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Editorial

Follow-up of patients with Barrett's esophagus; current recommendations

S.N. Sgouros, A. Mantides

INTRODUCTION

Barrett's esophagus is an acquired condition in which columnar epithelium replaces the squamous epithelium that normally lines the distal esophagus. The condition develops when gastroesophageal reflux disease (GERD) damages the squamous esophageal mucosa and the injury heals through a metaplastic process in which columnar cells replace squamous ones.[1] The abnormal columnar epithelium is an incomplete form of intestinal metaplasia (called specialized intestinal metaplasia).

Barrett's esophagus would be of little interest were it not for its well established association with adenocarcinoma of the esophagus, a cancer whose incidence has increased more than four-fold since 1970s. Previous data showed that the risk of adenocarcinoma in patients with Barrett's esophagus was 200 times greater than that of the general population. However, more recently published studies suggest that the risk is about 0,5% yearly for patients with long-segment Barrett's esophagus (defined as more than 3 cm above the gastroesophageal junction) and 0,4% for short-segment disease.[2] This means that the lifetime risk is about 10-15%.

Recent studies have failed to establish a positive relationship between the length of the metaplastic epithelium and the risk of adenocarcinoma.[3] It is not clear whether the long- and short-segment Barrett's esophagus have the same pathogenesis and natural history, or whether short-segment disease progresses to long-segment disease. Currently, short- and long-segment disease are managed similarly.

Barrett's esophagus is the only clearly recognized risk factor for adenocarcinoma of the esophagus. However, the majority of patients with Barrett's esophagus remain without diagnosis. Autopsy data suggests that for every known case of Barrett's esophagus, 20 additional cases go unrecognized.[4] Such studies suggest that earlier diagnosis of patients with Barrett's esophagus could be of value in the prevention of esophageal adenocarcinoma. Currently, there are two main strategies; I) endoscopic screening of patients with chronic GERD for earlier detection of Barrett's esophagus and, II) regular follow-up of patients with Barrett's esophagus with endoscopy and biopsies in an effort to recognize earlier low- and high-grade dysplasia or carcinoma in situ. Available evidence resulting from these approaches will be further discussed.

PREVENTION OF BARRETT'S ESOPHAGUS IN PATIENTS WITH GERD

It has been suggested that screening should focus on patients with GERD who have risk factors for Barrett's esophagus, such as male sex, white race, an age of more than 50 years, a long history of symptoms (more than five years). More frequent (>3/week) and severe reflux symptoms (heartburn and/or acid regurgitation), large (>3 cm) hiatal hernia, ineffective esophageal peristalsis, hypotensive lower esophageal sphincter and mixed (duodeno-gastro-esophageal) reflux, have all been associated with more severe GERD, which is more frequently complicated with Barrett's esophagus.[4,6] It should be noted however that a rigid endoscopy screening in all patients with severe longstanding GERD, will have a limited impact on the rates of death from esophageal ade-

Department of Gastroenterology, Athens Naval and Veterans Hospital, Athens, Greece

Address for reprint requests and correspondence:

Apostolos Mantides, MD, Head, Department of Gastroenterology, Athens Naval and Veterans Hospital,
Tel. & fax: (210)7242103, e-mail: mantides@otenet.gr

nocarcinoma, because up to 40% of patients with cancer have no history of GERD.

On the other hand, efficient control of acid reflux with protein pump inhibitors (PPIs) or antireflux surgery in these patients can prevent the development of Barrett's esophagus. Additionally, it has been suggested that these patients should be followed with 24h ambulatory pH-metry under therapy, in order to clarify effective control of acid reflux.

PREVENTION OF ADENOCARCINOMA IN PATIENTS WITH BARRETT'S ESOPHAGUS

DeMeester suggests that the whole procedure from GERD to Barrett's esophagus and low-grade dysplasia is directly associated with acid reflux, whilst currently unknown genetic factors may lead to progression from dysplasia to adenocarcinoma.[7] This assumption is supported by studies which show increased cell proliferation in an acidic environment (bolus reflux), in cell cultures from Barrett epithelia.[8] Additionally, decreased expression of a marker of cell proliferation was found in patients in whom GERD was effectively controlled with PPIs in comparison to patients who were also treated with PPIs but ineffectively.[9] Indirect evidence of such an approach, coming from previously published studies, shows total or subtotal regression of Barrett epithelium after conservative or surgical treatment.

The results of a large meta-analysis including 558 patients with GERD, treated surgically further support this concept.[7] In this study the authors suggest that efficient control of acid reflux after antireflux surgery may prevent the development of esophageal adenocarcinoma. Currently, there is a growing body of evidence suggesting that surgical and conservative treatment with PPIs are equally effective in controlling GERD and preventing the progression to Barrett's esophagus and esophageal adenocarcinoma. However, the surgical approach seems more appropriate in younger patients (<45 years old) who usually fail to comply with long-term antisecretory treatment.

Recent studies suggest that NSAIDs may decrease the proportion of patients with Barrett's esophagus who develop cancer. Such an approach is supported from studies suggesting increased expression of COX-2 and 15-lipooxygenase-l during neoplastic progression of Barrett epithelia.[11] Chronic or occasional aspirin use seems to reduce the risk of esophageal cancer[12], while the same effect may have selective and non-selective NSAIDs.

EFFECTS OF ENDOSCOPIC SURVEILLANCE OF PATIENTS WITH BARRETT'S ESOPHAGUS

Current practice guidelines recommend endoscopic surveillance of patients with Barrett's esophagus in an attempt to detect cancer at an early and potentially curable stage. Several retrospective studies clearly suggest that patients with Barrett's esophagus in whom adenocarcinoma was detected in a surveillance programme, have their cancers detected at an earlier stage with improved 5-year survival, compared with similar patients not undergoing routine endoscopic surveillance. Because esophageal cancer is stage-dependent, these studies suggest that survival may be enhanced by endoscopic surveillance.

However, it is also, argued that because most patients with Barrett's esophagus will not die from esophageal cancer,[12] endoscopie surveillance is not warranted until substantiated by prospective studies. However, proponents of surveillance suggest that these studies included predominantly older patients, many of whom died of unrelated diseases; thus the aforementioned results may not be applicable to younger patients with Barrett's esophagus.

Even though, a cost-effectiveness analysis in which it has shown that the cost per cure of surveillance-detected esophageal adenocarcinoma was comparable to that of breast cancer, more recently published data suggest that surveillance programmes may not be cost-effective, at least in countries where the cost of endoscopy is high, such as U.S. and United Kingdom. These results may not be applicable to Greece, where the cost of endoscopy is far lower.

CURRENT RECOMMENDATIONS FOR ENDOSCOPIC SURVEILLANCE OF PATIENTS WITH BARRETT'S ESOPHAGUS

The aim of surveillance is the detection of dysplasia. The description of dysplasia should use a standard 5-tier system advocated by a number of authors: 1) negative for dysplasia, 2) indefinite for dysplasia, 3) low-grade dysplasia, 4) high-grade dysplasia, 5) carcinoma. Active inflammation makes it more difficult to distinguish dysplasia from reparative changes. As such, surveillance endoscopy should not be done until any active inflammation related to GERD is controlled with antisecretory therapy. We must also keep in mind that among experienced pathologists, the extent of interobserver agree-

ment on the diagnosis of low-grade dysplasia in Barrett's esophagus may be less than 50%. However, in the case of high-grade dysplasia, it is about 85%.

Current guidelines suggest obtaining systematic 4-quadrant biopsy specimens at 2cm intervals along the entire length of the Barrett's segment. Subtle mucosal abnormalities, no matter how trivial, such as ulcuration, erosion, plaque, nodule, stricture or other luminal irregularity in the Barrett's segment, should also have biopsies performed.

A number of techniques have been shown to increase the diagnostic yield of endoscopy with biopsies in patients with Barrett's esophagus. Some authors suggest that mthylθne blue chromoendoscopy (the presence of staining in the esophagus which indicates the presence of intestinal metaplasia) increases the efficiency of detecting dysplasia, as fewer biopsy specimens are required and more patients are identified with dysplasia, compared with conventional endoscopic techniques.[13] However, these results have not been confirmed in other studies. Brush cytology may be complementary to endoscopic biopsies and is recommended by some to be part of the routine endoscopic surveillance of Barrett's patients. A variety of endoscopic optical techniques have the potential to obtain «light» biopsy specimens of Barrett's esophagus. Candidate techniques include fluorescence spectroscopy, light spectroscopy, optical coherence tomography, light scattering spectroscopy and light-induced fluorescence endoscopy. All of these techniques are based on the principle that benign and malignant tissues have different optical qualities. In theory, this would permit optical sampling of larger areas of the columnar-lined esophagus and improve the efficiency of biopsies by targeting areas thought to harbour dysplasia or cancer. Endoscopie fluorescence detection may be enhanced further by using a sensitizer, such as 5-aminolevulinic acid (5-ALA), which accumulates selectively in tumours and dysplasia.

SURVEILLANCE INTERVALS

Surveillance intervals, determined by the presence and grade of dysplasia, are based on our limited understanding of the biology of esophageal adenocarcinoma. However, these intervals are arbitrary and have never been subject to clinical trial. Surveillance every 2-3 years is recommended as adequate in patients without dysplasia. Many authors suggest that the interval could be safely increased to 3-5 years, since the risk of cancer is lower than previously thought. This recommendation is based solely on cost-effectiveness studies and cannot be generally applied to countries where the cost of endoscopy is significantly lower.

The interval is shortened to every 6 months for 1 year followed by annual endoscopy with biopsies, when low-grade dysplasia is present. Currently, there are limited data concerning the natural history of low-grade dysplasia. However, it seems to be a major risk factor for the development of adenocarcinoma.[14] Some studies suggest that low-grade dysplasia progresses to high-grade or adenocarcinoma in 10-28% of patients during a 5-year period.

When high-grade dysplasia is identified, the diagnosis should be confirmed blindly by an experienced pathologist. If the diagnosis is confirmed, there is no agreement on the most appropriate management of these patients. Esophagectomy is recommended by many authors to eliminate the risk of carcinoma or to detect and treat cancer at an early, curable stage because of the marked variability in the finding of unsuspected cancer in patients with high-grade dysplasia, which ranges form 0% to 73%.[15,16] In prospective studies it was found that as many as 60% of patients with high-grade dysplasia eventually develop cancer during a 5-year period.[17] In these patients, there is increased risk of local or distant metastasis at the time of surgery, resulting in a dismal prognosis.

On the other hand, esophagectomy is criticized because of the potential risks (mortality 3-12% and morbidity 30-50%)[18] and the variable natural history of high-grade dysplasia. This is the main reason for which some authors recommend a continuous rigorous endoscopie surveillance programme every 3 months, using a systematic biopsy protocol; biopsies should now be obtained at 1 cm intervals with large particle forceps, to maximize the ability to detect unsuspected cancer. According to this approach esophagectomy is reserved for patients with a preoperative diagnosis of intramucosal or submucosal carcinoma.

In the setting of high-grade dysplasia there are two recently proposed alternative options; I) surgical approach with esophagectomy without thoracotomy and regional lymph node resection; DeMeester et al[7] performed the aforementioned technique in patients without endoscopic lesions and it was found safe and effective on a long term basis, II) endoscopic ablative therapies using thermal, photochemical energy or mucosectomy to destroy the metaplastic esophageal epithelium. Ablative therapies are expensive, may not eradicate all

of the tissue with a neoplastic predisposition, and are accompanied by frequent minor side-effects. Even though there are some promising results,[19] no study has shown that these treatments decrease the long-term risk of cancer, and thus, they should be considered experimental. Many authors currently suggest that endoscopic ablative therapies should be reserved only for poor operative candidates, in the setting of rigorous protocols.

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