Surveillance and Screening for Barrett Esophagus and Adenocarcinoma

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Abstract: Current recommendations for screening and surveillance of Barrett esophagus and related lesions are based on recent guidelines by the Practice Parameters Committee of the American College of Gastroenterology. The purpose of this review is to critically examine the rationale and evidence behind these recommendations. There is strong rationale for vigorous initial testing to document the baseline status and identify early adenocarcinoma, and for surveillance of high-grade dysplasia. Recommendations for esophagectomy in patients with high-grade dysplasia need to be individualized. However, recommendations for surveillance of low-grade dysplasia and specialized intestinal metaplasia without dysplasia are largely opinion statements not well supported by objective data. Although cancers identified by surveillance are at earlier stages than those diagnosed without prior endoscopic evaluation, surveillance failures are common. Recommendations for screening and surveillance are not evidence-based and unlikely to alter national mortality from esophageal adenocarcinoma. Their impact on individual patients depends on individual circumstances. Current recommendations are limited by inconsistent endoscopic findings and sampling errors, inconsistent histologic diagnoses of Barrett esophagus and dysplasia, and our poor understanding of the natural history of various histologic lesions. Future directions include validation of methods that reduce these inconsistencies by in vivo detection of abnormalities and by objective diagnostic markers besides grades of dysplasia, such DNA content analysis and molecular markers, and improved understanding of the disease progression. Effective screening programs depend on development of simple, inexpensive, and reliable methods to identify the small group of patients truly at high risk for adenocarcinoma for endoscopic screening.

Key Words: Barrett's esophagus, surveillance, adenocarcinoma, dysplasia

(*J Clin Gastroenterol* 2005;39:S33–S41)

Barrett's esophagus (BE) is a condition in which normal squamous epithelium of the esophagus is replaced by metaplastic columnar mucosa. It is a complication of esophageal mucosal damage due to gastroesophageal reflux disease (GERD). BE does not produce any symptoms or health impairment other than its associated condition of GERD. However, it is a premalignant condition that may progress to esophageal adenocarcinoma (EAC).[1,2] Therefore, its diagnosis and management are focused around prevention, early recognition, and early treatment of EAC.[3] The goal of surveillance is to diagnose early stages of cancer in patients with known BE and to intervene so as to prevent progression to fatal cancer. Surveillance is structured follow-up testing of BE to detect progressive dysplastic changes in the mucosa that herald development of carcinoma. In contrast, the goal of screening is to detect patients with BE and then to enroll these patients in a surveillance program to reduce mortality from EAC in an individual patient or a population group. Screening involves testing for the presence of BE and related lesions. Thus, a defined surveillance program must be in place before screening is initiated.

The purpose of the present review is to examine the current recommendations for a surveillance program and for a screening and surveillance program for BE-associated EAC and to critically assess their rationale and clinical impact.

FACTORS PUSHING FOR A SURVEILLANCE PROGRAM

The surveillance program for BE has evolved over the years due to several factors including the realization of association of BE with EAC, slow progression of BE to carcinoma through escalating grades of histologic dysplasia, dismal outcome of EAC, rapidly rising incidence of EAC, and most importantly the awareness of the lay public regarding heartburn being complicated by BE and EAC.

Association of columnar lined esophagus with EAC was first described in 1952 by Morson and Belcher, and this was followed by several isolated reports of such an association.[1] In 1975, Naef et al pointed out that EAC was a frequent complication of BE that required early recognition and prevention.[4] Trier characterized the histologic lesion of specialized intestinal metaplasia (SIM) in 1970.[5] It was subsequently appreciated that it is the SIM in BE that is associated with the development of the adenocarcinoma. Because of the importance of SIM in cancer development, this term is often used synonymously with BE. Several surgical series that included patients who usually presented with invasive carcinoma

Received for publication December 28, 2004; accepted January 29, 2005.
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Supported in part by NIH Grant Nos. DK031092 and DK62867 and Merit Review Award from the Research Service, VHA (to R.K.G.); and by Merit Review Award from Research Service, VHA (to H.M.).
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revealed a high prevalence of associated BE of approximately 10%. In those patients who did not have associated BE, it was thought that their underlying BE might have been overcome by the growing EAC. On the other hand, the prevalence of EAC in cases of BE was reported to be upwards of 80%.[1]

In 1953, Allison and Johnston proposed that reflux esophagitis may lead to columnar lined esophagus and metaplasia that may progress to carcinoma.[1] The prevalence of cancer is high with low-grade dysplasia (LGD) and even higher with high-grade dysplasia (HGD).[6] It is thought that histologic disease in BE progresses sequentially from no dysplasia to LGD, then to HGD, and eventually to EAC (Fig. 1). This stepwise progression was deemed to be slow and therefore suitable for surveillance program. It now appears that not all cases progress to cancer in a predictable sequence of worsening dysplasia. Moreover, there has been increasing recognition that progression to cancer is not inevitable, and the process can halt itself at any of the stages along its course. There is also evidence that LGD or even HGD may regress. Additionally, not all patients are observed to progress through each step.

Another factor that pushed the cause for surveillance is the dismal prognosis of EAC. The reported 5-year survival was 11% in the early 1990s. Because the lymphatic supply of the esophagus extends into the lamina propria, lymphatic spread is common even in early disease. Lymph node metastasis has been reported in up to 5% of the cases of intramucosal and up to 24% of the cases with submucosal extension of the tumor.[7]

Although esophageal EAC has been considered as an uncommon tumor, its incidence has been EAC has increased over 300% in recent decades since 1970s, making it one of the most rapidly increasing cancers in the United States. This increase is most prominent in white men over 65 years of age. The reason for this increase is not clear.[8]

In addition to the above factors, the heightened awareness of the lay public has been an important factor for promoting screening and surveillance measures. Several articles published in high-profile newspapers such as the *New York Times* drew attention of the lay population regarding increased cancer risk in GERD and BE[9] and the rapid rise in the incidence of EAC.

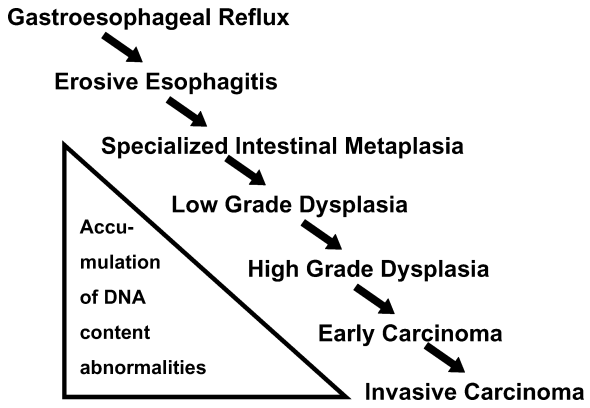

FIGURE 1. Development and stepwise histological progression of BE to invasive carcinoma.

CURRENT RECOMMENDATIONS FOR SURVEILLANCE

The current recommendations for surveillance of BE and related lesions are based on recent guidelines by the Practice Parameters Committee of the American College of Gastroenterology.[10] These recommendations can be considered as having two distinct components, namely, the initial documentation for BE and related lesions (Fig. 2), and the follow-up surveillance (Fig. 3).

Initial Documentation

Usually, the first endoscopy is performed for evaluation of heartburn or other symptoms of gastroesophageal reflux or other indications, and BE and associated lesions are identified unexpectedly. Moreover, in many such studies, mucosal inflammation is encountered and a thorough examination with intensive biopsy protocol is not performed at that time. In most of these cases, a repeat, planned, and comprehensive endoscopy and biopsy protocol to identify histology, extent of the lesion, and associated abnormalities is performed 1 to 3 months afterward, depending upon the circumstances. For example, if acute erosive esophagitis is present, the repeat endoscopy is performed after vigorous acid inhibition therapy for 2 to 3 months to heal the associated esophagitis. If the biopsy shows HGD, repeat examination is performed at an earlier time (Fig. 2).

The technique of endoscopic biopsy is not standardized. However, the "turn-and-suction" technique is good for targeting of esophageal biopsies and maximizing sample size.[11] All mucosal irregularities in BE, including erosions, nodules, and strictures, are sampled because of the likelihood of cancer. Four quadrant biopsies every 2 cm are commonly taken from BE. In the presence of HGD, 4-quadrant biopsies every 1 cm are recommended.

In patients with endoscopic mucosal biopsies showing HGD, concurrent early cancer has been reported in up to one third of the cases.[3] This high incidence of carcinoma at esophagectomy in patients diagnosed preoperatively as having only HGD is one of the arguments advanced for recommending esophagectomy in all cases of HGD. Positive predictors of cancer at esophagectomy in patients with HGD include mucosal nodularity on endoscopy and diffuseness of HGD. Nodularity is defined as a subtle mucosal elevation of $\leq$1 cm. In one study, 63% of the patients with HGD and nodularity had cancers as compared with 13% without nodularity. Nodularity was associated with a 2.5-fold risk of cancer compared with

- Endoscopy and biopsy showing Barrett-related columnar metaplasia and related lesions
- Treat esophagitis, if present, until healed
- Repeat endoscopy in 1 to 3 months. Obtain 4-quadrant biopsies every 2 cm (every 1 cm for HGD) to establish base line of the histological abnormalities and the extent of the lesion

FIGURE 2. ACG guideline for initial documentation. (Adapted from Sampliner 2002.[10])

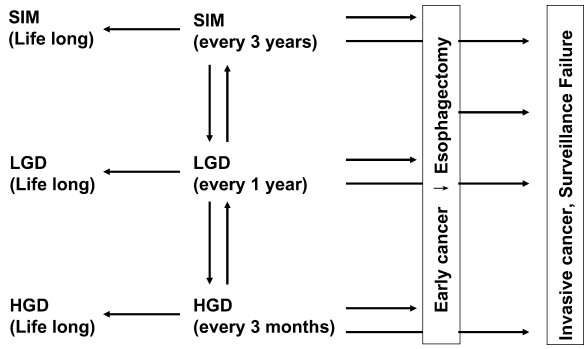

FIGURE 3. ACG guidelines for surveillance following initial documentation. (Adapted from Sampliner 2002.[10])

those without it after adjusting for extent of dysplasia.[12] Moreover, 36% of the patients with diffuse HGD and 7% of those with focal HGD had cancer at esophagectomy. The patients with diffuse HGD had a 3.7-fold increased risk of esophageal cancer compared with focal HGD limited to 5 or fewer crypts.[12] The diagnosis of early EAC may be difficult in some cases and requires second expert opinion. The diagnosis of carcinoma is made when dysplastic columnar epithelial cells invaded through the epithelial basement membrane and into deeper tissue.

If early cancer is found, esophagectomy is recommended in surgically suitable cases. In patients who are not good surgical candidates because of comorbid conditions, endoscopic mucosal resection or a mucosal ablative therapy may be undertaken. Success of combined endoscopic mucosal resection and photodynamic therapy for intramucosal carcinoma was recently reported.[13] These techniques are currently considered experimental (Fig. 4).

Rationale of aggressive initial thorough examination is to establish a baseline diagnosis, which forms the basis of follow-up surveillance. These studies also help exclude the complicating factor of inflammation in establishing a proper baseline diagnosis of BE-associated lesions. Moreover, it is important in identifying early carcinoma that may occur concurrently with HGD.

- Surgical mucosal stripping
- Endoscopic mucosal resection
- Thermo-ablation using:
  - bipolar probes
  - laser
  - argon plasma coagulation
  - radiofrequency
- Photodynamic therapy

FIGURE 4. Alternatives to esophagectomy: endoscopic mucosal ablation therapies.

Follow-up Surveillance

Follow up surveillance is based on the baseline diagnosis of the histologic abnormality (Fig. 3). Patients are assigned diagnoses based on the highest grade of abnormality (dysplasia) found in the biopsies.

Surveillance for HGD

Patients are classified as having HGD only after undergoing intensive surveillance endoscopies. However, this may not be sufficient to rule out a diagnosis of concurrent adenocarcinoma. It is suggested that diagnosis of "true HGD" without concurrent carcinoma be made only after excluding carcinoma by repeating the vigorous surveillance and biopsy program every 3 months for 1 year.

HGD is diagnosed by the presence of specific architectural and nuclear changes. The architectural changes consist of distortion of crypt architecture that is usually present and may be marked. It is composed of branching and lateral budding of crypts, a villiform configuration of the mucosal surface, or intraglandular bridging of epithelium to form a cribriform pattern of "back-to-back" glands. Goblet and columnar cell mucus is usually absent. The abnormalities extend to the mucosal surface. The nuclear abnormalities are severe; nuclear stratification reaches the crypt luminal surface. There may be a loss of nuclear polarity, and nuclei often vary markedly in size, shape, and staining characteristics that are indicative of increased DNA content.[14] Different pathologists give different weights to different abnormalities that lead to large interobserver variations in the diagnosis of HGD (Table 1).

When a diagnosis of HGD without concurrent cancer has been made, intensive surveillance with endoscopies every 3 months with a rigorous biopsy protocol has been suggested. This intensive program is to continue until the patient develops early cancer, when esophagectomy is offered. It has been estimated that approximately 16% to 22% of such patients will develop early cancer over a 5- to 7-year follow-up period.[15] The rest (approximately 80%) would undergo the intensive surveillance program throughout their life, until they develop early cancer or die of some unrelated cause. To be in this intensive surveillance program, the patient should be willing and be a candidate for esophagectomy, so that this treatment can be provided, should an early cancer develop.[16] This fact is used by some clinicians to favor esophagectomy for all surgically suitable patients with HGD. If the cancer cases in the first year washout period for the diagnosis of HGD are not excluded, up to 60% of patients with HGD may be considered to progress to carcinoma in 5 to 7 years.[16]

TABLE 1. Interobserver Agreement in the Diagnosis of Various BE-Associated Histologic Lesions

Histology	Set 1	Set 2	Agreement
SIM without dysplasia	0.44	0.58	Poor
Indefinite dysplasia	0.13	0.15	Very poor
Low-grade dysplasia	0.23	0.31	Very poor
High-grade dysplasia-carcinoma	0.63	0.64	Poor

Adapted from Montgomery et al.[28]

The required intensity of the surveillance for HGD to an end point that includes whole life until death and at best postponement of esophagectomy to a later date makes the surveillance program an unattractive management option. Moreover, an invasive adenocarcinoma may develop despite the surveillance owing to program failure. Therefore, alternatives such as esophagectomy and endoluminal mucosal resection or ablation are considered. Many have advocated esophagectomy for all patients with BE and HGD in whom concurrent cancer cannot be excluded or in young patients who are good surgical candidates.[17] The downside of esophagectomy is that it is associated with a high complication rate up to 57%, morbidity of up to 30%, and mortality of 1% to 5%.[18] The complication rate is higher in centers with low surgical volumes. Therefore, esophagectomy should only be undertaken at centers with high surgical volumes.[19]

Patients with HGD are often elderly, have other comorbid illnesses, and are not suitable candidates for esophagectomy. Such patients are evaluated carefully to determine their individualized management plan. Endoscopic mucosal resection or ablation is offered as an alternative to esophagectomy (Fig. 4). The rationale of endoscopic resection or ablation of HGD in BE is that, after destruction of the dysplastic epithelium, mucosal healing occurs with squamous epithelium in an acid-free environment.[20] Endoluminal ablative therapies include thermal application including bipolar probes, laser, radiofrequency, and argon plasma coagulation; cytotoxic agents such as photodynamic therapy; and surgical stripping or endoscopic mucosal resection. Broad ablative therapies are better suited for treatment of large macroscopically indistinct lesions, while endoscopic mucosal resection may be more effective in removing focal lesions. These therapies have several potential limitations: there may be residual foci of HGD or new carcinoma may develop under the neo-squamous epithelium, and this approach needs intensive posttreatment surveillance with multiple frequent endoscopies. These techniques are currently considered experimental as their outcomes are not fully known.

Surveillance for LGD

The presence of LGD as the highest grade of abnormality should be considered as baseline finding when it is reproduced at two different examinations. Histologically, in LGD, the crypt architecture tends to be preserved and distortion is minimal; the nuclei may be stratified, but the stratification does not reach the apical surface of the glands; nuclei are enlarged, crowded, and hyperchromatic; mitotic figures may be present in the upper portion of the crypt; goblet and columnar cell mucus is usually diminished or absent, but goblet cells in which the mucous droplet does not communicate with the luminal surface may be observed. The abnormalities extend to the mucosal surface. The diagnosis of LGD must be confirmed by two expert gastrointestinal pathologists. Also, active esophagitis must be adequately treated with aggressive acid suppression and endoscopy repeated before interpreting biopsy findings as LGD.

The recommended subsequent surveillance includes repeated intensive endoscopy and biopsy program every year (Fig. 3). This program is to continue until the examination shows that LGD has changed when the follow-up plan is also changed accordingly. When the lesion reverts to BE without dysplasia, surveillance is decreased to 3-year intervals. When progression to HGD is observed, endoscopy and biopsies are increased to every 3 months and the four quadrant biopsies are taken every 1 cm. Some cases of LGD may progress to early carcinoma without going through the stage of HGD. In that case, esophagectomy is considered. If the LGD does not change, yearly surveillance is continued throughout the patient's life. An invasive carcinoma should not occur in patients in the surveillance program. If this happens, it indicates failure of the program.

Surveillance for SIM

The metaplastic columnar mucosa is a mosaic of different types of mucosa, including gastric fundic, cardiac, and intestinal types.[21] The intestinal type of the mucosa, described as SIM, is dysplastic in nature and is distinguishable from normal small bowel or colonic mucosa. It is characterized by the presence of barrel-shaped goblet cells containing acid mucin that stains with Alcian blue.[5] It is this SIM that is associated with the risk of cancer development. Hence, many observers diagnose BE only when SIM is identified histologically.

Another issue related to the diagnosis of BE is the extent of the columnar mucosa lining the esophagus. It was thought that the distal 2 to 3 cm of the esophagus was normally lined by columnar mucosa. Therefore, diagnosis of BE was made only when the columnar-lined distal esophagus was more than 2 to 3 cm long. In 1994, Spechler et al reported that the type of mucosa in the distal 2 to 3 cm of the esophagus could also be of the specialized intestinal variety, which was found in 18% of unselected patients undergoing elective upper endoscopies regardless of reflux symptoms.[22] This led to appreciation of short segments of SIM.

Based on the extent of involvement, SIM is classified as long segment (>2–3 cm) BE (LSBE), or short segment (<2–3 cm) BE (SSBE). According to the guidelines, the zigzag squamocolumnar junction that appears "abnormal" and shows SIM on biopsy is given the diagnosis of SSBE. The prevalence of endoscopically recognizable SSBE is reported to be around 5% to 7%, as compared with the prevalence of 1% to 3.4% for long segment. Thus, SSBE may be 2 to 5 times as common as the LSBE. The prevalence of dysplasia in LSBE and SSBE is around 6% and 8%, respectively.[23] Studies have shown that the risk of carcinoma in LSBE is around 0.5% per year that is similar to that of the SSBE.[24,25]

After the diagnosis of SIM (BE) without dysplasia is established by the initial documentation, it is suggested that these cases be followed with surveillance endoscopies performed every 3 years. The end points of the follow-up are development of dysplasia either LGD or HGD or early cancer or until death due to unrelated causes (Fig. 3).

CRITICAL EVALUATION OF THE RECOMMENDATIONS FOR SURVEILLANCE

Many of the above recommendations appear to be limited by the lack of key requirements for sound surveillance recommendations. To produce evidence-based recommendations:

1) the endoscopic findings should be reproducible; 2) there should be no or minimal sampling errors; 3) histologic lesions should be reliable and reproducible; and 4) natural history of the disease and in particular the risk and the time sequence for progression to cancer should be known. However, the available data indicate that endoscopic diagnosis of BE is not highly reproducible, histologic diagnoses show considerable interobserver variability, and the natural history of BE is not well understood.

The poor reproducibility of endoscopic diagnosis of BE is in part due to poor reproducibility and reliability of the endoscopic recognition of anatomic landmarks at the gastroesophageal junction. This is particularly true when a hiatal hernia is present, which is the case in most of the patients with BE. These problems are greatly exaggerated in the diagnosis of the BE. According to the recommendations, the columnar mucosa or its upward extensions that lines <2–3 cm of the distal esophagus, appears "abnormal" on endoscopy and show SIM on biopsy is given that diagnosis of SSBE. If the junction appears "normal" to the endoscopist but shows SIM on histology of the biopsy, it is arbitrarily excluded from the diagnosis of BE without providing precise definition of the abnormality. The lack of precise endoscopic diagnosis of SSBE may lead to large variability in its diagnosis. To complicate matters further, intestinal metaplasia has also been reported in the proximal gastric mucosa, and it has been suggested that intestinal metaplasia of the gastric fundus is not associated with high risk of cancer. Further clarifications are needed to determine whether the histologic abnormality of the mucosa or its endoscopic appearance determines its biologic behavior of BE. Depending upon the definition used, the prevalence of SSBE may be as low as 5% or as high as around 20%. Although sampling error is minimized by a very vigorous biopsy protocol, such a protocol is difficult to follow in general practice and has a low compliance rate.

The diagnosis of dysplasia also has very poor reproducibility. Alikhan et al reported that experts showed poor agreement with the diagnoses of BE and dysplasia made in community practice. The agreement with the diagnosis of gastric metaplasia, SIM without dysplasia, LGD and HGD was only 60%, 58%, 35%, and 22% respectively.[26] Reid et al found that pathologists only agreed between 58% and 61% of the time in distinguishing negative versus indefinite/LGD from HGD/intramucosal adenocarcinoma.[27] In a more recent study, 250 biopsy specimens representing the spectrum of BE-dysplasia-carcinoma were divided into two groups of 125 slides. The first group of 125 slides was evaluated by 10 gastrointestinal pathologists from different institutions, using one set of the criteria and Kappa statistics, the statistical method that accounts for agreement that occurs by chance alone, were performed. The second set of 125 specimens was blindly reviewed by the same 10 gastrointestinal pathologists using a newly agreed upon criteria and subjected to Kappa statistics. The study found poor reproducibility of the diagnosis of histologic dysplasia (Table 1).[28]

The natural history of BE and associated lesions is not well understood. In LGD, for example, the incidence of cancer is 0.6% to 2% per year, which is only minimally higher than the risk of cancer in BE without dysplasia, which is reported to be 0.5% to 1% per patient per year (Table 2).[29] Reports also demonstrate that LGD may move back and forth between LGD and no dysplasia on surveillance biopsies. This may reflect true regression, sampling error, or incorrect pathologic interpretation. Since the rate of progression of LGD to cancer is not much different from that of BE without dysplasia, surveillance intervals of only 1 year for LGD do appear to be justified. On the other hand, recent reports suggest that some patients with LGD may progress to carcinoma without going through the stage of HGD. Another marker such as DNA content determination may help identify LGD patients that are at high risk for developing carcinoma.[30]

Although the natural history and course of HGD are also not fully understood, it is clear that these patients are at very high risk for developing cancer. It has been reported that 16% to 60% of patients with BE and HGD may progress to adenocarcinoma in 5 to 7 years.[31] However, careful analysis of this data suggests that majority of these cases progress to cancer in the first year of follow-up. It has been argued that such cases may represent cases of concurrent cancer that have remained undiagnosed. In any case, if the cases that develop cancer in the first year of follow-up are excluded, the rate of cancer development is 16% to 22% over a 5- to 7-year period of follow-up, yielding a rate of cancer development of approximately 3% to 5% per year. Moreover, most of these cancers are found in the earlier years of follow-up. All these observations indicate that the surveillance intervals for HGD require reconsideration.

In summary, and in view of the limitations of the available data that form the basis of the current recommendations, the current recommended intervals may need to be revised. In general, the recommended surveillance intervals appear to be shorter than they need to be. In any case, the recommended surveillance intervals must be considered as opinions that are not evidence based.

Despite the many limitations of the current surveillance program, studies suggest that surveillance-detected cancers have better outcome than those not under surveillance. Corley et al reported that, in a community-based population, 73% of the surveillance-detected cancers but none of the prevalent cancers survived. Moreover, surveillance detected earlier stages of cancers.[32] Similarly, several retrospective surgical series suggest better outcome in the surveillance-detected cancers than those not under surveillance (Table 3).[33–35] In many of these studies, details of the surveillance program are not described in any detail, and the protocol used does not appear to be that currently recommended. Therefore, true advantage of the recommended surveillance program is not known. However, it is clear that some sort of surveillance

TABLE 2. Cancer Risk in BE With Different Grades of Hysplasia

Dysplasia	No. of Cases*	Cancer Cases*	Estimate (% per year)
None	382	9 (2%)	0.5–1
Low-grade	72	5 (7%)	0.6–2
High-grade	170	37 (22%)	5–10

*Adapted from Sampliner et al.[10]

TABLE 3. Survival Advantage of Endoscopic Surveillance at 5 Years in Patients Other Than HGD

Reference (year)	Surveillance Cancers [N (%)]	Prevalence Cancers [N (%)]	*P*
Streitz at al[33] (1993)	19 (62)	58 (20)	0.007
Peters et al[34] (1994)	17 (90)	35 (35)	0.05
VanSandick et al[35] (1998)	16 (86%)-2 yr	64 (64)	0.003

may be of benefit in reducing mortality from esophageal adenocarcinoma in individual cases.

FUTURE DIRECTIONS FOR THE SURVEILLANCE PROGRAM

Future directions in surveillance programs are to address current limitations of the recommendations (Fig. 5) and may include: 1) methods to reduce endoscopic variability and reducing sampling error by in vivo recognition of BE-associated lesions and directed biopsies; 2) developing tests that may supplement the diagnosis of, or present alternatives to, histologic dysplasia; 3) better definition of surveillance intervals; and 4) use of chemopreventive therapy during the surveillance follow-up.

Reducing Endoscopic Variability and Sampling Error

Recently, a number of methods have been proposed to improve endoscopic variability and reduce sampling error of BE and dysplasia and early carcinoma (Fig. 6). These methods involve in vivo recognition and differentiation of the various BE-associated lesions that may allow directed biopsies for detailed histologic examination.

Chromoendoscopy involves use of dyes that can be used in vivo to stain or highlight areas of BE, dysplasia, or carcinoma for easy endoscopic recognition and targeted biopsies. Methylene blue selectively stains intestinal metaplasia so that it can be targeted for biopsy. Thus, methylene blue chromoendoscopy has been shown to enhance the yield of intestinal metaplasia and increase the detection of short-segment BE. Intramucosal adenocarcinoma remains unstained or inhomogeneously stained by methylene blue. Targeted biopsies of these areas allow higher yield of HGD and carcinoma.[36] Similarly, oral 5-aminolevulinic acid in a dose lower than that is used for phototherapy may be sufficient to identify dysplasia not otherwise visible at endoscopy.[37] Light scattering spectroscopy was used in vitro and in vivo to measure nuclear crowding and enlargement and compared with histologic interpretation. Light scattering spectroscopy has been reported to accurately identify dysplasias.[38] Optical coherence tomography is a high-resolution optical backscatter analysis of laser light rather than sound waves that can produce images of mucosa and submucosa that approximates histologic appearance. This technique has been reported to identify areas of BE, dysplasia, and early invasive carcinoma in vivo.[39] These areas can be selected for targeted biopsies. Enthusiasts believe that further developments in optical coherence tomography and in vivo confocal microscopy may obviate the need for mucosal biopsies all together.

Alternative or Additional Tests for Histologic Dysplasia

As the histologic diagnosis is not very reliable, other more objective and reproducible methods that might predict progression to cancer need to be found. Determination of aneuploidy or DNA content abnormalities has been proposed to be one such method. EAC appear to be associated with progressive accumulation of abnormal DNA content due increase in the content of individual chromosome as well as the number of chromosomes (Fig. 1). The escalating nuclear abnormalities are important ingredients to the histologic diagnosis of increasing grade of dysplasia. It has been suggested that an objective determination of DNA content abnormality may provide a more reproducible test for the dysplastic

- Sedated endoscopies are invasive, costly and have inherent risks
- Suboptimal reproducibility of endoscopic findings
- Sampling errors and laborious biopsy protocol
- Poorly reproducible histological diagnoses
- Arbitrary surveillance intervals
- Poor compliance with the recommended program
- Not cost effective except for HGD
- Detection of early stage disease, but common program failures

FIGURE 5. Limitations of current surveillance recommendations.

- Chromoendoscopy
- Flourescent endoscopy
- Magnification endoscopy
- Laser-induced fluorescence
- Spectroscopy
- Optical coherence tomography
- Esophageal confocal microscopy

FIGURE 6. Methods to improve endoscopic variability and sampling error.

abnormality than the subjective assessment of nuclear abnormalities in the histologic evaluation.[40,41]

Aneuploidy refers to an alteration in DNA content other than the normal diploid (2N) and indicates genomic instability and an increased risk of neoplastic progression. Increased 4N fraction greater than 6% has the same implication as aneuploidy. Aneuploidy and elevated 4N fractions can be detected by flow cytometry, and these increase with the grade of dysplasia and carcinoma. In one study, biopsies of BE were taken from patients upon study entry (baseline) for histology and flow cytometry, and the patients were followed for the development of cancer. The rate of cancer incidence in patients whose biopsies at baseline did not have aneuploidy or elevated 4N was approximately 5% at 5 years, and all these patients had HGD on biopsy. In patients with only aneuploidy at baseline, the 5-year incidence of cancer progression was 64%; in patients with only elevated 4N fractions, the 5-year cancer incidence was 57%; and in patients with both aneuploidy and elevated 4N, it was 75% (Fig. 7).[31,42]

Further studies are needed to establish reproducibility, sensitivity, and specificity of DNA content analysis by flow cytometry. Newer techniques of image cytometric DNA content analysis may provide better estimates of DNA content of the affected cells.[30] Establishing the most reproducible and objective method of DNA content analysis would be useful. However, the presence of aneuploidy alone may not be a predictor of progression to carcinoma. DNA markers that identify development of new abnormal clones may be more useful in identifying cases that are at higher risk of disease progression. In addition to DNA content determination, a panel of molecular markers that may predict progression more reliably than dysplasia would be required. These include cell cycle regulators, apoptotic pathway molecules, telomerase, growth factors, growth inhibitors, invasion and metastasis mediators, and angiogenesis pathway mediators. These new markers may also be complementary to histologic diagnosis of dysplasia in more accurately predicting lesions that are at high risk of progression to cancer.

Defining Surveillance Intervals

Further studies are also needed to better define the surveillance intervals. A careful review of the rate of cancer development shows that there is a higher risk of developing cancer in the first 1 to 3 years of surveillance than subsequent years. If so, intensive screening can be relaxed and performed at longer intervals.

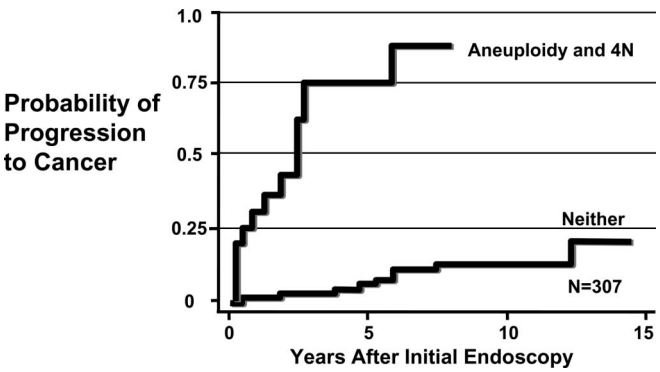

FIGURE 7. DNA content abnormalities at initial endoscopy predict progression to cancer. (Adapted from Rabinovitch PS et al. 2002.[42])

Chemopreventive Therapy During Surveillance Intervals

Surveillance of the patients without offering any chemopreventive therapy in the interval appears to be a lost opportunity for studying agents that may halt the progression of the disease. Despite present looming concerns regarding the use of COX-2 inhibitors, some other chemopreventive agents will be used during the surveillance period in the future.

PROGRAM OF SCREENING AND SURVEILLANCE

Screening subjects actively for the presence of BE followed by surveillance evolved as advancement from simply instituting cancer surveillance for subjects who are unexpectedly found to have BE or associated lesions on endoscopy performed for some other reason. The purpose of a program of screening and surveillance is to prevent deaths from esophageal adenocarcinoma. As with the surveillance program, this approach was promoted by the appreciation by the care providers as well the lay population that GERD leads to BE and esophageal adenocarcinoma and that the incidence of EAC was rising at an alarming rate. Since GERD is a very common clinical condition, a large number of such patients began wondering whether they should be screened for BE.

The recent guidelines published by the Practice Parameters Committee of the American College of Gastroenterology[10] concluded that patients with chronic GERD symptoms are most likely to have BE and recommended that they should be screened by upper endoscopy for the presence of BE. If BE is detected, they should enter a screening and surveillance program. Screening and surveillance is particularly recommended for GERD patients who are at high risk for having BE and developing the adenocarcinoma. The high-risk group includes white males over 50 years of age with GERD symptoms for over 10 years. Family history of BE or adenocarcinoma may now be added to this high risk group.[10,43–46]

Approximately 14% of Americans older than 50 years have weekly reflux symptoms,[47] making 10 million patients potential candidates for screening. Selection of high-risk groups will decrease the number of patients to be tested but still remains formidable. Estimated prevalence of all endoscopically diagnosable BE in GERD with chronic symptoms is around 10%. In one study of patients with GERD, cumulative prevalence of all BE was 10.6% with LSBE in 3.4% and SSBE in 7.2% of the cases. In another study, prevalence of LSBE was found to be 6-fold more common in patients with chronic reflux symptoms than in those without them. In contrast, prevalence of SSBE was similar in patients with heartburn and in those without heartburn. These observations suggest that symptomatic GERD is risk factor for LSBE but not the SSBE. These observations are consistent with the finding of LSBE in 1% and SSBE in 5.5% of patients undergoing endoscopy and regardless of the presence of GERD symptoms.[48] Therefore,

screening of the high-risk group as defined may not affect cancers developing in SSBE. If the cancer risk is similar in the LSBE and the SSBE, the advantage of using GERD symptoms for selection of high-risk cases may be lost.

The effectiveness of the screening and surveillance program should be considered in relation to the yield as measured in terms of preventable deaths from esophageal adenocarcinoma. Esophageal adenocarcinoma is an uncommon cancer and an uncommon cause of death. It has been estimated that in the United States mortality rates in patients with BE are similar to those of the general population.[49] Prevalence of EAC in patients with heartburn is estimated to be 8-fold increased compared with the general population,[9] but mortality from esophageal adenocarcinoma is low: 4.7% in a population-based study[47] and 2.5% in a cohort study.[50] The absolute number of preventable deaths from esophageal adenocarcinoma is 6,000 per year. Since 95% of the adenocarcinoma has advanced cancer at the time of first presentation,[51] only 5% (300 of 6,000) of adenocarcinomas per year may be prevented by highly successful screening and surveillance. Because almost 40% of the cancer patients do not have antecedent symptomatic GERD,[45] even a most effective program of screening and surveillance will miss almost half the cases with esophageal adenocarcinomas.

From a cost-effectiveness point of view, screening followed by surveillance of patients with BE without dysplasia in a model of a hypothetical 50-year-old white man with chronic heartburn was prohibitively expensive at $596,000 quality adjusted life-year. In contrast, screening and continued surveillance only if HGD was found was $10,440 quality adjusted life-year.[52] Thus, only a rare patient who is found to have unsuspected early cancer or HGD may benefit from this program (Fig. 8).

The impact of the proposed screening and surveillance program for BE on national mortality rate from this cancer and on the care of the individual patient must be considered separately. It is quite clear that this program would have no impact on national mortality rate from esophageal adenocarcinoma. The impact on an individual patient is hard to generalize. A rare finding of HGD may lead to early cancer

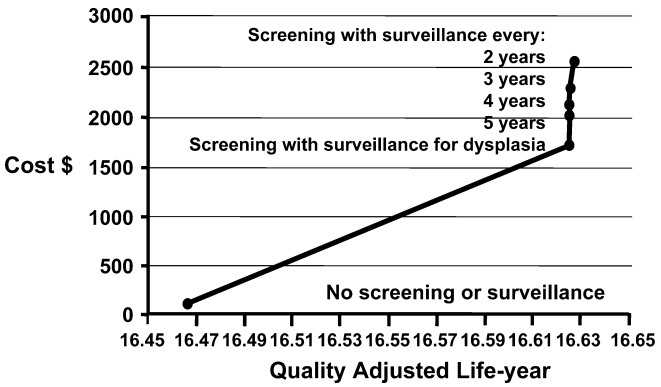

FIGURE 8. Cost-utility analysis of screening and surveillance for BE at various intervals. (Adapted from Inadomi, *Ann Intern Med.* 2003;138:181.[52])

- Identification of objective and reliable marker of high risk cases rather than histological dysplasia
- Elimination of sampling errors by *in vivo* recognition of the lesions and directed biopsies
- Better definition of surveillance intervals
- Chemoprevention therapy during follow-up period
- Identification of truly high risk cases
- Development of less invasive methods such non-sedated endoscopy, "optical biopsy," and cytology

FIGURE 9. Future directions in BE screening and surveillance.

detection and prevention. In some anxious individuals, ruling out a dysplastic BE lesion may be of value.

In the future, screening and surveillance for high-risk precancerous condition may become more pertinent when a noninvasive reliable marker such a molecular marker for BE becomes available.

In summary, the available data suggest that a large part of the current recommendations for surveillance for BE-associated histologic lesions are largely opinion statements that are not well supported by objective evidence. There is strong rationale for a vigorous initial testing to establish baseline status and particularly to identify early adenocarcinoma. There is also strong support for surveillance for HGD that is also cost-effective. Whether a patient with HGD should receive esophagectomy needs to be individualized. Recommendations for surveillance for LGD are not supported by the available data and for SIM without dysplasia appear to be arbitrary. However, surveillance does appear to identify early-stage cancers than those adenocarcinomas that are diagnosed without prior endoscopic evaluation.

The current recommendations for screening and surveillance are not evidence-based. These recommendations are unlikely to have any impact on national mortality from esophageal adenocarcinoma, and their effect on individual patient is difficult to determine. An educational program that provides objective data to patients and the insurers without generating fear and alarm regarding the finding of BE would be very useful.

The current recommendations are limited by the lack of consistency of endoscopic findings and sampling errors, inconsistencies of histologic diagnoses of BE and dysplasia, and limited understanding of the natural history of various histologic lesions.

In the near future, methods should be developed and validated that will reduce the endoscopic variability and sampling errors by allowing in vivo diagnosis of abnormalities and directed biopsies (Fig. 9). There should also be development of objective diagnostic markers other than the grades of dysplasia, Optical coherence tomography such as DNA content analysis and molecular markers. There should also be better definition of natural history of the disease. Effectiveness of a screening program will necessitate methods to further identify high-risk cases and the use of a simple and inexpensive screening method.

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