Barrett's Esophagus – State of the Art

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Abbreviations:

BE - Barrett's Esophagus;
PD - Photodynamic therapy;
GERD - Gastroesophageal Reflux Disease;
PPI - Proton Pump Inhibitors;
PUD - Peptic Ulcer Disease;
BMI - Body Mass Index;
NSAIDs - Non-Steroidal Anti-Inflammatory
Drugs;
EGJ - Esophagogastric Junction;
NBI - Narrow-Band Imaging;
HGIN - High-Grade Intraepithelial Neoplasia;
IMSP - Irregular Microstructural Pattern;
AMSP - Absent Microstructural Pattern;
RMVP - Regular Microvascular Patterns;
IMVP - Irregular Microvascular Patterns;
COX - Inhibit Cyclooxygenase;
ER - Endoscopic Resection;
PDT - Photodynamic Therapy;
RFA - Radiofrequency Ablation;
EMR - Endoscopic Mucosal Resection;
ESD - Endoscopic Submucosal Dissection.

Rezumat

Esófagul Barrett – "State of the art"

Esófagul Barrett (EB) este definit ca o stare premalignă prin care epiteliul scuamos esofagian este înlocuit cu epiteliul de tip intestinal. Metaplazia columnară intestinală specializată tipică pentru esófagul Barrett nu produce simptome. Majoritatea pacienților sunt văzuți inițial pentru simptomele asociate cu boala de reflux gastroesofagian (BRGE), cum ar fi pirozis, regurgitare și disfație. Progresiunea histologică de la metaplazie intestinală la displazie și apoi la adenocarcinom asociat EB, reprezintă rațiunea unui screening și a unei supravegheri endoscopice. Examinarea esófagului Barrett este controversat. Unele grupuri sugerează screening pacienților cu mai mulți factori de risc pentru dezvoltarea adenocarcinomului esofagian (de exemplu, boala de reflux gastro-esofagian, vârsta > 50 ani, sex masculin, indice de masă corporală crescută cu un model abdominal de distribuție a lipidelor). Rațiunea principală din spatele tratamentului refluxului acid este că poate duce la inflamatie cronică esofagiană, care la rândul sau poate predisune la dezvoltarea cancerului.

Cuvinte cheie: esofag Barrett, stare premalignă, metaplazie columnară, ablație endoscopică

Abstract

Barrett's Esophagus (BE) is defined as a premalignant condition, where the esophageal squamous epithelium is replaced by

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intestinal epithelium. Specialized intestinal columnar metaplasia, typical for Barrett's esophagus, does not generate any symptoms. Most of the patients are initially seen for symptoms associated with the gastroesophageal reflux disease (GERD), such as heartburn, regurgitation and dysphagia. The histological progression from intestinal metaplasia to dysplasia and then to BE-associated adenocarcinoma forms the argument for screening and endoscopic monitoring. The examination of Barrett's esophagus is controversial. Certain groups suggest a screening of the patients who exhibit more risk factors for the development of esophageal adenocarcinoma (for instance, gastroesophageal reflux disease, age > 50, male, high body mass index with abdominal fat distribution). The main reason behind the treatment of acid reflux is that it may lead to chronic esophageal inflammation, which in its turn may predispose to the development of cancer.

Key words: Barrett's esophagus, premalignant condition, columnar metaplasia, endoscopic ablation

Definition

Barrett's Esophagus (BE) is defined as a premalignant condition, where the esophageal squamous epithelium is replaced by intestinal epithelium. This intestinal epithelium, also called specialized intestinal metaplasia (SIM) (with caliciform cells) forms the essence of the concept of Barrett's esophagus (1,2).

Epidemiology

Barrett's Esophagus is usually detected during the endoscopic examinations of middle aged adults and elderly, with an average age - at the time of diagnosis - of 55 years (3). Even though Barrett's esophagus may also affect children, it rarely occurs before the age of five (4). This observation supports the claim that Barrett's esophagus is an acquired and not a congenital condition.

The estimations concerning the prevalence of Barrett's esophagus in the general populations have varied a lot from 0.4 to over 20%, depending on the studied population and definitions used (5-8). The men-women genderratio is approximately 2:1 (9). The following studies illustrate the range of discoveries:

- A study in Sweden estimated that Barrett's esophagus is present in 1.6% of the general population (10). The application of these estimations on the prevalence in the United States of America would translate to approximately 3.3

million people suffering from Barrett's esophagus (11,12).

- In patients who underwent endoscopic examinations, based on the chronic symptoms of GERD, long-segment Barrett's esophagus may be encountered in 3 out of 5 percent, while 10-15 percent exhibit short-segment Barrett's esophagus (13,14).

Barrett's esophagus appears to be unusual in African-Americans. The data concerning prevalence in the Hispanic population is contradictory, some studies show a similar prevalence to that in Caucasians (15), while some a smaller prevalence (16,17). Barrett's esophagus is also predominantly found in Asian countries. In a meta-analysis of 51 studies, which included 453,157 individuals, the global prevalence of histologically confirmed Barrett's esophagus was 1.3%, 82% of which was short-segment Barrett's esophagus.

Etiology

Gastroesophageal reflux is accepted as a primary etiological factor for BE, which in its turn is a major predisposing condition for esophageal adenocarcinoma. From a physiopathological perspective, it is considered that BE represents the response of the esophageal epithelium to lesions. The action induced by lesions to the epithelium native squamous cell of the esophagus leads to epithelial repair; eventually, but only in some cases, the columnar

epithelium may replace the native epithelium (14), providing higher tolerance to low pH, but also a tendency towards dysplastic change which predisposes to esophageal adenocarcinoma.

What is interesting is the fact that, while the duration of the GERD symptoms is clearly a risk factor both for the development of BE (19,20,21), as well as for the greater length of the BE segment (22), the BE extension does not usually correlate with time; meaning that the length of the distal Barrett esophagus segment is established within a relatively short period of time (months) and it changes to a small extent over the following years (22). Moreover, the use of proton pump inhibitors (PPI) to prevent acid reflux does not lead to a significant decrease in the length of the existing Barrett's esophagus (23).

The additional factors that seem to be risk factors for the presence of BE include obesity, hiatal hernia and, interestingly, the absence of a helicobacter pylori infection. It is being speculated that all these factors contribute to BE by increasing the risk and severity of acid reflux. Hiatal hernia distorts the anatomy which normally protects against reflux by reducing the pressure in the inferior esophageal sphincter, by creating a hernial sac between the diaphragm and esophagus and lowering the efficiency of peristalsis (24). Another recent study shows that, out of 50 patients with GERD, who have developed BE, 63% have had hiatal hernia (25) and another study has proven that the greater length of the hiatal hernia correlates with the longer segment of BE (26).

Helicobacter pylori, compared to obesity and hiatal hernia, may affect the risk of BE, by physiological rather than anatomic means; *H. pylori* may reduce gastric acidity by urease (23). The fact that *H. pylori* may be a protector against BE is in contrast with its well established condition as a risk factor for the peptic ulcer disease (PUD) and gastritis and indeed the eradication of *H. pylori* for PUD may increase the risk for BE. A *H. pylori* stem which contains the gene associated with the virulence factor of cytokine (*cagA*) may be extremely protective. In patients with *H.*

pylori cagA+ stems, a study carried out on 153 patients - who have been subjected to endoscopy- revealed that the patients with BE, and especially those with BE and dysplasia and cancer, were much more susceptible to being infected than the control patients; 42% of the control patients were positive for this *H. pylori* stem, compared to 13% of the patients with BE and 0% of the patients with BE and dysplasia and cancer (27). Also, in what this reverse correlation with BE is concerned, studies also show a protective effect of *H. pylori* in the development of esophageal adenocarcinoma (28).

Obesity is a risk factor for the gastro-esophageal reflux disease (GERD) and it may be a risk factor for Barrett's esophagus (29, 30). A meta-analysis from 2009, which included 11 observation studies, demonstrated a slight increase in the risk of Barrett's esophagus in patients with a body mass index (BMI) > 30 kg/m², compared to patients with BMI < 30 kg/m² (29). Nevertheless, other studies have suggested that abdominal obesity, measured as the waist-hip ratio (≥ 0.9 in men and ≥ 0.85 in women) is more likely associated with an increase in the risk of Barrett's esophagus than BMI (31-33).

It is not clear whether the use of aspirin or of non-steroidal anti-inflammatory drugs (NSAIs) – through the inhibition of the expression of COX-2 – is associated with a decrease in the risk of Barrett's esophagus (34-36). In another controlled clinical study on 434 patients, current aspirin, but no other NSAIs, has been associated with a low risk of Barrett's esophagus (34). Still, a large population-based case-control study, did not prove an association between the use of aspirin and Barrett's esophagus; and the use of NSAID non-aspirin was associated with a slight decrease in the risk of Barrett's esophagus (35).

Morphopathology

Macroscopically, Barrett-type mucosa has a red color, being in contrast with the normal esophageal epithelium which is pink. In fact, metaplastic mucosa continues the gastric-type

mucosa over a shorter or longer length (short or long-segment BE), having either a circular or insular form. Its aspect is that of a “tongue” or “candle flame” (1,2).

Microscopically, metaplasia is represented by three distinct types of unevenly distributed, mosaic-type epithelium. The three types of epithelium are: cardiac or junctional epithelium, oxyntic-type epithelium and intestinal epithelium. The latter form is associated with progression towards esophageal adenocarcinoma. It is in fact an incomplete, villiform type of intestinal metaplasia, which resembles intestinal epithelium, with caliciform cells, absorbing-type cells with brush-like edges, mucous secreting cells. The presence of caliciform cells is considered pathognomonic for the diagnosis of BE (1,37).

Prague Classification

The identification of the esophagogastric junction and squamous tissue is essential, being followed by a determination of the circumferential length of the intestinal metaplasia in centimeters (C=?) and non-circumferential length of the intestinal metaplasia in centimeters (M=?). The distance from the esophagogastric junction to the dental arch is measured in centimeters. Special care is required for the identification of hiatal hernia, which in some cases is incorrectly considered when calculating the length of BE (37).

Clinically

Specialized intestinal columnar metaplasia, typical for Barrett's esophagus, does not generate any symptoms. Most of the patients are initially seen for symptoms associated with the gastroesophageal reflux disease (GERD), such as heartburn, regurgitation and dysphagia.

GERD, associated with long-segment Barrett's esophagus, is frequently complicated with esophageal ulceration, stricture and hemorrhages (3). In patients with symptomatic GERD, erosive esophagitis is an independent risk factor for Barrett's esophagus, providing 5 times higher risk for Barrett's disease over a

five-year observation period (38). Certain studies suggested that patients with peptic stricture exhibit higher prevalence of Barrett's esophagus than those without strictures. This relationship is not surprising as both peptic stricture, as well as Barrett's esophagus, are associated with a more severe GERD (39).

Differences between long and short segment Barrett's esophagus – The prevalence of short-segment Barrett's esophagus is substantially greater than that of long-segment Barrett's esophagus. Both conditions are diagnosed most frequently in patients aged 55 and above and occur mostly in Caucasian males.

These observations have been illustrated in a study, which included 889 patients who underwent superior endoscopic examinations with protocol biopsies obtained from the esophagogastric junction (EGJ) (3). The general prevalence of specialized intestinal metaplasia was of 13.2%, with the following distribution:

- Long-segment - 1,6%
- Short-segment - 6,4%
- EGJ intestinal metaplasia - 5,6%

The patients with long and short segment Barrett's esophagus were predominantly white males. The patients with short-segment Barrett's esophagus have had a shorter history of stomach burns and many exhibited GERD-specific symptoms. While those with EGJ intestinal metaplasia had a similar gender distribution and were most likely to have been infected with helicobacter pylori.

The degree and mechanism of the exposure to acid in patients with short and long segment Barrett's esophagus indicate that the patients who developed segment Barrett's esophagus had been predisposed to more severe reflux (40).

Diagnosis

The histological progression from intestinal metaplasia to dysplasia and then to BE-associated adenocarcinoma forms the argument for screening and endoscopic monitoring.

From an endoscopic perspective, Barrett's

esophagus was identified by contrast between the pink esophageal mucosa and the red one perceived as a flame or tongue shaped extension of the gastric mucous membrane. The surface of Barrett's mucosa is usually even, plain, rarely with a fine nodular aspect. The junction between the two mucous membranes may be regular, circular or to the contrary irregular, fringed or Barrett's mucosa takes on the shape of a red island in the pink esophageal mucosa (1-3) (*Fig. 1 A, B*).

Many endoscopic techniques are still being developed, including magnification endoscopy, chromoendoscopy, optical coherence tomography, confocal endomicroscopy, narrow-band imaging and echoendoscopy.

Narrow-band imaging (NBI) is a high-resolution endoscopic technique which improves the fine structure of the mucous surface without the use of coloring agents. NBI is based on the phenomenon that the penetration depth of light depends on wavelength; the longer the wavelength, the deeper the penetration. The blue light penetrates only superficially, while the red light penetrates deeper layers (41,42).

NBI has more advantages as compared to chromoendoscopy; (1) there is no need for coloring agents; (2) it is easy to use; (3) it allows the inspection of the entire endoscopic field,

while in chromoendoscopy, the coloring agent is not equally distributed on the mucous membrane. In addition to these practical advantages, NBI reveals superficial vascularization with high contrast, while the vascular pattern is often less visible in chromoendoscopy (*Fig. 2 A, B*).

Initial reports have suggested that narrow-band imaging (NBI) may be useful for the detailed inspection of the mucosa features of different gastrointestinal pathologies, including Barrett's esophagus (41). Several studies have described characteristic patterns in patients with Barrett's esophagus using NBI. The followings illustrate the most extensive prospective studies.

- A study involved a systematic assessment of the image and biopsy of nearly 200 randomly chosen areas in 63 patients with Barrett's esophagus (41). A regular pattern of vascular mucosa and a plane mucosa (meaning, without any villus or cavities) were significantly associated with specialized intestinal metaplasia, while all the areas with high-grade intraepithelial neoplasia (HGIN) exhibited at least irregular patterns of the mucosa or abnormal blood vessels.
- Another group suggested a classification

Figure 1. Endoscopic aspect of Barrett's esophagus: (A) white light; (B) NBI

Figure 2. Endoscopic aspect of Barrett's esophagus: (A) vascularization (B) dysplastic elements

system based on the results of indigo carmine staining and NBI (42,43). The authors described three categories of mucous patterns (notched/villous circular, irregular/distorted) and two categories of vascular patterns (normal and abnormal). The prospective assessment of 51 patients using this classification system determined that the notched/villous pattern exhibited 90% sensitivity in the detection of intestinal metaplasia, while the irregular / distorted pattern exhibited 100% sensitivity to HGI.

- A third classification system is based on two common microstructure patterns (linear/tubular/villous and round type), the irregular microstructural pattern (IMSP), the absent microstructural pattern (AMSP), regular microvascular patterns (RMVP), irregular microvascular patterns (IMVP) (44). In a prospective assessment of 50 patients, the common microstructural pattern of the linear/tubular/villous and/or RMVP with AMSP exhibited 100% sensitivity to intestinal metaplasia. Five out of the six patients with HGIN exhibited IMVP or IMSP.

Echoendoscopy – allows an echographic assessment of the esophagus layer, highlighting

a possible invasion of its layers in the area of the pathological mucosa detected by endoscopy.

The performance of EUS for the correct selection of patients for endoscopic or surgical resection in a tertiary referral center was analyzed in a retrospective study on 335 patients; EUS revealed poor testing patterns to be correct (50% sensitivity, 40%PPV, 90% precision), 11% of the patients being incorrectly present; out of these patients, 7% would have suffered unnecessary esophagectomy had they relied entirely on EUS (45).

Also, EUS had revealed low performance in testing for the detection of invasive cancer ($\geq T1a$) with sensitivity, PPV namely accuracy of 49%, 77% namely 85% (45).

Screening for Barrett's Esophagus

In order to lower the mortality rate due to esophageal adenocarcinoma, the patients with gastroesophageal reflux disease (GERD) specific symptoms were asked to undergo an endoscopic examination for Barrett's esophagus (46,47).

Nevertheless, it is not clear if the screening of patient with GERD-specific symptoms reliably identifies individuals exhibiting high risks for the onset of esophageal adenocarcinoma or if it

has an impact on the mortality rate. Long-segment Barrett's esophagus may be encountered in 3 up to 5% of the patients who underwent an endoscopic examination for chronic GERD-specific symptoms, while 10-15% exhibit long-segment Barrett's esophagus (48).

Another limitation of the screening of patients with GERD-specific symptoms for Barrett's esophagus and esophageal adenocarcinoma is that over 40% of the patients with esophageal adenocarcinoma have no history of stomach burnings (48, 49). Thus, any screening program targeting only patients with stomach burning may only have a limited impact on the mortality rate for cancer and there is little evidence that these programs have prevented deaths caused by esophageal adenocarcinoma.

The American College of Gastroenterology – The orientations of the American College for Gastroenterology concerning the diagnosis and management of GERD shows that superior endoscopy is not required if there are GERD-specific symptoms (50). Superior endoscopy is recommended in case of alarming symptoms (such as dysphagia, weight loss, signs of gastrointestinal bleedings) and for the screening of patients with high risks for complications (including Barrett's esophagus and esophageal adenocarcinoma).

Superior endoscopy may be recommended for the screening for Barrett's esophagus in male patients, above the age of 50, with GERD-specific symptoms lasting over 5 years and who exhibit the following additional risk factors (51):

- Nocturnal reflux symptoms;
- Hiatal hernia;
- High body mass index;
- Smoking;
- Intra-abdominal fat distribution.

There are some proposals for screening techniques for high-risk patients. Nasogastros-copy is a technique which does not use sedation and is well tolerated by patients (51,52). The capsule endoscopy might theoretically represent a BE screening and monitoring technique, it is comfortable and reliable, but expensive and not currently recommended (52). The use of NBI

endoscopes has proven that there are certain factors which seem to predict high grade dysplasia: irregular/destroyed pattern, irregular vascular pattern and abnormal looking blood vessels (50-52).

Alternative screening methods–non-endoscopic screening methods are also being studied. One method uses a certain device called capsule sponge (Cytosponge, Surepath, BD Diagnostics, Durham, NC), combined with an immunohistochemical biomarker (trefoil factor 3) (50-52). The patient swallows a gelatin capsule which is attached to a string and contains a compressed mesh. The mesh is exposed when the gelatin capsules dissolve in the stomach. The mesh is then retracted through the esophagus, where it collects samples from the cells forming the esophageal lumen. The biomarker is then used to differentiate Barrett's epithelial cells from gastric cardia and squamous cells.

In a study performed on 504 patients, who have used suppressive therapy for more than three months, in the previous five years, 501 (99%) of the patients were able to swallow the capsule (52). The results obtained with the capsule sponge were compared to superior endoscopy for the diagnosis of Barrett's esophagus. The capsule sponge revealed 73% sensitivity and 94% specificity for the patient with at least 1 cm circumferential Barrett segment. For the patients with segments of 2 cm or more, sensitivity was 90% and specificity 94% (52).

Managing Barrett's Esophagus

The examination of Barrett's esophagus is controversial. Certain groups suggest a screening of the patients who exhibit more risk factors for the development of esophageal adenocarcinoma (for instance, gastroesophageal reflux disease, age > 50, male, high body mass index with abdominal fat distribution).

General Management

The Management of Acid Reflux

Treatment of patients with Barrett's esophagus

over an indefinite period of time with a proton pump inhibitor (PPI), based on the data obtained from observed studies and in vitro, which suggests that an aggressive anti-reflux therapy might prevent cancer (53). Also, many patients with Barrett's esophagus also exhibit symptomatic gastroesophageal reflux disease (GERD) or endoscopic evidence of reflux esophagitis, both justifying a treatment with PPI. Normally, patients start with a standard PPI dosage once a day (for instance, omeprazole 20 mg daily) and the dosage is increased if the elimination of GERD-specific symptoms is required or for healing reflux esophagitis.

The main reason behind the treatment of acid reflux is that it may lead to chronic esophageal inflammation, which in its turn may predispose to the development of cancer. Acid may also cause a deterioration of carcinogenic DNA in Barrett's epithelial cells (54). In a meta-analysis of seven studies, which included 2813 patients with Barrett's esophagus and 317 patients with high-grade dysplasia or esophageal adenocarcinoma, the use of PPI was associated with a low risk for high-grade dysplasia and/or esophageal adenocarcinoma (54).

The aggressive anti-reflux treatment may lead to the partial regression of specialized intestinal metaplasia in Barrett's esophagus (55). In a randomized study, 68 patients with Barrett's esophagus and acid reflux were divided for the administration of profound acid suppression (omeprazole 40 mg twice a day) or slight acid suppression (ranitidine 150 mg twice a day) (55). The symptoms of acid reflux have improved in both groups, but the degree of acid suppression was higher with omeprazole. There was no slight regression of Barrett's esophagus in patients receiving omeprazole, but none in the patients receiving ranitidine. All in all, it is not clear whether the partial regression of Barrett's metaplasia means that the risk of cancer had decreased.

Chemoprevention

Epidemiological data suggests that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclooxygenase

(COX) may protect against the development of Barrett's esophagus (56) or the development of cancer in patients with Barrett's esophagus (57). Specialized intestinal metaplasia in Barrett's esophagus presents an increased expression of COX-2 and it has been proven that COX-2 inhibition has anti-proliferative and pro-apoptotic effects in Barrett's-associated adenocarcinoma esophageal cell lines (57). Nevertheless, considering the potential for adverse drug reactions and the overall low risk of developing esophageal adenocarcinoma, we do not usually recommend NSAIDs to patients with Barrett's esophagus solely for chemoprevention (56, 57).

Endoscopic Monitoring

The purpose of monitoring is to improve results by detecting dysplasia or esophageal adenocarcinoma early enough to ensure efficient treatment. Our approach is to perform an initial endoscopy with four-quadrant biopsies every 2 cm in patients suspected with Barrett's esophagus (for instance, "salmon" colored esophageal mucosa). If four-quadrant biopsies every 2 cm have not been taken during the initial endoscopy, we repeat the endoscopy within one year so that we can obtain the biopsies (3,4).

Any diagnosis of dysplasia needs to be confirmed by a second pathologist who has experience with Barrett's esophageal neoplasia (3,7).

- Without dysplasia: if the initial biopsies reveal no dysplasia, we discuss with the patient the potential risks and benefits of regular endoscopic monitoring. Generally, we suggest continual monitoring every three to five years.
- Indefinite for dysplasia: If the initial biopsies are indefinite for dysplasia, it is recommended to optimize the medical anti-reflux therapy (e.g. proton pump inhibitor (PPI) twice a day, making sure that the PPI treatment is followed, that PPI is correctly administered). The anti-reflux therapy minimizes reactive esophageal modifications caused by reflux esophagitis, which

can be mistaken for dysplastic modifications. After an optimization of the anti-reflux therapy, we repeat the endoscopy with biopsy samples taken every 1 cm. Usually, we perform the endoscopy after two months of treatment (in order to allow enough time for the healing), even though the orientation of the American College of Gastroenterology suggests waiting for at least three months (3). The endoscopic reexamination should not be postponed for more than six months. Any irregularity of the mucosa needs to be eliminated by endoscopic resection.

If repeated biopsies are still indeterminate for dysplasia, the diagnosis needs to be confirmed by a pathologist with experience in esophageal histopathology. If the diagnosis is confirmed, the management options include endoscopic monitoring every 12 months.

- Low-grade dysplasia, high-grade dysplasia or intramucosal carcinoma: if the biopsies reveal dysplasia or intramucosal carcinoma, we suggest for the diagnoses to be confirmed by another pathologist, who has experience in Barrett's esophagus-related neoplasia. All the patients who were initially diagnosed with low-grade dysplasia need to undergo repeated upper endoscopies using high-definition/high-resolution white light endoscopy, under intense suppression of acids (for instance, after proton pump inhibitor therapy over 8-12 weeks). Four quadrant biopsy samples every 1 cm will be taken and every irregularity of the mucosa needs to be eliminated by endoscopic resection for the precise assessment of the grade of dysplasia (4,5).

There are recommendations either for monitoring or endoscopic eradication of patients with low-grade dysplasia (3-6,8). In patients who choose to undergo endoscopic eradication, the preferred procedure is endoscopic radio-frequency ablation for the prevention of dysplasia progression. If endoscopic monitoring is the approach chosen for low-grade dysplasia, then the patients require biopsies taken every 1 cm.

A meta-analysis of 14 studies, with a total of

843 patients, examined whether advanced imaging techniques may increase the detection of dysplasia or cancer in comparison white light endoscopy with random biopsies (58). Researchers found that advanced imaging techniques have improved diagnosis efficiency for dysplasia or cancer by 34% (58).

A number of molecular markers for the risk of cancer have been proposed as an alternative for the sampling of random biopsies for the detection of dysplasia in Barrett's esophagus (59). Promising molecular markings, associated with carcinogenesis in Barrett's esophagus, include anomalies in the expression of p53 and cyclin D1 and abnormal cellular DNA content, which can be supported by flow cytometry or methylation matrix. An additional assessment of the markers is required before these are recommended for routine clinical use (6,59).

Treatment

Managing Dysplasia or Intramucosal Carcinoma

Dysplasia in Barrett's esophagus was conventionally treated by esophagectomy, a procedure associated with considerable morbidity and mortality rates. Today, dysplasia is usually treated by endoscopic eradication therapy, which includes the use of endoscopic ablation techniques and/or endoscopic resection (ER). Any diagnosis of dysplasia needs to be confirmed by a second pathologist with experience in esophageal pathology (3).

The endoscopic ablation techniques use thermal or photochemical energy to destroy Barrett's mucosa and do not supply a tissue sample for histological analysis. ER uses a diathermal component to remove a segment from Barrett's mucosa and submucosa and the removed tissue undergoes histological examination. Thus, ER may be therapeutic and may provide priceless information concerning the depth of the tumor (stage T).

Low-grade Dysplasia

Even though current recommendations refer

to monitoring and endoscopic eradication of patients with low-grade dysplasia, studies suggest that RFA may be the preferred alternative for patients who are willing to accept the risks of the procedure (60). The alternative methods for achieving eradication include photodynamic therapy (PDT), spray cryotherapy and the endoscopic resection of the entire segment of Barrett's mucosa, but at this moment RFA is the preferred ablation technique. If the patient does not suffer an endoscopic eradication therapy, monitoring endoscopy needs to be performed every 6 months for one year and then annually until the therapy for non-dysplastic Barrett's esophagus is resumed (7). Four-quadrant biopsies need to be taken every 1 cm.

The efficiency of RFA was examined in a randomized study on 136 patients with low-grade dysplasia (60). RFA reduced the risk of progression up to a high-grade dysplasia or adenocarcinoma. Nevertheless, there are still many unanswered questions concerning the durability of the ablation procedure and the need for endoscopic monitoring after ablation for low-grade dysplasia (59,60).

High-grade Dysplasia or Intramucosal Carcinoma

The factors that need to be taken into consideration when choosing a treatment for high-grade dysplasia and intramucosal cancer in Barrett's esophagus include:

- Patient's age and life expectancy;
- Patient's comorbidities;
- Extension of dysplasia (short segments of Barrett's esophagus are more easily ablated than longer segments with multifocal dysplasia);
- Local expertise in surgery and endoscopy
- The patient's preferences concerning surgical intervention, undergoing repeated endoscopies and acceptance of possible recurrent neoplasia in the absence of esophagectomy.

Most patients with high-grade dysplasia or intramucosal carcinoma need to undergo an endoscopic eradication therapy in order to

eliminate all the dysplastic and metaplastic tissues (3-6, 8). Any visible irregularity of the mucosa should be eliminated by ER and the sample sent for histological examination before the ablation therapy. If the resected sample shows submucosal invasion, an endoscopic therapy is generally not recommended.

Our preference for endoscopic eradication after ER of any visible lesion is RFA, since it is efficient and has a good safety profile. Generally, esophagectomy is no longer used as first class treatment for dysplasia, although esophagectomy is still being used in special circumstances, such as patients who do not accept the uncertainties concerning the long-term results of endoscopic eradication therapy. The monitoring frequency will depend on the elimination of the intestinal metaplasia.

All the treatment approaches are associated with unclear long-term risks and benefits. In most of the studies concerning the treatment for dysplasia in Barrett's esophagus, the duration of monitoring is considerably shorter than five years. Therefore, the long-term efficiency of these therapies for the reduction of death caused by cancer has not been determined, even though two cost-efficiency analyses had concluded that endoscopic ablation offered the longest life expectancy adjusted to the quality of life (58,59).

Endoscopic Ablation Therapies

Endoscopic ablation therapies use thermal or photochemical energy or radiofrequency to remove abnormal epithelium in Barrett's esophagus (63,64). The most frequently used form is RFA.

The efficiency of endoscopic radiofrequency was examined in a retrospective study on 166 patients with high-grade dysplasia or early-onset cancer (55). The patients were treated with PDT, RFA and/or argon plasma coagulation. Also, endoscopic resection was performed for focal nodular Barrett's esophagus, for limited expansions of the flat Barrett's esophagus and for focal residual Barrett's esophagus after the ablation therapy. A complete neoplasia eradication was performed on 157 patients (95%), with complete eradication of intestinal metaplasia in 137 (83%)

patients. From those with complete eradication of the intestinal metaplasia, recurrent intestinal metaplasia has been detected in 48 (35%), dysplasia in 12 (9%) patients. From the patients with neoplasia eradication, but without complete eradication of the intestinal metaplasia, recurrent metaplasia was detected in 6 out of 19 (32%) patients. Neoplasia (dysplasia or carcinoma) was less likely to appear in patients with multifocal dysplasia and who were older, while neoplasia was less likely in patients who suffered complete eradication of the intestinal metaplasia (56).

Radiofrequency Ablation

RFA uses the radiofrequency energy supplied by a balloon with a number of closely spaced electrodes to eliminate Barrett's mucosa (63, 64). RFA rapidly generates a circumferential, uniform, thermal lesion with limited depth. For patients with visible irregularities of the mucosa associated with dysplasia, an endoscopic resection needs to be performed before the RFA. A series of well conceived studies, including one randomized, falsely-controlled study, suggests that RFA is very efficient in the removal of the entire Barrett's epithelium both at endoscopic and histological level, with a favorable safety profile. Studies also suggest that RFA reduces the risk of malignant progression. In a randomized study, patients with low-grade or high-grade dysplasia, who underwent RFA, were less susceptible to progress to superior dysplasia grades or cancer than patients who underwent false therapy (4 versus 16%) (54).

Even though early studies suggested that relapses are less frequent, more recent studies documented considerably higher recurrence rates, underlying the necessity for permanent monitoring after RFA. For instance, a study performed on 246 patients with high-grade dysplasia or intramucosal carcinoma describes an initial complete eradication of all intestinal metaplasias in 80% of the cases. Nevertheless, neoplasia (dysplasia or cancer) occurred in a percentage of nearly 25% after 60 months and metaplasia in a percentage of nearly 50% after 48 months (55,56).

Photodynamic Therapy

PDT is based on the capacity of chemical agents, known as photosensitisers, to produce cytotoxicity in the presence of oxygen after light stimulation of an appropriate wavelength. Several studies concerning PDT have been published. A wide randomized study has proven that it was superior to omeprazole only for the eradication of dysplasia and cancer prevention in Barrett's esophagus. Nevertheless, there were frequent severe complications, such as esophageal stricture, and 15% of the patients who received PDT have developed esophageal cancer, in the end. This technique was replaced by RFA to a large extent.

Endoscopic Spray Cryotherapy

Endoscopic spray cryotherapy is a newer technique used for the ablation of Barrett's mucosa. A cryotherapy system is used for the endoscopic application of cold nitrogen or carbon dioxide in Barrett's esophagus. The tissue is frozen for approximately 40 seconds (two 20 second applications or four 10 second applications). Observational studies have shown an eradication of high-grade dysplasia in approximately 95 to 100% of the patients, of the entire dysplasia in 85-90% and all intestinal metaplasias in 55% (58,59). However, there is very little long-term data available.

After endoscopic ablation, a proton pump inhibitor is administered to the patients (if one is not already taken), so that the injured mucosa will heal along with the growth of new squamous epithelium. The relative values of different endoscopic ablation therapies are being contested. A major concern is that the procedures cannot eradicate all the dysplastic cells. Partially ablated metaplastic mucosa can heal with a superior layer of squamous epithelium, which hides the "buried" metaplastic tissue from the endoscope and adenocarcinomas develop from these residual metaplasia deposits (59).

Subsequent endoscopic monitoring will depend on the initial dysplasia grade and the existence of complete eradication of the intestinal metaplasia.

Endoscopic Resection

Endoscopic resection includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Endoscopic resection involves the excision of a large segment of the esophageal mucosa up to the submucosa (58,59). Contrary to endoscopic ablation techniques, endoscopic resection supplies large tissue samples which can be examined by a pathologist to determine the character and volume of the lesion and adequacy of the resection. Thus, it can provide significant information on staging (which reveals the invasion of the submucosa, that might not be visible using less invasive techniques and that would require submucosal extension). Endoscopic resection may also be combined with endoscopic ablation therapies for the eradication of Barrett's mucosa in patients with visible lesions.

In a systematic revision which included 11 studies on patients with Barrett's esophagus, who had suffered EMR, a complete eradication of the high-grade dysplasia or early stage esophageal adenocarcinoma was achieved in 95% of the patients and complete eradication of Barrett's mucosa in 85% (60).

A complete endoscopic resection of Barrett's mucosa is not usually recommended because of the high rate of stricture formation after circumferential resections. Gradual radical endoscopic resection (in which endoscopic resection is repeated for the eradication of Barrett's mucosa) with endoscopic resection of the irregularities of the mucosa followed by RFA (59,60) was performed in a study carried out on 47 patients with Barrett's mucosa ≤ 5 cm, containing high-grade dysplasia or early-stage cancer. Both groups have had high percentages of full remission both of the neoplasia as well as of the intestinal metaplasia (varying between 96 and 100% namely 92 and 96%), but the percentage of stenosis was significantly higher in patients who suffered gradual radical endoscopic resection (88 versus 14%).

Esophagectomy

Esophagectomy is the only therapy for high-grade dysplasia which removes the entire neoplastic epithelium along with any occult malignancy and regional lymphatic ganglions. Nevertheless, it also has the highest mortality rates associated with the procedure and long-term morbidity. Mortality rates for esophagectomy in institutions vary in inverse ratio to the frequency with which the operation is performed. In a study of the data from the National Dutch Medical Register, mortality rates for esophagectomy were 12.1, 7.5 and 4.9% in the centers that performed 1 up to 10, 11 up to 20 and over 50 esophagectomies per year (58,59). Since the development of efficient endoscopic therapies, esophagectomy can now be often avoided.

The average hospital stay for open esophagectomy is approximately two weeks, and 30 to 50% of the patients develop at least one severe post-surgery complication, such as pneumonia, arrhythmia, myocardial infarction, cardiac insufficiency, wound infection or anastomotic leaks (59,60). Esophagectomy is frequently associated with long-term problems, such as dysphagia, weight loss, gastro-esophageal reflux. Some of these complications are connected to the resection of the vagus nerve and may be reduced by vagus-sparing esophagectomy (60).

Intensive Endoscopic Monitoring

Some authors recommended an intensive endoscopic monitoring program (e.g. endoscopic examinations every three to six months) for patients with high-grade dysplasia in Barrett's esophagus, withholding invasive treatment such as endoscopic eradication or esophagectomy until biopsy samples indicating adenocarcinoma are taken. Still, few published studies directly support the safety and efficiency of intensive monitoring for high-grade dysplasia. Considering the safety and efficiency of endoscopic eradication therapy proven in randomized studies, medical societies recommend an eradication therapy rather than intensive monitoring for patients with high-grade dysplasia (3-6,8).

- A study was performed on 75 patients with high-grade dysplasia subjected to intense endoscopic monitoring (42). Over an average monitoring period of 7.3 years, 12 patients (16) had developed adenocarcinomas. The cancer had been healed at the time of detection in all the 11 patients, who were complying with the monitoring program, but one patient who had been lost during the monitoring period returned several years later with an inoperable tumor (42).
- In another series of 32 patients with high-grade dysplasia, who had developed adenocarcinoma during intensive endoscopic monitoring, only one patient suffered an incurable disease (metastases) when cancer was detected in the monitoring endoscopy (57).
- In a third study, the investigators performed intense endoscopic monitoring of 15 patients with high-grade dysplasia for an average period of 37 months and in this interval four adenocarcinomas had occurred (59). One of the four suffered a metastatic disease. The authors concluded that an observational approach of the management of high-grade dysplasia should be discouraged.

Management of Invasive Esophageal Adenocarcinoma

Patients with invasive adenocarcinoma of the esophagus should be guided towards an oncologist for staging and discussion of the treatment options. Choosing a treatment will depend on the general health of the patient and cancer stage and may include chemotherapy with or without esophagectomy or even endoscopic resection in very carefully selected cases.

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