Endoscopic follow-up of Barrett's esophagus : protocol and implications

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Abstract

The purpose of endoscopic surveillance in Barrett's esophagus is to detect dysplasia and to diagnose carcinoma in an early, treatable stage. Prospective trials that study the efficacy of a surveillance program in reducing mortality from esophageal adenocarcinoma are lacking. Retrospective studies have shown a significantly better outcome in patients with esophageal cancer that is detected during a surveillance program. Obviously, surveillance is only indicated for those patients fit enough to undergo esophagectomy if high-grade dysplasia (HGD) or malignancy is detected. There is no consensus upon what to do with HGD : some recommend esophagectomy when HGD is diagnosed, because an important proportion of these patients host an adenocarcinoma ; others feel that histological proof of malignancy should be established before esophagectomy is proposed. Dysplasia is not a uniform process, causing sampling problems. Using a strict biopsy protocol is helpful to differentiate HGD from carcinoma, but contradictory results about this type of rigorous biopsy protocol have been published. Most groups propose four biopsy specimens, in a circular fashion, from every 2 cm of the Barrett-epithelium, with additional biopsies from any mucosal abnormality. Patients with long-segment Barrett's esophagus need endoscopic surveillance, even if they underwent antireflux surgery. At this moment there are not enough data to support a systematic surveillance of patients with short-segment's Barrett's esophagus. The following endoscopic strategy can be proposed. No dysplasia : surveillance every 2 years. Low-grade dysplasia : surveillance every year ; in these cases it is recommended to repeat four-quadrant biopsies at 1 cm interval if numerous biopsies reveal dysplasia to detect foci of HGD/cancer. High-grade dysplasia : repeat immediately four-quadrant biopsies at 1 cm interval ; if HGD is confirmed esophagectomy is advised to a patient with acceptable operative risk. Ablation therapy remains experimental. (Acta gastroenterol. belg., **2000**, 63, **29-35**).

Key words : Barrett's esophagus, endoscopic surveillance.

Barrett's esophagus is defined as the presence of specialised columnar epithelium (i.e. goblet cells) in the esophagus, irrespective of its length (1). It is a premalignant condition and the yearly incidence of adenocarcinoma in Barrett's esophagus varies between 1 in 48 to 1 in 441 patient-years of follow-up (1). This means that patients with Barrett's esophagus have a 30 to 125 fold increased risk of developing an esophageal cancer. Therefore prevention or early detection of malignant transformation of the Barrett's mucosa is warranted. Clear-cut pathofysiological factors that make one Barrett's esophagus more susceptible to malignant degeneration than another have, until now, not been identified (2). On the other hand, long-segment Barrett's mucosa (> 10 cm) and a Barrett's ulcer at the time of diagnosis are risk factors for the development of esophageal cancer (3). Regression of Barrett's mucosa can be obtained by long-term medical acid suppression or anti-reflux surgery, but until now there is no proof that this will prevent cancer development later on (4,5). Photodynamic or laser destruction of Barrett's mucosa are still experimental techniques and reports of persistent intestinal metaplasia underneath the reepithelised mucosa are emerging (6). Therefore at this moment endoscopic surveillance is the only tool we have to detect those patients who are at high risk of developing an esophageal adenocarcinoma. The purpose of endoscopic surveillance is the early detection of an esophageal neoplasia in a potentially curable stage. Curation in esophageal cancer means esophagectomy. Therefore patients that are submitted to an endoscopic follow-up protocol should be fit enough to undergo an esophagectomy at any given moment of their follow-up period ! Age and co-existing diseases will thus largely determine if a patient should be taken into account for endoscopic surveillance.

Is the game worth the candle ?

No prospective, large-scale studies are available to show that endoscopic surveillance in Barrett's esophagus is able to reduce the mortality caused by esophageal cancer. Indirect evidence is offered by the results of 3 retrospective series of adenocarcinoma in which it is shown that the adenocarcinomas are detected in an earlier stage if patients are in an endoscopic follow-up program (7,8,9). The earlier detection of cancers in these studies correlates with a higher percentage of curative resection and better 5-year survival rates in the endoscopic surveillance groups. A Dutch cohort study that followed 155 patients with Barrett's esophagus for a mean of 9.3 years (1440 patient years) finds that only 2.5% of patients with Barrett's esophagus actually die from esophageal cancer (3). This study confirms earlier reports by Spechler *et al.* and Cameron *et al.* (10,11). In these series patients with Barrett's esophagus often have associated cardiopulmonary diseases, being their most important cause of death. Despite these not convincing data, endoscopic surveillance is considered "reasonable" and "desirable" by the gastroenterological associations and consensus meetings (1,12). Furthermore, it may be considered unethical

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to refuse a patient in otherwise good health and with Barrett's esophagus to step into an endoscopic surveillance program because of the lack of large-scale, prospective series (which will never be developed because of this ethical issue).

Endoscopic features of Barrett's esophagus

Three conditions can be considered as premalignant situations :long-segment Barrett's esophagus, short-segment Barrett's esophagus and intestinal metaplasia at the cardia. There is no difficulty recognising the *long-segment Barrett's mucosa*. The presence of intestinal metaplasia is however the cornerstone of the diagnosis and should therefore always be looked for by means of biopsy. There are no macroscopic features suggesting the presence of goblet cells (i.e. intestinal metaplasia) in Barrett's mucosa. Randomly taken biopsies may miss the sometimes focal distribution of intestinal metaplasia. Methylene blue staining is considered highly accurate for selectively staining the specialised columnar epithelium and it has been shown to detect more intestinal metaplasia than random biopsies in long and short segments of Barrett's mucosa (13). Vital staining requires an experienced endoscopist who is trained in interpreting the mucosa after methylene blue staining ; furthermore one should keep in mind that before the staining a mucolytic agent (e.g. acetylcysteine) should be sprayed in the esophagus in order to remove the mucus which can bind the dye (13).

Short segment Barrett's mucosa is defined as the presence of a short segment (< 3 cm) of intestinal metaplasia in the distal esophagus, above the gastro-esophageal junction (14). The gastro-esophageal junction is the demarcation between the tubular esophagus and the upper lining of the gastric folds. Sometimes it is difficult to differentiate the esophageal from the gastric mucosa, especially in patients with a large hiatal hernia. Biopsies taken from the herniated stomach will be staged as "Barrett's mucosa from the junctional or fundic type" if the pathologist is told that the material arises from the esophagus. Endoscopic features suggestive of short segment Barrett's esophagus are short tongues of pink mucosa that extend in the white esophageal mucosa or 1 or more small, oval patches of red-pink mucosa less than 2 cm above the gastro-esophageal junction (fig. 1) (15). A cranial displacement of the Z-line or squamo-columnar lining (seen as a circumferential extension of pink mucosa) is not related to short segment Barrett's mucosa (fig. 2) (15). Histological confirmation of the diagnosis always remains necessary. The risk of malignant degeneration in short-segment Barrett's esophagus is lower than in classical Barrett's esophagus, but exists (16).

In the third condition, *intestinal metaplasia at the cardia*, the endoscopic findings are normal. At this moment there are no data to support a risk of malignant transformation in this region (17).

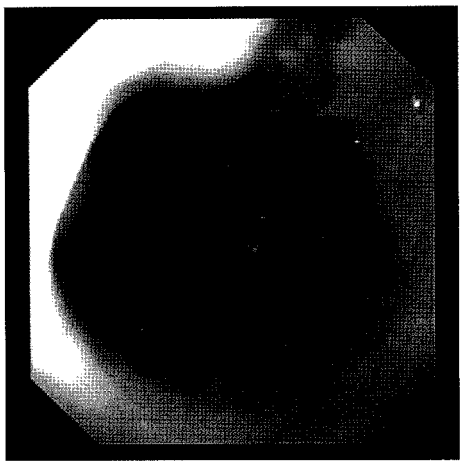


Fig. 1. — Short-segment Barrett's esophagus with short tongues of pink mucosa extending in the white esophageal mucosa. Histologic examination shows intestinal metaplasia.

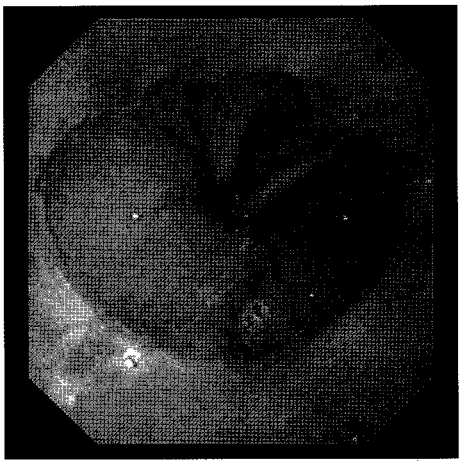


Fig 2. — Cranial displacement of the squamo-columnar lining (Z-line) which is no short-segment Barrett's esophagus. Histologic examination shows columnar epithelium of the stomach.

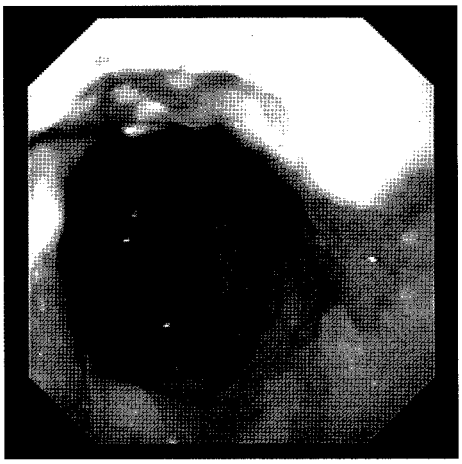


Fig 3. — Typical Barrett's esophagus. Biopsies at the ulcer (head of the picture) at first showed low-grade dysplasia ; control biopsies after a 2 months treatment with a proton-pumpinhibitor showed high-grade dysplasia ; control biopsies 1 month later on showed adenocarcinoma. The resected specimen showed an intramucosal adenocarcinoma.

Endoscopic features in Barrett's dysplasia

The main goal whilst doing endoscopy in patients with Barrett's esophagus is the detection of dysplasia. Unfortunately, there are no macroscopic features typical of dysplasia in the columnar-lined mucosa. Rigorous biopsy protocols to avoid sampling errors are proposed and will be discussed later. Several techniques have been developed to obtain more directed biopsies. The oldest of them is vital staining with methylene blue. Until now only one study was able to show that it improves the diagnosis of dysplasia but more evidence is needed before this technique can be generally recommended (18). Fluorescence detection of dysplasia using 5-amino levulinic acid-induced protoporphyrin IX or by means of laser light-induced fluorescence endoscopy seem to be very promising but until now there is not enough evidence to promote their worldwide use in Barrett's esophagus (19).

Endoscopic features in Barrett's associated intramucosal adenocarcinoma

Intramucosal cancer ("carcinoma in situ") can show no abnormalities of the mucosa but sometimes a macroscopic lesion is found. Tytgat identifies 3 types of macroscopic lesions that may mimick an early cancer : elevated, flat or depressed lesions (20). These lesions may look as an innocent looking Barrett ulcer but are always highly suspicious and should be thoroughly biopsied. If the results of the biopsy are negative control biopsies should be undertaken after 4 weeks of high dose proton pump inhibitors (fig. 3).

Who needs endoscopic surveillance ?

There is no doubt that patients with intestinal metaplasia in the esophagus are at risk for developing an adenocarcinoma. Thus, any columnar-lined esophagus with specialised intestinal metaplasia, regardless of its extent (ie long- or short-segment) needs endoscopic surveillance (21). In the situation of a columnar-lined esophagus without intestinal metaplasia endoscopic surveillance is probably not warranted. However, one must consider the possibility of sampling errors during biopsy taking and the missing of foci of intestinal metaplasia. There are no hard data at this moment to submit patients with specialised intestinal metaplasia at the cardia (not extending above the esophagogastric junction) to an endoscopic surveillance, except for investigational purposes.

A sometimes forgotten group are the patients who have been treated by means of fundoplicature. If Barrett's esophagus exists before the antirefluxprocedure, endoscopic surveillance, even after surgery, remains necessary because of the persisting risk of malignant degeneration (5). Also patients that undergo ablative therapy for Barrett's esophagus should remain in follow-up, but this shouldn't be a problem since these therapies are still experimental at this moment.

How to avoid sampling errors ?

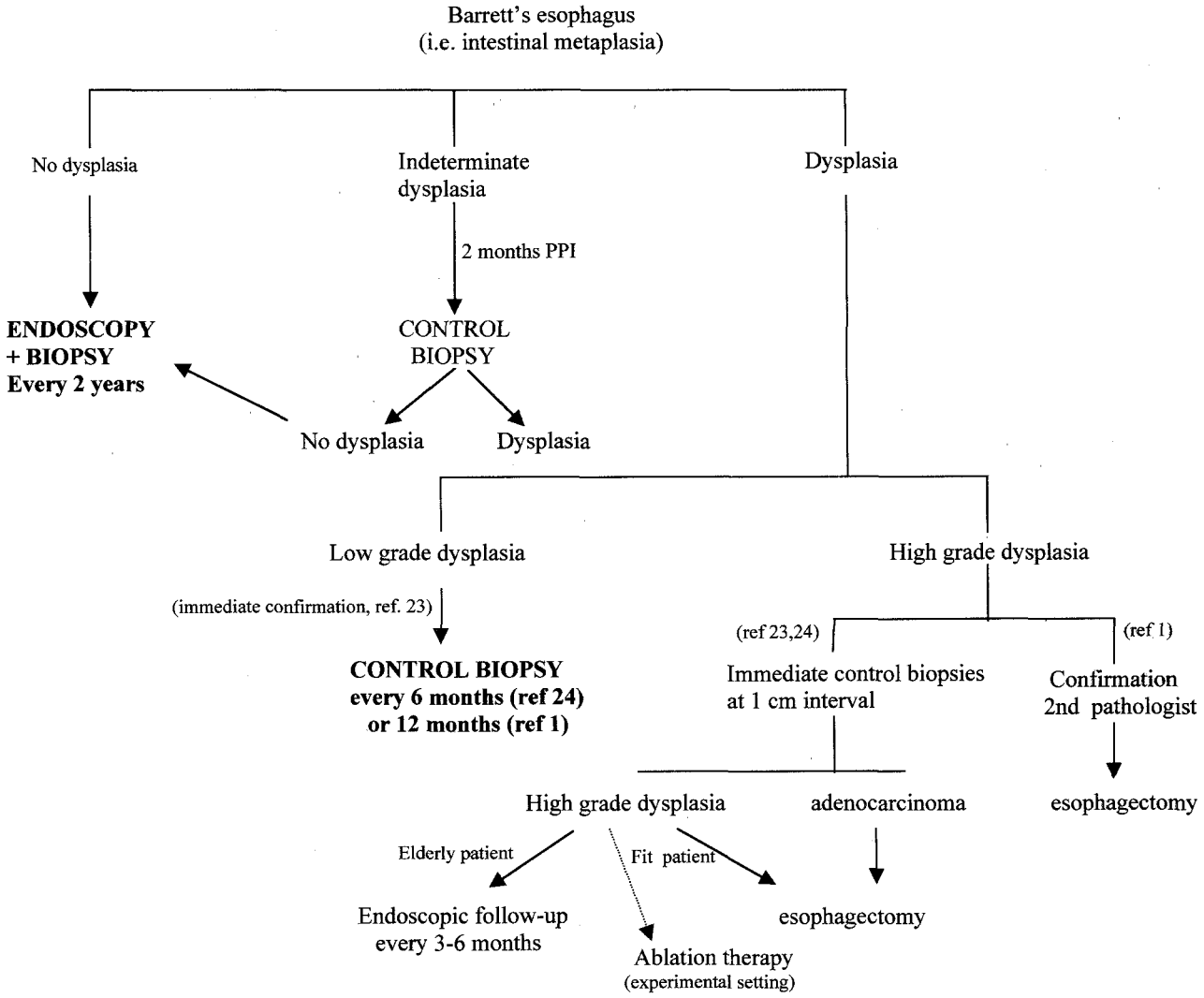
Since dysplasia most often is detected in innocent looking mucosa, at random taken biopsies are less likely to detect dysplasia. Therefore the use of a strict biopsy protocol seems logical. Although there are no comparative studies using different biopsy protocols, every expert in the field recommends 4 quadrant biopsies every 2 cm of the columnar-lined esophagus, beginning at the gastro-esophageal junction and ending cranially at the proximal border of the columnar lining and its tongues. In the situation of a short-segment Barrett's esophagus (< 3 cm) 4 quadrant biopsies are taken every 1 cm. Furthermore, it is of the most ultimate importance to biopsy every macroscopically visible lesion !

Practical guidelines for endoscopic surveillance

No comparative trials exist that look for the ideal frequency of endoscopic surveillance in patients with Barrett's esophagus. The guidelines, proposed by national consensus meetings or experts, are based on the presumption that there is a chronological sequence from metaplasia over dysplasia to carcinoma. The duration of this sequence is unknown but some evidence comes from a study by Katz *et al.* who have shown that it takes longer than 2 years for metaplasia to develop into carcinoma, and it takes longer than 1 year for low-grade dysplasia to develop into carcinoma (22). Detection of dysplasia and its severity is the crucial element in the endoscopic surveillance program. Several drawbacks are to be taken into account : sampling errors should be avoided by the use of a strict biopsy protocol ; esophageal biopsies should contain sufficient material for the pathological exam (a larger, angulated biopsy forceps can be used) ; inflammatory changes caused by the reflux disease can mimick dysplasia and the difference between low-grade and high-grade dysplasia may vary between different pathologists.

In table I practical guidelines for endoscopic surveillance are presented. They are based on the Canadian consensus meeting on this topic in '97 and the opinion of a Dutch (Tytgat) and French (Robaszkiewicz) expert in the field of gastroenterology (1,23,24). Endoscopic surveillance is only recommended in patients fit enough to undergo an esophagectomy if somewhere during follow-up high-grade dysplasia or cancer is detected. The condition of the patient is more important than his/her age ; this latter being no criterium for exclusion from endoscopic follow-up. If no dysplasia is found (and 4 quadrant biopsies every 1-2 cm have been taken) endoscopic control with biopsies is proposed every 2 years. The data of Katz *et al.* support this 2-year interval if no dysplasia is found at the initial endos-

Table I. — **Practical guidelines for endoscopic surveillance in Barrett's esophagus (pooled data from the Canadian consensus meeting on reflux disease and the opinion of 2 experts, Tytgat and Robaszkiewicz) (1,23,24)**



copy (22). In the situation of indeterminate dysplasia, whereas the pathologist can not come to a definite diagnosis, control biopsies are proposed after 2 months of adequate acid suppression by means of proton pump inhibition. In the meanwhile inflammatory changes caused by the acid reflux are corrected. If dysplasia is confirmed in the control biopsies the patient enters a more stringent follow-up. The pathologist determines how we should proceed : the differentiation between low and high grade dysplasia makes all the difference. If low-grade dysplasia is found the French and Canadian experts propose a control biopsy after 6 and 12 months, respectively. Tytgat proposes to repeat biopsies immediately at 1 cm intervals, in order to detect formerly missed foci of high-grade dysplasia. Especially if macroscopic lesions are seen (e.g. an innocent looking ulcer) control biopsies are mandatory. It has been shown that low-grade dysplasia can disappear after acid suppression (22). In this study only 13% of patients with low-grade dysplasia ultimately progressed to high-grade dysplasia or cancer (22). If high-grade dysplasia is found the Canadians let it confirm by a second pathologist and if so, they send the patient immediately for esophagectomy (or experimental ablative therapy) (1). The Europeans propose to biopsy the columnar-lined esophagus thoroughly at 1 cm intervals and all macroscopically visible lesions in order to confirm the high-grade dysplasia or to detect foci of cancer (23,24). The difference between high-grade dysplasia and cancer is very important since a "prophylactic" esophagectomy in the situation of high-grade dysplasia is associated with significant morbidity and loss of quality of life imposed on a patient with a benign disease at the moment. There remains however a lot of discussion about the possibility of adequate endoscopic differentiation between high-grade dysplasia and cancer. In the operative specimen for high-grade dysplasia 25 - 67% of previously unrecognized intra/extramucosal adenocarcinomas are found (9,25). On the other hand studies are available which show that

high-grade dysplasia doesn't progress to carcinoma during follow-up periods up to almost 4 years (26,27, 28). Levine *et al.* have proposed a strict endoscopy + biopsy protocol which can accurately differentiate between high-grade dysplasia and cancer (28). Their protocol consisted of sufficient numbers of biopsy samples (4 quadrant biopsies every 1-2 cm of the entire length of the Barrett mucosa, leading to 11-84 samples/ patient in this study), large mucosal samples (use of a jumbo forceps with a 9 mm open span ; therefore need of a large-channel endoscope), rigourous histopathological examination (serial sections of the material and double check by 2 independent, experienced pathologists) and prompt control biopsies if high-grade dysplasia is found. With this kind of protocol their preoperative diagnosis of high-grade dysplasia or cancer is correct in 93% of cases. The limitations of this protocol are clear : only a very dedicated endoscopist and pathologist will be able to reach analogous good results. These data are not confirmed by a recent report showing 33% of unsuspected cancer in patients undergoing esophagectomy for high-grade dysplasia, diagnosed by means of this rigourous protocol (29). Therefore, there is an urgent need for a better method to differentiate high-grade dysplasia from cancer. If biological markers such as p53 will be able to give a clear-cut diagnosis is still a matter of debate. The role of endoscopic ultrasound has been investigated but no surplus value could be shown of this technique in the differential diagnosis between high-grade dysplasia and intra/submucosal adenocarcinoma (30,31).

At this moment esophagectomy is recommended when high-grade dysplasia is confirmed by a second pathologist and/or by means of new, thoroughly taken biopsies, especially if the patient is young or if a macroscopic lesion is visible. In an experimental setting patients with high-grade dysplasia can be treated with ablation therapy. In elderly patients or patients with underlying morbidity one can take a chance of no cancer lying underneath the high-grade dysplasia and an endoscopic follow-up is proposed every 3-6 months. If an adenocarcinoma is diagnosed during the endoscopic follow-up the patient should undergo an esophagectomy. Patients who are not fit enough to undergo an esophagectomy may profit from an endoscopic surveillance if they are taken into account for ablation therapy when high-grade dysplasia or intramucosal adenocarcinoma arises.

Some critical thoughts...

It is known from autopsy series that the prevalence of Barrett's esophagus varies from 0,3 tot 1% in the population (32). This means that for every patient with known Barrett's esophagus that is in endoscopic follow-up, there are 20 unrecognized patients who are not in a control program. For short-segment Barrett's esophagus this is even more true. Therefore, we should be very humble when we think we are doing something against esophageal cancer by following patients with Barrett's esophagus : we are just seeing the top of the famous iceberg...

Since patients with Barrett's esophagus often are oligosymptomatic one can easily foresee that compliance for regular endoscopies in patients will not be great. This has been confirmed by an Italian study in asymptomatic patients with Barrett's esophagus : 54% underwent a control endoscopy after 1 year, and less than 50% of this group underwent a second and third endoscopic examination later on (33). On the contrary,

Table II. — **Attitude of Flemish gastro-enterologists toward endoscopic surveillance (ES) in Barrett's esophagus (BE). (unpublished personal data)**

N = 33 Response rate = 27/33 (82%)			
Need for ES in long-segment BE ?	yes	27 (100%)	
Upper limit of age for ES ?	70 years	6 (22%)	
	80 years	10 (37%)	
	no limit	11 (41%)	
Interval of ES ?	6 months	1 (4%)	
	12 months	25 (92%)	
	24 months	1 (4%)	
Biopsy sampling	4/quadrant, every 2 cm		9 (33%)
	at random		15 (55%)
	only macroscopic lesions		3 (12%)
Strategy if "high grade dysplasia" is detected			
Control endoscopy + biopsies	immediately	9 (33%)	
	at 3 months	10 (37%)	
	at 6 months	2 (7,5%)	
Immediate esophagectomy		2 (7,5%)	
Endoscopic ultrasound		4 (15%)	
Need for ES in short-segment BE ?	yes	8 (30%)	
	no	19 (70%)	

the patients with symptomatic gastro-esophageal reflux disease are far more compliant to the proposed regimen of endoscopic surveillance in this Italian study.

Another thought that should raise our mind is : will gastro-enterologists be compliant enough to rigourously schedule their patients for endoscopy and make use of a strict biopsy-protocol as proposed by the scientific community ? A study in the United Kingdom in 58 endoscopists shows that 90% finds endoscopic surveillance in Barrett's esophagus worthwile (34). Thirty-five percent however never takes biopsies and the remaining 65% samples at random, not following the proposed biopsy protocol. The interval for surveillance varies between 1 and 3 years and 75% stops endoscopic follow-up at a certain age, varying between 60 and 80 years. In table II the results are presented of a questionnaire filled out by 33 Flemish gastro-enterologists/endoscopists. Twenty-seven responded (82%), all of whom advise their patients with long-segment Barrett's esophagus to take part in an endoscopic surveillance program. Only 30% advises patients with short-segment Barrett's esophagus to go in surveillance. For 41% of the endoscopists there is no upper limit of age ; 37% considers 80 as the age above which no endoscopic follow-up should be done and 22% puts this limit at 70 years. Ninety-two percent proposes a yearly endoscopic follow-up to their patients. Biopsies are taken at random by 55%, systematic (4 quadrant biopsy every 2 cm) by 33% and 12% only biopsies macroscopic lesions. In the case of high-grade dysplasia 7,5% sends the patient immediately for surgery, 7,5% does a control endoscopy with biopsies after 6 months, 37% after 3 months and 33% immediately.

At the end of the 20th century it is "bon ton" to consider the costs of the proposed regimen for endoscopic surveillance in Barrett's esophagus. Provenzale *et al.* use a Markov model to estimate life expectancy in a computer cohort simulation of 10.000 hypothetical 55-year-old patients with Barrett's esophagus and no evidence of dysplasia by biopsy (35). Their results show that an interval of 5 years is the most viable strategy, in terms of costs, life expectancy and quality of life. They find that the incremental cost-effectiveness ratio is comparable to other, generally accepted practices such as heart transplantation.

Conclusion

At the moment large consensus more or less exists in the gastroenterological community about the protocol of endoscopic surveillance and its implications in Barrett's esophagus. One can expect however that during the next century these protocols will change considering new data on dysplasia detection (biochemical markers, flow cytometry, fluorescence techniques), the development of better ablative techniques, changing ethical behaviour towards premalignant conditions and, last but not least, changing public health policy that will take control over prevention programmes of esophageal cancer (amongst others).

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