www.journalofcancerology.com PERMANYER J Cancerol. 2015;2:140-50

JOURNAL OF CANCEROLOGY REVIEW ARTICLE

# Oncological Perspectives in Barrett's Esophagus

OSVALDO A. QUIROZ-SANDOVAL*, ALEJANDRO E. PADILLA-ROSCIANO, HORACIO N. LÓPEZ-BASAVE, ALBERTO M. LEÓN-TAKAHASHI, LEONARDO S. LINO-SILVA AND ÁNGEL HERRERA-GÓMEZ

*Department of Gastrointestinal Tumors, Instituto Nacional de Oncología (INCan), Mexico City, Mexico*

## ABSTRACT

Barrett's esophagus refers to an acquired condition in which the normal squamous esophageal epithelium is replaced by a specialized type of columnar epithelium. Patients with Barrett's esophagus have a 30-60-fold greater risk of developing adenocarcinoma of the esophagus than the rest of the population; however only a small percentage of the population develops it. Even though its cause is unknown, it is related to chronic gastroesophageal reflux disease. Nevertheless, the relationship between gastroesophageal reflux disease and the risk of developing cancer of the esophagus has shown that an increase in the frequency, seriousness, and chronicity of the symptoms of reflux could be related to a increase of up to 2-16-fold in the risk of developing adenocarcinoma, irrespective of the presence of Barrett's esophagus.

Tumors of the esophagogastric junction classified as Siewert I have a relationship of close to 80%, whereas the presence of Barrett's esophagus is only associated in 5.6 and 0.8% for Siewert II and III tumors of the esophagogastric junction, respectively.

Without any treatment, the invasive cancer develops in up to 50% of patients with Barrett's esophagus and high-grade dysplasia over the course of three years. Endoscopic techniques for the resection and ablation of the metaplastic mucous are reserved for patients with high-grade dysplasia because of the elevated risk of progression to adenocarcinoma. In young patients with high-grade, multifocal dysplasia, whose condition has not been eradicated after one year of endoscopic treatment and with low surgical risk, vagus-preserving esophagectomy is considered the first treatment option. (J CANCEROL. 2015;2:140-50)

Corresponding author: Osvaldo A. Quiroz-Sandoval, osvaldo_quiroz80@hotmail.com

***Key words:*** Barrett's esophagus. Metaplasia. Dysplasia. Adenocarcinoma. Ablation. Vagus preserving esophagectomy.

**Correspondence to:**
*Osvaldo A. Quiroz-Sandoval
E-mail: osvaldo_quiroz80@hotmail.com

Received for publication: 10-03-2015
Accepted for publication: 25-04-2015

## DEFINITION

Barrett's esophagus refers to an acquired condition in which the normal squamous esophageal epithelium is replaced by a specialized type of columnar epithelium, with the required criteria in the West of finding goblet cells, considered to be pure or combined, and specialized intestinal metaplasia with a growth pattern that is usually multifocal[1-3].

## ETIOLOGY

Even though its cause is unknown, Barrett's esophagus is related to chronic gastroesophageal reflux disease (GERD). Nevertheless, the implication of the possible participation of alkaline reflux in the development of Barrett's esophagus is based on the appearance of intestinal metaplasia in patients with pernicious anemia as well as in those with a history of total gastrectomy, situations that develop with achlorhydria[4]. It has been suggested that the metaplastic epithelium originates from pluripotential germinal cells located in the basal layer of the denuded squamous epithelium, with capacity for differentiation into various cell phenotypes depending on the stimulus. This means that when the stimulus is predominantly acid, the metaplastic model suggests a gastro similar differentiation of the mucous in order to give it more resistance. On the other hand, when the stimulus is predominantly biliary, the differentiation suggests an intestinal-type cell line. In the same way, other factors such as duodenum-pancreatic reflux, in addition to smoking and the intake of > 50 g of alcohol a week, have been related as independent factors, with a risk threefold greater than each one individually[5].

## EPIDEMIOLOGY

The incidence is unknown as up to 40% of patients present no symptoms. Nevertheless, one international multicentric study, including Eastern European countries, Asia, and Central and South America, reported an incidence of 0.6-1.0% of the upper endoscopic procedures mainly performed in white male patients, over 60 years of age[6], with this prevalence increasing to 2.3-5.0% in those presenting symptoms of gastroesophageal reflux. The prevalence in Europe is about 1-4% of adults attending endoscopic services, with a predominance of men in a ratio of 2.5:19; in Japan it is 0.3-0.6%[7,8], where the causes for medical consultations for symptoms related to gastroesophageal reflux in the adult population is 1.3-1.6%, whereas in the West this represents around 29-44%[9].

In Africa and the Middle East, Barrett's esophagus and adenocarcinoma of the esophagus are infrequent (< 5% of the cases of cancer of the esophagus), with epidermoid carcinoma being the prevalent malignancy.

## RISK FACTORS

Some risk factors have been reported to favor the evolution of Barrett's esophagus into adenocarcinoma, including being male, white, obese, a smoker, aged over 50, and with a family history of adenocarcinoma[10].

These factors indicate a relative risk 30-60 times higher for the development of adenocarcinoma than the rest of the population. However, 95% of patients with Barrett's esophagus do not develop adenocarcinoma at all. It is estimated that only 5-8% of patients with GERD develop Barrett's esophagus, and of these, the risk of developing cancer is 0.5% per year, or as high as 6.6% a year in subjects with severe dysplasia[11].

The relationship between GERD and the risk of developing cancer of the esophagus has shown that any increase in the frequency, seriousness, and chronicity of reflux symptoms could be related to an increase of up to 2-16 times the risk of developing adenocarcinoma, irrespective of the presence

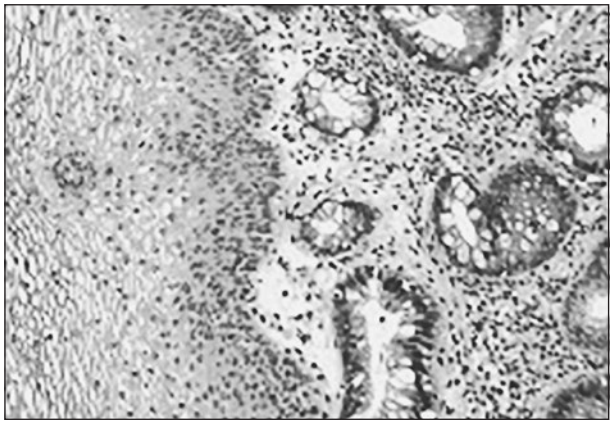

**Figure 1.** Hematoxylin and eosin stain revealing groups of glands with intestinal metaplasia with goblet cells (Barrett's esophagus) beneath the squamous epithelium. Hematoxylin and eosin × 100.

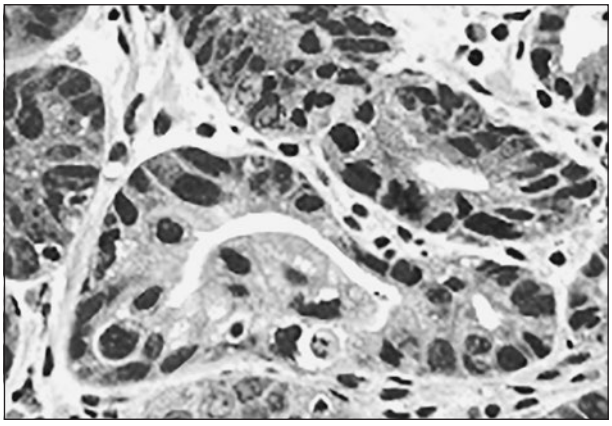

**Figure 3.** High-grade dysplasia in Barrett's esophagus. The nuclei are pleomorphic and irregular, the glands are irregular and with little surrounding stroma. Hematoxylin and eosin × 200.

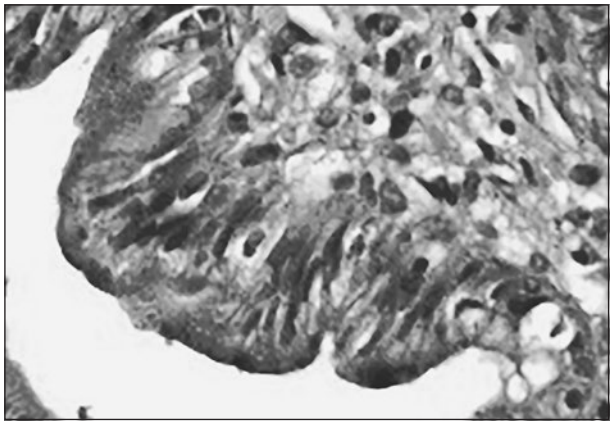

**Figure 2.** Low-grade dysplasia in Barrett's esophagus. The nuclei acquire a "cigar-like" shape and reveal their slight de-stratification. Hematoxylin and eosin × 200.

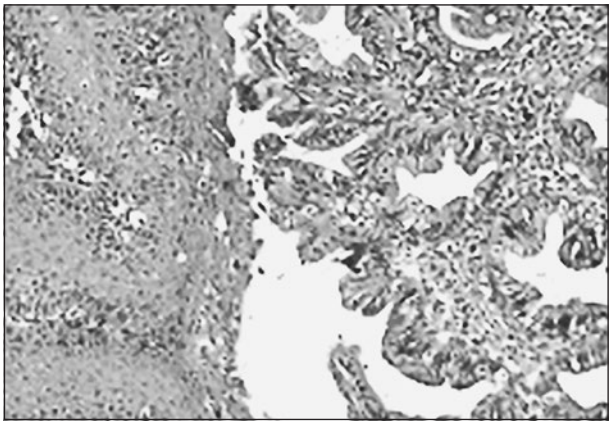

**Figure 4.** Invasive adenocarcinoma originating from Barrett's esophagus. A malignant neoplasia forming glands and papillate shapes can be seen beneath the squamous epithelium. Hematoxylin and eosin × 100.

of Barrett's esophagus. Individuals with GERD who experience weekly symptoms have a fivefold higher risk of developing adenocarcinoma of the esophagus compared to asymptomatic individuals, whereas for individuals who experience daily symptoms, this risk increases by up to sevenfold[12].

## DIAGNOSIS

According to the American Gastroenterological Association (AGA), establishing the diagnosis of Barrett's esophagus requires endoscopically corroborating a proximal displacement of the squamocolumnar mucosal junction in the distal esophagus, and the histological determination of a specialized intestinal epithelium with presence of goblet cells that are PAS-positive or stain with Alcian blue[13]. The diagnostic sensitivity can be increased by taking biopsies from the four quadrants, initiating at a height of the proximal edge of the gastric folds and ascending every 2 cm to the squamocolumnar mucosal junction as per the Seattle protocol. However, multiple studies have shown that even in spite of the extension and number of biopsies, up to 30-50% of patients diagnosed for Barrett's esophagus and high-grade dysplasia undergoing esophagectomy present occult invasive carcinoma[14,15] (Fig. 1-4).

Chromo-endoscopy increases the diagnostic specificity by allowing adequate recognition of the squamocolumnar mucosal junction, taking targeted biopsies of the columnar epithelium, and the recognition of residual metaplasia following ablative treatments. However, it has not yet been possible to verify its superiority compared to high-definition endoscopy, and the lack of studies comparing its use with conventional endoscopy minimizes its use to already identified lesions[16,17]. Methylene blue offers a sensitivity of 75.2% for the detection of intestinal metaplasia and 83.1% for dysplastic lesions, and some authors even report a certainty of 95% for taking biopsies, thus considering that a smaller number of biopsies is necessary for correct assessment of intestinal metaplasia and dysplastic lesions in comparison to conventional techniques[18,19]. Studies by Edge, et al.[20] showed increased detection of dysplastic lesions with methylene blue in the metaplastic epithelium using pan-Barrett. However, these results have not been able to be consistently reproduced, thus limiting their recommendation in clinical practice. Guelrud, et al. described the use of acetic acid with magnification endoscopes to predict the existence of intestinal metaplasia through the observation of crypt patterns, arguing that their use could simplify the detection of dysplastic lesions with a red flag technique through its application in pan-Barrett; nevertheless, its use in clinical practice has not been adequately studied.

The application of virtual chromo endoscopy in combination with optical magnification endoscopes could be useful as confirmatory proof in lesions suspected of dysplasia, using auto-fluorescence in trimodal imaging endoscopy. The application of narrow band imaging with magnification enables reducing the number of false positives from 81 to 26%[21]. This diagnostic approach for the detection of dysplastic lesions seems attractive, but the results must yet be studied.

The confocal laser endomicroscopy using fluorescein sodium enables an *in vivo* microscopic vision at the same time as the standard endoscopic examination, thus being capable of providing *in vivo* images magnified 1,000-fold in a field of vision of 500 × 500 µm, taking slices from the surface tissue at intervals of 7 µm and reaching a maximum depth of 250 µm; it has a sensitivity of 92.9% and a specificity of 98.4%[21].

## ANATOMIC PATHOLOGY

From the macroscopic point of view and depending on how the columnar epithelium unfolds in the distal esophagus, it can be classified in two main models: circumferential or tongue-forming.

The circumferential type is more conventional and characterized by presentation as a continuous layer of columnar epithelium from the Z-line up to the esophagogastric junction (OGJ). In turn, circumferential Barrett's esophagus is subdivided into two types, depending on the length of the segment of columnar epithelium lined by the squamous epithelium: short-segment and long-segment Barrett's esophagus.

Short-segment Barrett's esophagus is when the length of the columnar epithelium is less than 3 cm (risk of dysplasia 6-8%) and long-segment is when it is 3 cm or more (risk of dysplasia 15-24%). It is estimated that the risk of adenocarcinoma in patients with long-segment Barrett's esophagus is 1/100 patients per year (2-15 times higher)[22,23]. This division was initially made for research purposes and to prevent false positive diagnosis. However, limiting the diagnosis to a length of 3 cm or more was disregarding the presence of columnar epithelium, especially the intestinal type, in the last 2-3 cm of the distal esophagus.

The risk of adenocarcinoma seems to vary with the length of the esophagus lined by intestinal metaplasia; patients with long-segment Barrett's esophagus have a greater risk of malignancy. However, short-segment Barrett's esophagus is much more common than long-segment Barrett's esophagus,

and many (if not the majority of) cancers associated with Barrett's esophagus in the general population occur in patients with short-segment Barrett's esophagus. Even though the prevalence of Barrett's esophagus increases with age, this does not happen with its length. Various authors suggest that Barrett epithelium develops its maximum length quickly and remains stable for many years[23-25]. However, the demographic and pathogenic aspects of both entities seem similar, suggesting that they represent the continuity of a single entity.

When Barrett's esophagus forms tongues, this is because the columnar epithelium grows towards the esophagus irregularly in the form of tongues. Another less common form of endoscopic presentation is islands of columnar mucosa.

The Prague criteria (C and M) have been proposed to standardize endoscopic criteria, where C refers to the length of the circumferential metaplastic epithelium and M its maximum extension. This means that a circumferential extension that goes beyond 3 cm of the OGJ with 5 cm tongues is designated as C3 M5; and an extension only in tongues of up to 3 cm is described as C0 M3[26].

Because of the reticence of the western world to recognize the terms flat or depressed adenoma and non-invasive carcinoma in the gastrointestinal tract, as well as the discrepancy in the term dysplasia (which is not normally used in Japanese clinical practice, with the exception of squamous lesions bordering the esophagus) the Vienna classification was developed for epithelial lesions of the gastrointestinal tract[27,28] to establish histological criteria that define the grade of epithelial dysplasia in a practical way by dividing the epithelial malignancy into five categories:

– No dysplasia;

– Indefinite for dysplasia;

– Low-grade intraepithelial neoplasia;

– High-grade intraepithelial neoplasia;

– Invasive epithelial neoplasia;

- Intramucosal cancer: Invasion of the lamina propria, but not further than the mucous muscle;
- Submucosal cancer: Invasion beyond the mucous muscle, affecting the submucous but not the muscularis propria.

On many occasions it is difficult to establish a difference between regenerative or reactive histological changes and those caused by neoplasia, especially when the degree of esophagitis is accompanied by erosion and ulceration in the epithelium. For this reason, when the classification is indefinite for dysplasia, the biopsy should be repeated after controlling the inflammatory process with proton pump inhibitors (PPI). When high-grade dysplasia is present in Barrett's epithelium, there is a probability of 10-50% that other sectors of the metaplastic epithelium present foci of invasive adenocarcinoma that were not detected due to sampling errors.

## PROGNOSIS

Without any treatment, invasive cancer develops in up to 50% of patients with Barrett's esophagus and high-grade dysplasia over the course of three years. As the screening programs currently used for Barrett's esophagus cannot identify the 50% of patients with short-segment Barrett's esophagus without symptoms of GERD, the impact on the mortality from esophageal adenocarcinoma in the general population is limited. At present, less than 5% of patients with esophageal adenocarcinoma have a previous diagnosis of Barrett's esophagus[29]. In the same way, patients with high-grade dysplasia with a diffuse growth pattern have greater risk of developing adenocarcinoma than those with a focal growth pattern[30]. Nevertheless, close to 50% of patients with high-grade focal dysplasia progress to high-grade dysplasia with multifocal growth

pattern[31]. It is important to note that the extension of high-grade dysplasia is not predicted by the presence of occult adenocarcinoma.

## MEDICAL TREATMENT

As Barrett's epithelium is a complication of GERD, theoretically any effective anti-reflux treatment could induce regression of the metaplasia or at least prevent its progression. Even though it has been reported that PPIs increase cellular differentiation, promote apoptosis, and reduce cell proliferation as well as cyclooxygenase-2 levels (COX-2), the results of different studies are contradictory, there being no overwhelming evidence supporting the fact that acid suppression prevents the development of adenocarcinoma in individuals with Barrett's esophagus[32,33].

It has been shown that the increased COX-2 expression is associated in a step-like way in the progressive sequence of metaplasia-dysplasia-adenocarcinoma[34]. Two recent meta-analyses and a combined analysis of six population studies mainly based on studies of cases and controls revealed very similar results: a reduction of 32-36% in the risk of esophageal adenocarcinoma among users of aspirin and non-steroidal anti-inflammatory drugs (NSAID), compared to the general population[35-37]. However, the factors influencing the use of NSAIDs constitute a threat for the validation of observational studies[38,39].

## SURGICAL TREATMENT

### Surgical anti-reflux treatment

Surgical anti-reflux treatment has not shown any regression or reduction in the probability of developing adenocarcinoma in patients with Barrett's esophagus. The Veterans Affairs Cooperative Study made a prospective comparison of the results of 10 years follow-up of 239 patients with symptoms of severe GERD who underwent surgical vs. medical anti-reflux treatment without there being any significant difference compared to the incidence of cancer in the long term[40]. Moreover, the results of various randomized clinical trials have not provided evidence to support that medical or surgical anti-reflux treatment can eradicate Barrett's dysplasia[41]. Bearing in mind that the primary purpose of surgical anti-reflux treatment is symptomatic control, and not to reduce the risk of progression to adenocarcinoma, a program of close endoscopic surveillance should continue, especially because even after partial regeneration of the esophageal mucous, there is still a risk of malignancy in the subsistent metaplastic area[42,43]. One explanation for the lack of a preventive effect of anti-reflux surgery could be that many patients experience recurrence of symptoms after surgery as it has been reported that in this sub-group, only one third of patients who develop adenocarcinoma have a functional funduplication[44], thus showing that recurrence of the reflux is the main risk factor for the development of adenocarcinoma after treatment with anti-reflux surgery[45].

The American College of Gastroenterology (ACG) recommends endoscopic follow-up every three years in patients with Barrett's esophagus, and with at least two endoscopic procedures taking biopsies without any previous indication of dysplasia. In the event of finding low-grade dysplasia, annual follow-up is recommended. In young patients with high-grade, multifocal dysplasia, whose condition has not been eradicated after one year (three or four sessions) of endoscopic treatment, and with low surgical risk, vagus-preserving esophagectomy is considered the first treatment option. In the event of finding high-grade unifocal dysplasia, some authors recommend less-aggressive procedures for eradication, such as ablative or resective endoscopic procedures vs. surveillance by close endoscopic follow-up every three months until adenocarcinoma is diagnosed. In those cases where it is present in an irregular area of mucous, endoscopic mucosal resection is recommended[46].

Curvers, et al.[47] reported a progression of 9.1% annually of low-grade dysplasia to high-grade dysplasia in a retrospective analysis of 293 patients with GERD, where 27% had been diagnosed for low-grade dysplasia after an average follow-up of 39 months, compared to patients with Barrett's esophagus without evidence of dysplasia, or those with an indefinite diagnosis for dysplasia (risk of progression to dysplasia of 0.6 and 0.9% annually, respectively).

## ENDOSCOPIC TREATMENT

### Endoscopic resection

Endoscopic techniques for the resection and ablation of the metaplastic mucous are reserved for patients with high-grade dysplasia because of the elevated risk of progression to adenocarcinoma. As these techniques are not free of complications, and the risk of progression in patients with Barrett's esophagus with or without low-grade dysplasia is extremely low, its indication in this sub-group of patients is restricted to research protocols only.

Endoscopic resection of the metaplastic epithelium enables assessing the character and extension of the lesion, offering similar results to surgical esophagectomy, but with significantly lower morbidity and mortality rates. Ell, et al.[48] reported excellent survival at five years of 98% in 100 patients with well-differentiated, unifocal intramucosal adenocarcinoma, < 20 mm and without evidence of lymphovascular invasion, treated only with endoscopic resection and high doses of PPIs. However, the majority of patients had short-segment Barrett's esophagus and, in spite of the relatively short follow-up, 11% developed metachronous tumors at 33 months of follow-up (treated successfully by endoscopic resection). Probably, in a larger case mix with longer follow-up, this percentage would be even higher, thus leading to consider the high risk these patients with early, unifocal adenocarcinomas with residual dysplasia have for developing metachronous neoplasias. For this reason, some form of ablation should be included to treat residual dysplasia in patients with early esophageal adenocarcinoma treated by endoscopic mucosectomy. Complete eradication of the epithelium with Barrett's esophagus is recommended in patients with high-grade dysplasia.

### Endoscopic ablation

Ablative treatments are implemented as a therapeutic alternative to surgical treatment in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma. Schnell, et al.[49] reported re-epithelization with pluristratified epithelium in 75-100% of patients with short-segment Barrett's esophagus who underwent ablative treatment.

### Photodynamic therapy

Photodynamic therapy is a laser ablation technique that uses a Nd YAG (neodymium-doped yttrium aluminum garnet) crystal as a lasing medium for solid state lasers (Nd: Y3Al5O12). Its characteristic emission has an infrared wavelength of 1,064 nanometers and is applied through a fiber optic diffuser along the working channel of a standard endoscope. The patient is previously given an intravenous administration of a photosensitizer derived from hematoporphyrin (photofrin II) 48 hours before the procedure to enable its selective accumulation in tissues in proliferation phase. The absorption of light by the photosensitized tissue enables the transmission of energy through the oxygen molecules, producing peroxidative reactions leading to apoptosis. With success rates for the eradication of high-grade dysplasia in patients with Barrett's esophagus of between 51-84% and 56-100% for high-grade dysplasia (combined with high doses of PPIs), stenosis of the esophagus is the most common complication reported in up to 40% of cases, followed by photo-sensitivity reactions in 10%[50,51].

## Radiofrequency ablation

Radiofrequency ablation is indicated for circumferential lesions longer than 2 cm using an ablation catheter in a Halo 360MR radiofrequency balloon, which contains microelectrodes capable of emitting the transmitted energy circumferentially and the possibility of treating residual lesions using a Halo 90MR balloon. This technique enables eradicating the microscopic disease, reporting residual disease in < 0.1% of neosquamous mucous biopsies during follow-up of these patients. The macroscopic disease should be eradicated using endoscopic mucosectomy with posterior radiofrequency ablation once the eschar of the endoscopic mucosectomy has re-epithelized[52].

Various authors have reported a percentage of eradication for mild dysplasia at 12 months of 90%, severe dysplasia 81%, and metaplastic epithelium in 77.4% of cases, with less progression towards adenocarcinoma than in the control group. The stenosis rate is less than 10%. However, about four applications are required per session; moreover, the majority of series reported needed up to four or more sessions over a period of time exceeding nine months before being able to report complete eradication of the lesion[53,54].

## Argon plasma coagulation

This technique consists of ablation of the mucous membrane through thermocoagulation using an argon cannula that is introduced through the biopsy channel of a conventional endoscope. Its application enables destruction of the mucous to a depth of up to 5 mm. In general, 2-4 sessions are required every eight weeks for complete eradication of the metaplasia. The most frequent complications are chest pain, stenosis, fever, and bleeding. Recent cohorts assessing the endoscopic treatment of Barrett's esophagus based on ablation with argon plasma and high-dose PPIs report complete ablation in ranges of 61.0-98.6%, depending on the amount of energy used, and better results being observed with 90 W[55,56].

Furthermore, just like other ablative therapies, there may be occult metaplastic epithelium areas on the lamina propria below the regenerated squamous epithelium, with the possibility of evolving into adenocarcinoma[57,58]. These areas of occult metaplastic epithelium beneath the neosquamous epithelium are usually reported on the Z-line in 28% and in islands of regenerated squamous epithelium in 38.5%[59]. Some studies with heterogeneous universes and variable follow-up (four weeks to five years) have reported this possibility in 0-28% of cases[59-61]. Nevertheless, in an attempt to establish the frequency with which this condition is reported in the literature, after analysis of 953 patients reported in 22 cohorts treated with photodynamic therapy and high doses of omeprazole, and using analysis of serial biopsies with sampling that included the lamina propria, it was found that 14.2% of patients had occult metaplasia beneath the newly formed epithelium[60]. In the same way, the reported frequency of occult metaplasia beneath the neosquamous epithelium was 0.9% in 1,004 patients treated with radiofrequency, reported in 18 series that included sampling at a level of the lamina propria and with a varied follow-up of eight weeks to five years[62].

This is why some authors do not consider it prudent to suggest ablative endoscopic therapies as first-line treatment in patients with Barrett's esophagus and high-grade dysplasia, it being reserved for patients with high surgical risk after discussing other therapeutic alternatives.

Only one study made a controlled analysis of this condition in patients with high-grade dysplasia who underwent ablation with photodynamic therapy (n = 130) vs. only follow-up with biopsy (n = 70). Occult metaplasia was found in 30% of patients undergoing ablation vs. 33% in the control group[61]. Moreover, the same situation has been reported in up to 38.7% of cases in patients in follow-up who had never received ablative treatment[63].

It is important to mention that no report in the literature mentioned the development of adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia treated with radiofrequency and a maximum reported follow-up of five years[62].

The associated risk of developing adenocarcinoma in these patients is not precisely known, even though some authors consider that the occult metaplasia beneath newly formed squamous epithelium provides a certain protection against aggressive stimuli from the external environment. Others promote the hypothesis that changes on a DNA level bring about the transformation of metaplastic epithelium and may imply a certain cell resistance to ablative therapies; this would hypothetically condition the burial of these cells with risk of malignancy beneath the neosquamous epithelium formed following ablation[64]. Hornik, et al.[65] reported finding less proliferation of crypts and lower number of DNA disorders in biopsies at a level of the lamina propria with occult metaplasia beneath neosquamous epithelium in patients in follow-up after ablation in comparison to biopsies of surface metaplasia. Nevertheless, the level of proliferation and DNA disorders in order to determine the risk of adenocarcinoma in patients with metaplasia is open to debate. To date, none of the studies reported in the literature contains sufficient evidence to support any of these hypotheses.

The indication for ablative or resective endoscopic therapies as well as the possibility of esophagectomy in patients with Barrett's esophagus and high-grade dysplasia will depend on the experience of each center, the possibility of access to the various alternative technologies, as well as the condition of each patient, in particular taking into account the benefit and consequences of each procedure.

## FOLLOW-UP

All patients subjected to ablative or resective treatments of the mucous should receive chronic treatment with high doses of PPIs (120 mg of omeprazole a day) in order to diminish the acidity caused by reflux and so reduce the possibility of recurrence. They should also be submitted to endoscopic follow-up to detect any recurrent lesions. Even though endoscopic follow-up is not standardized, the majority of studies recommend performing it every three months during the first year and then on an annual basis.

There is a strong relationship between the duration of the chronic symptoms of GERD and the development of Barrett's esophagus, this probability being 10% at five years, 15% for 5-10 years, and 20% for more than 10 years[66]. Based on the above, the Latin American GERD Council recommends performing fibrogastroscopy in patients who have presented symptoms of GERD for more than five years[67]. In addition, the guidelines of the ACG recommend performing fibrogastroscopy for the early detection of Barrett's esophagus in patients with long duration GERD[46].

Remember that these recommendations are based on the opinion of a committee and these benefits following screening are not confirmed. There is no scientific evidence supporting the use of fibrogastroscopies in patients with a greater risk of developing Barrett's esophagus, as a cost-effective reduction in the adenocarcinoma mortality rate has not been demonstrated. Based on prospective studies, it would seem more appropriate to only offer close surveillance to patients with intestinal metaplasia and additional risk factors such as ulceration, stenosis, and long segments of more than 8 cm[68].

However, a strategy of long-term follow-up using endoscopy with biopsies taken every three years would result in 15 or more endoscopic examinations for a 30-year-old patient with Barrett's esophagus, seven or more for one 45 years old, and four or more for one 60 years old, representing more than half a million endoscopic examinations a year, thus making this unsustainable and impractical for the patient. Hence, ablative endoscopic therapies are considered an alternative treatment[69].

Furthermore, it is estimated that up to 95% of the deaths recorded in patients with Barrett's esophagus occur because of secondary complaints, the majority being cardiovascular diseases[70]. For this reason, the AGA and the American Society of Gastroenterology and Endoscopy (ASGE) do not recommend it[71,72].

The guidelines of the American College of Gastroenterology recommend endoscopic surveillance every three years in subjects diagnosed for Barrett's esophagus, with a background of two previous endoscopic examinations over the last six months, without evidence of dysplasia in the biopsies. In the presence of low-grade dysplasia and without evidence of high-grade dysplasia at the six-monthly endoscopic control, annual endoscopic follow-up is recommended until two consecutive endoscopies show no evidence of dysplasia in the biopsies. In the presence of high-grade dysplasia, three-monthly endoscopic control is recommended to reject the presence of adenocarcinoma, especially in patients with a high risk of developing adenocarcinoma and who refuse resective endoscopic treatment[73].

## REFERENCES


1. Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. Hum Pathol. 1994;25:982-93.
2. Van Dekken H. Histopathology of Barrett's esophagus. In: Tilanus HW, Attwood SEA (eds). Barrett's Esophagus. Dordrecht, the Netherlands: Kluwer Academic Publishers; 2001:159-67.
3. Van Dekken H, Wim CJ, Tilanus HW, et al. Immunohistochemical evaluation of a panel of tumor cell markers during malignant progression in Barrett esophagus. Am J Clin Pathol. 2008;130:745-53.
4. Jankowski J. Gene expression in Barrett's mucosa: Acute and chronic adaptative responses in the oesophagus. Gut. 1993;34:1649-50.
5. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: An endoscopic study. Gastroenterology. 2005;129:1825-31.
6. Sharma P. The geoprevalence of Barrett´s esophagus. Aliment Pharmacol Ther. 2004;20:48-54.
7. Cameron AJ. Epidemiology of Barrett's esophagus and adenocarcinoma. Dis Esoph. 2002;15:106-8.
8. Sharma P. The Worldwide Prevalence of Barrett´s Esophagus. World Gastroenterology News. 2001;6:22-5.
9. Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. Am J Gastroenterol. 1998;93:1816-22.
10. Brown LM, Swanson CA, Gridley G, et al. Adenocarcinoma of the esophagus: Role of obesity and diet. J Natl Cancer Inst. 1995;87:104-9.
11. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett esophagus and high-grade dysplasia: A meta-analysis. Gastrointest Endosc. 2008;67:394-8.
12. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: The AGA Chicago Workshop. Gastroenterology. 2004;127:310-30.
13. Peuchmaur M, Potet F, Goldfain D. Mucin histochemistry of the columnar epithelium of the esophagus (Barrett's esophagus): A prospective study. J Clin Pathol. 1984;37:607-10.
14. Dar MS, Goldblum JR, Rice TW, Falk GW. Can extent of high grade dysplasia in Barrett's oesophagus predict the presence of adenocarcinoma at oesophagectomy? Gut. 2003;52:486-9.
15. Shailender S, Prateek S. Magnifying endoscopy in upper GI tract and lower GI tract. Digest Endosc. 2005;17:17-19.
16. Vázquez-Iglesias JL, Alonso-Aguirre P, Diz-Lois MT, Vázquez-Millán MA, Alvarez A, Lorenzo MJ. Acetic acid allows effective selection of areas for obtaining biopsy samples in Barrett's esophagus. Eur J Gastroenterol Hepatol. 2007;19:187-93.
17. Curvers WL, Singh R, Song LM, et al. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: A multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut. 2008;57:167-72.
18. Howhat JD, Maydonovitch CL, Ramos F, et al. A Randomized comparison of methylene blue directed biopsy versus conventional four-quadrant biopsy for detection of intestinal metaplasia and dysplasia in patients with long-segment Barrett´s esophagus. Am J Gastroenterol. 2008;103:546-54.
19. Ngamruengphong S, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: A meta-analysis. Gastrointest Endosc. 2009;69:1021-8.
20. Canto MI, Setrakian S, Willis J, et al. Methylene-blue directed biopsies improve detection of intestinal metaplasia and dysplasia in Barrett's esophagus. Gastrointest Endosc. 2000;51:560-8.
21. Kiesslich R, Gossner L, Goetz M, et al. In vivo histology of Barrett's esophagus and associated neoplasia by confocal laser endomicroscopy. Clin Gastroenterol Hepatol. 2006;4:979-87.
22. Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus: The need for standardization of the definition and of endoscopic criteria. Am J Gastroenterol. 1998;93:1033-6.
23. Pera M. Trends in incidence and prevalence of specialized intestinal metaplasia, Barrett's esophagus, and adenocarcinoma of the gastroesophageal junction. World J Surg. 2003;27:999-1008.
24. Skinner DB, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett´s esophagus: Comparison of benign and malignant cases. Ann Surg. 1983;198:554-65.
25. Cameron AJ. Epidemiology of columnar-lined esophagus and adenocarcinoma. Gastroenterol Clin North Am. 1997;26:487-94.
26. Prateek S. The current approach to Barrett's esophagus and dysplasia. WGN. 2006;11:10-11.
27. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000;47:251-5.
28. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut. 2002;51:130-1.
29. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett´s esophagus correlates with risk of adenocarcinoma. Gastroenterology. 2001;120:1630-9.
30. Buttar NS, Wang KK, Lutzke LS, Krishnadath KK, Anderson MA. Combined endoscopic mucosal resection and photodynamic therapy for esophageal neoplasia within Barrett´s esophagus. Gastrointest Endosc. 2001;54:682-8.
31. Weston AP, Sharma P, Topalovski M et al. Long-term follow-up of Barrett´s high-grade dysplasia. Am J Gastroenterol. 2000;95:1888-93.
32. Katz PO. The role of non-acid reflux in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000;14:1539-51.
33. Tamhankar AP, Peters JH, Portale G, et al. Omeprazole does not reduce gastroesophageal reflux: New insights using multichannel intraluminal impedance technology. J Gastrointest Surg. 2004;8:890-7.
34. Bazuro GE, Torino F, Gasparini G, Capurso L. Chemoprevention in gastrointestinal adenocarcinoma: For few but not for all? Minerva Gastroenterol Dietol. 2008;54:429-44.
35. Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: Results from a cohort study and a meta-analysis. Br J Cancer. 2009;100:551-7.
36. Liao LM, Vaughan TL, Corley DA, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. Gastroenterology. 2012;142:442-52.

37. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: A quantitative review to 2011. Ann Oncol. 2012;23:1403-15.
38. Lindblad M, Lagergren J, Garcia R. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:444-50.
39. Anderson LA, Johnston BT, Watson RG, et al. Nonsteroidal anti-inflammatory drugs and the esophageal inflammation metaplasia-adenocarcinoma sequence. Cancer Res. 2006;66:4975-82.
40. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of randomized controlled trial. JAMA. 2001;285:2331-8.
41. Rees JR, Lao-Sirieix P, Wong A, Fitzgerald RC. Treatment for Barrett´s oesophagus. Cochrane Database Syst Rev. 2010;(1):CD004060
42. Chang EY, Morris CD, Seltman AK, et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with Barrett esophagus: A systematic review. Ann Surg. 2007;246:11-21.
43. Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. N Engl J Med. 2008;359:1700-7.
44. Kauttu TM, Rantanen TK, Sihvo EI, Räsänen JV, Puolakkainen P, Salo JA. Esophageal adenocarcinoma arising after antireflux surgery: A population-based analysis. Eur J Cardiothorac Surg. 2011;40:1450-4.
45. Lofdahl HE, Lu Y, Lagergren P, Lagergren J. Risk factors for esophageal adenocarcinoma after antireflux surgery. Ann Surg. 2013;257:579-82.
46. Sampliner RE; Practice Parameters Committee ACG. Updated guidelines for the diagnosis, surveillance and therapy of Barrett´s esophagus. Am J Gastroenterol. 2002;97:1888-95.
47. Curvers WL, ten Kate FJ, Krishnadath KK et al. Low-grade dysplasia in Barrett's esophagus: Overdiagnosed and underestimated. Am J Gastroenterol. 2010;105:1523-30.
48. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc. 2007;65:3-10.
49. Schnell TG, Sontag SJ, Chejfec G, et al. Long term nonsurgical management of Barret's esophagus with high-grade dysplasia. Gastroenterology. 2001;120:1607-19.
50. Overholt B. Acid suppression and reepithelialization after ablation of Barrett's esophagus. Dig Dis. 2001;18:232-9.
51. Gray J, Fullarton GM. Long term efficacy of Photodynamic Therapy (PDT) as an ablative therapy of high grade dysplasia in Barrett's oesophagus. Photodiagnosis Photodyn Ther. 2013;10:561-5.
52. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol. 2010;8:23-9.
53. Sharma VK, Wang KK, Overholt BF, et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc. 2007;65:185-95.
54. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360:2277-88.
55. Schulz H, Miehlke S, Antos D, et al. Ablation of Barrett´s epithelium by endoscopic argon plasma coagulation in combination with high-dose omeprazole. American Society for Gastrointestinal Endoscopy. Gastrointest Endoscop. 2000;51:659-63.
56. Nomura T, Yamashita K, Miyashita M, Tajiri T. [Argon plasma coagulation in Barrett´s esophagus.] Nihon Rinsho. 2005;63:1458-62.
57. Van Laethem JL, Peny MO, Salmon I, Cremer M, Devière J. Intramucosal adenocarcinoma arising under squamous re-epithelialisation of Barrett's oesophagus. Gut. 2000;46:574-7.
58. Shand A, Dallal H, Palmer K, Ghosh S, MacIntyre M. Adenocarcinoma arising in columnar lined oesophagus following treatment with argon plasma coagulation. Gut. 2001;48:580-1.
59. Chennat J, Ross AS, Konda VJ, et al. Advanced pathology under squamous epithelium on initial EMR specimens in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: Implications for surveillance and endotherapy management. Gastrointest Endosc. 2009;70:417-21.
60. Mino-Kenudson M, Ban S, Ohana M, et al. Buried dysplasia and early adenocarcinoma arising in Barrett esophagus after porfimer-photodynamic therapy. Am J Surg Pathol. 2007;31:403-9.
61. Bronner MP, Overholt BF, Taylor SL, et al. Squamous overgrowth is not a safety concern for photodynamic therapy for Barrett's esophagus with high-grade dysplasia. Gastroenterology. 2009;136:56-64.
62. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: A systematic review. Am J Gastroenterol. 2011;106:1899-909.
63. Sharma P, Morales TG, Bhattacharyya A, Garewal HS, Sampliner RE. Squamous islands in Barrett's esophagus: What lies underneath? Am J Gastroenterol. 1998;93:332-5.
64. Prasad GA, Wang KK, Halling KC, et al. Utility of biomarkers in prediction of response to ablative therapy in Barrett's esophagus. Gastroenterology. 2008;135:370-9.
65. Hornick JL, Mino-Kenudson M, Lauwers GY, Liu W, Goyal R, Odze RD. Buried Barrett's epithelium following photodynamic therapy shows reduced crypt proliferation and absence of DNA content abnormalities. Am J Gastroenterol. 2008;103:38-47.
66. Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE Consortium. Gastroenterology Outcomes Research Group in Endoscopy. Am J Gastroenterol. 1997;92:1293-7.
67. Cohen H, Tomasso G, Cafferata M, et al. An evidence-based, Latin-American consensus on gastrooesophageal reflux disease. Eur J Gastroenterol Hepatol. 2006;18:349-68.
68. Dent J, Bremner CG, Collen MJ, Haggitt RC, Spechler SJ. Barrett´s oesophagus. J Gastroenterol Hepatol. 1991;6:1-22.
69. Fennerty MB. Perspectives on endoscopic eradication of Barrett´s esophagus: Who are appropriate candidates and what is the best method? Gastrointest Endosc. 1999;49:24-8.
70. Wright TA, Gray MR, Morris AI, et al. Cost effectiveness of detecting Barrett's cancer. Gut. 1996;39:574-9.
71. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett's oesophagus in high-risk groups: a cost-utility analysis. Ann Intern Med. 2003;138:176-86.
72. Eckardt VF, Kanzler G, Bernhard G. Life expectancy and cancer risk in patients with Barrett's esophagus: A prospective controlled investigation. Am J Med. 2001;11:33-7.
73. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett´s esophagus. N Eng J Med. 2011;365:1375-83.