional endoscopy (in the treatment of early cancer) and combined radiotherapy/chemotherapy (in treatment of regional and more advanced esophageal cancer).\[55\]

Endoscopic eradication therapy for BE includes endoscopic mucosal resection (EMR) and/or the endoscopic ablative techniques, which use thermal, photochemical, or radiofrequency energy to destroy the Barrett’s epithelium without providing a tissue specimen. Results from a large multicenter cohort study highlight the low annual incidence rates of dysplasia and early EAC in patients with BE (EAC, 0.27%; HGD, 0.48%; and HGD/EAC 0.63%).\[50\]

For patients with verified HGD or early cancer in BE, there are generally four proposed management options: esophagectomy, endoscopic therapies that ablate the neoplastic tissues, EMR and intensive endoscopic surveillance in which invasive therapies are withheld until biopsy specimens reveal adenocarcinoma.\[41\]

An emerging concept in the endoscopic management of neoplasia in BE is that endoscopic eradication may be best achieved by first removing visible abnormalities with EMR, a process which provides invaluable staging information as well as therapy, followed by the ablation of all remaining Barrett’s metaplasia.\[84\]

The largest reported experience with EMR as the primary technique to eradicate HGD and early cancer in BE involved 349 patients followed up for a mean of 63.6 mo. The early complete eradication rate for neoplasia was 97%, but metachronous neoplasms subsequently developed in 21.5% of patients; 85% of those received further endoscopic eradication therapy and achieved a second complete remission. Risk factors for metachronous neoplasm included piecemeal resection of the lesion, long-segment BE, no use of mucosal ablative therapies after EMR, time for complete remission over 10 mo, and multifocal neoplasia.\[85\]

This fact highlights the importance of total eradication of intestinal metaplasia and not only areas of HGD/EAC. Recently the role of complete BE removal in patients with HGD/early EAC by using EMR has been explored. It involves the endoscopic resection of the entire BE, including the neoplastic lesion. In a recent study, Peters et al.\[86\] evaluated the efficacy of this technique in 39 BE patients with early neoplasia (25 HGD, 14 EAC). Complete eradication of early neoplasia was achieved in all patients (mean number of 3 sessions), and complete removal of BE in 89% of patients. During a mean follow-up of 11 mo, none of the patients had a recurrence of intestinal metaplasia or dysplasia.

Among all the endoscopic techniques, photodynamic therapy (PDT) clearly has been most extensively used and reported in a randomized, controlled trial. Overholt et al.\[83\] were the first to provide long-term results of a randomized, controlled trial that compared treatment alternatives in HGD patients. In this study, 208 patients with HGD were randomized 2:1 to receive either omeprazole alone or omeprazole with sodium porfimer PDT. In the initial report of this study, with a 2-year follow up, the primary goal of complete eradication of HGD was achieved in 77% of patients in the PDT group and 39% of patients in the control group (P < 0.0001). In a subsequent follow up study with these patients 5 years later, intention-to-treat analyses showed that PDT was significantly more ef-
effective than omeprazole alone for eradicating HGD [77% (106/138) vs 39% (27/70), P < 0.0001] and that PDT-treated patients were less likely to progress to cancer (15% vs 29%, P = 0.027), although the trial was not designed specifically to test this outcome\(^\text{58}\).

RFA is the only technique besides PDT that has been evaluated in a multicenter, prospective, sham-controlled, randomized trial in BE patients with dysplasia, including 63 patients with HGD (42 RFA, 21 sham). Complete eradication of dysplasia was achieved in 81% in the RFA arm compared with 19% in the sham group (\(P < 0.0001\)), and complete eradication of intestinal metaplasia was achieved in 74% vs 0% (\(P < 0.0001\)) with no progression to cancer in patients in the RFA arm\(^\text{59}\).

The use of RFA for complete eradication of BE has shown promise in trials conducted predominantly at tertiary academic centers, however less is known regarding outcomes in the community. Recently a multicenter study conducted at four community-based practices observed that safety and efficacy outcomes associated with RFA for BE are comparable to those reported in multicenter trial predominantly from tertiary academic centers. In addition, RFA was associated with improvement in disease-specific health-related quality of life\(^\text{60}\). RFA use in patients in whom ablative therapy has previously failed was described by Dunn et al\(^\text{61}\) in 14 patients with residual HGD following PDT. An overall complete reversal of dysplasia was achieved in 86% with a combination of RFA and rescue EMR. The median total follow-up was 19 mo. The rate of strictures was 7% (1/14) and there was a low rate of burned glands (0.5% follow-up biopsies). This study is limited by its relatively small sample size and non-randomized design.

After endoscopic RFA of dysplastic BE, endoscopic biopsy samples are obtained to assess response to therapy. Whether these biopsies are of adequate depth to assess efficacy is unknown. Shaheen et al\(^\text{62}\) analyzed 5648 biopsy fragments from 113 subjects (78 RFA, 35 sham; mean 50.0 fragments per subject). Squamous biopsy samples from RFA and sham subjects demonstrated subepithelium at similar rates (78.4% vs 79.1%, respectively). Columnar biopsy samples from RFA and sham subjects also included subepithelium at similar rates (99% vs 98.8%, respectively). Almost 80% of all biopsy samples were adequate to evaluate for submucosal intestinal metaplasia.

If an ablation procedure does not destroy all of the metaplastic epithelium, then the partially ablated mucosa may heal with an overlying layer of neosquamous epithelium that buries metaplastic glands in the lamina propria, hiding them from the endoscopist’s view. This “buried metaplasia” may have malignant potential\(^\text{63}\). A recent systematic review found in 22 reports on PDT for 953 patients, with buried metaplasia in 135 (14.2%). In 18 reports on RFA for 1004 patients, buried metaplasia was found in only 9 (0.9%). A major problem limiting the conclusions that can drawn from these reports is that they do not describe specifically how frequently biopsy specimens contained sufficient subepithelial lamina propria to be informative for buried metaplasia\(^\text{64}\). A different result was found by Vaccaro et al\(^\text{65}\) who performed a retrospective analysis of patients with BE who underwent RFA. The cumulative incidence of newly detected intestinal metaplasia at 1 year was 25.9%, Pouw et al\(^\text{66}\) evaluated the post-RFA neosquamous epithelium for genetic abnormalities and buried glandular mucosa and found neither persistent genetic abnormalities nor buried glandular mucosa. Therefore, the frequency and importance of buried metaplasia after endoscopic ablation remain unclear.

In conclusion, prospective, randomized trials have established that endoscopic ablation therapy with PDT and RFA is superior to treatment with PPIs alone for preventing the progression from HGD to cancer in BE. RFA has a similar efficacy to PDT, but gives less patient inconvenience and fewer side effects\(^\text{67}\).

It is important to note that recurrence of intestinal metaplasia following endoscopic eradication therapy and the risk of squamous glands are associated with all ablative therapies and routine surveillance of these patients is required\(^\text{68}\).

Unfortunately, the follow up duration of most report studies on treatments for HGD and early cancer in BE is considerably less than 5 years, which severely limits the conclusions that can be drawn regarding the efficacy of therapy. In addition, most studies on this issue are not randomized or controlled and involve relatively small numbers of patients. Also, it remains unclear whether the excellent results for endoscopic eradication therapy reported by the few expert centers that have studied those techniques can be reproduced in the community\(^\text{69}\).

Presently, the choice between surgical or endoscopic therapy for early Barrett’s esophageal cancer is, in most institutions, still primarily based on the available expertise with one or other treatment modality and the patient’s operation risk, and both treatments have limitations\(^\text{68,69}\).

**CONCLUSION**

In the 1950s, Norman Barrett and other colleagues published a study on the association between EAC and esophageal columnar metaplasia. Ever since then, we have been looking forward to achieving a world-wide definition of BE, the best screening, surveillance and treatment modality.

Aggressive antireflux therapy with PPI can protect against but cannot prevent the development of dysplasia and its progression to adenocarcinoma. Both endoscopic and surgical treatments still have important limitations. It should be remembered that the best evidence will come from direct comparison in the form of a prospective trial, and this has not yet been carried out.

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