

REVIEW

Surveillance in Barrett's Esophagus: A Failed Premise

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Abstract

Background: It is recommended that patients in whom Barrett's esophagus is diagnosed undergo surveillance endoscopy. However, multiple issues regarding the efficacy and feasibility of surveillance remain.

Methods: Quantitative techniques were used to examine surveillance in patients with Barrett's esophagus. A retrospective case-control study was performed to determine whether surveillance endoscopy prolonged survival in a cohort of U.S. veterans diagnosed with esophageal adenocarcinoma. Cost-effectiveness analysis was employed to compare competing strategies of management for patients with Barrett's esophagus to determine whether surveillance strategies using alternative biomarkers could out-perform dysplasia based surveillance, and whether new techniques for eradicating Barrett's metaplasia would constitute cost-effective strategies.

Results: Surveillance did not improve long-term survival among veterans diagnosed with esophageal adenocarcinoma. Lead-time bias has confounded previous reports claiming the efficacy of endoscopic surveillance. Cost-effectiveness analysis revealed that while screening 50-year old Caucasian males with heartburn may be cost-effective, surveillance even at 5 year intervals among patients with Barrett's esophagus without dysplasia exceeded the threshold of cost-effective care. If a biomarker were developed whose sensitivity and specificity to predict cancer development exceeded 80%, this could represent a more viable strategy than dysplasia-based surveillance and overcome the inherent inter- and intra-observer variations in dysplasia diagnosis that currently limit the effectiveness of surveillance programs. Finally, techniques that reduce cancer incidence such as endoscopic mucosal resection or ablation will likely be more cost-effective than current surveillance strategies that rely on early detection of cancer.

Conclusions: Current recommendations for the management of patients with Barrett's esophagus are flawed. Future guidelines should include alternative markers of cancer risk and focus on strategies that reduce cancer incidence instead of cancer detection. (Keio J Med 58 (1) : 12–18, March 2009)

Keywords: Barrett's esophagus, surveillance, screening, esophageal adenocarcinoma

Background

Barrett's esophagus is the accepted precursor responsible for the majority if not all cases of esophageal adenocarcinoma. The definition of Barrett's esophagus per the

American College of Gastroenterology guidelines is the presence of endoscopically identifiable columnar appearing mucosa within the tubular esophagus in which histological examination reveals the presence of intestinal metaplasia.¹ While it has become routine practice to

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perform screening to detect Barrett's esophagus in populations believed to be at high risk for the development of esophageal adenocarcinoma, namely people with symptoms consistent with gastroesophageal reflux, little evidence supports this practice.¹ Moreover, one is faced with the dilemma of how best to conduct surveillance after screening has diagnosed Barrett's esophagus. Problems with the grading of dysplasia, the major factor by which management is stratified for purposes of surveillance or intervention, inter- and intra-observer variability, sampling error and unclear natural history compound the complexity of issues surrounding optimal care of patients with Barrett's esophagus.

The purpose of this review is to critically examine the key areas that impact the effectiveness of screening and surveillance for Barrett's esophagus. The main points to be covered include determination of the efficacy of screening to reduce mortality from esophageal adenocarcinoma, identification of the economic impact of screening and surveillance, and exploration into whether better alternatives to surveillance exist and should be pursued.

The Risk of Cancer

The risk of cancer among patients with Barrett's esophagus, while not precisely documented, is lower than initially reported. Early studies quoted a cancer incidence as high as 2% annual risk.² More recent data downgrade the risk to 0.5% annual risk of cancer,³ with publication bias likely explaining the discrepancy between the new and old estimates. Dysplasia has been used as the means to stratify patients' risk of cancer, with the risk being lowest in those without dysplasia and highest in those with high grade dysplasia.^{2,4–6} However, a concerning proportion of patients who eventually develop cancer do not have dysplasia on their initial biopsies.⁷

The association between *H. pylori* and esophageal adenocarcinoma is complex. The distinction between adenocarcinoma of the distal esophagus and adenocarcinoma of the cardia is difficult if not impossible to make based on histology or pathology codes. Therefore *H. pylori* associated gastric cardia adenocarcinoma cannot be separate from Barrett's esophagus associated distal esophageal adenocarcinoma when analyzing information from administrative databases. Screening for either disease involves upper gastrointestinal endoscopy where detection of early stage cancer can be achieved. A more complex association may be present from an epidemiological perspective. The time trends in the United States for peptic ulcer disease, and by inference *H. pylori* infection, is inversely associated with the time trend for Barrett's esophagus and esophageal adenocarcinoma.⁸ For this reason there is speculation that the rise in gastroesophageal reflux disease, Barrett's esophagus and associated

esophageal adenocarcinoma is due to the population decline in *H. pylori* infection. While unproven, it has been suggested that chronic gastric inflammation from *H. pylori* infection decreases acid secretion thereby providing protection against acid-associated esophageal injury. Environmental conditions that have reduced *H. pylori* infection in the U.S. may then allow unopposed acid secretion to persist through adulthood resulting in the increased prevalence of gastroesophageal reflux disease and associated complications including esophageal adenocarcinoma.⁸

Current Guidelines for Screening and Surveillance

The American College of Gastroenterology recently updated its guidelines for screening and surveillance in Barrett's esophagus.¹ Recall that screening is defined as testing an average-risk population for the presence of disease while surveillance involves repeated testing in a cohort previously identified at high risk for disease progression. The yield from screening would be highest among Caucasian men age 50 years and older with symptoms of gastroesophageal reflux disease since although the risk of esophageal adenocarcinoma is rising in all races and genders, the greatest increase has been observed in this cohort. It should be noted that environmental factors play an important role in cancer development and race and/or gender may be a surrogate for these factors; therefore it is premature to eliminate non-Whites or women from consideration of screening. Recommendations from the American Gastroenterological Association and the American College of Gastroenterology support surveillance among persons diagnosed with Barrett's esophagus.^{1,9,10} The interval between surveillance endoscopies depends on the presence and severity of dysplasia: no dysplasia on 2 exams allows for a 3-5 year interval, low-grade dysplasia prompts 1 year intervals while high-grade dysplasia can be managed by surveillance every 3 months. Alternatively, high-grade dysplasia can be treated by endoscopic ablation (photodynamic therapy, radiofrequency ablation) or mucosal resection. Although some centers still perform esophagectomy for a diagnosis of high-grade dysplasia this is no longer routinely advocated by the guidelines. Esophagectomy is recommended for cancer, although newer reports indicate that lesions confirmed by endoscopic ultrasound (EUS) to be confined to the mucosa can be successfully treated endoscopically.^{11,12}

Evidence Supporting Surveillance among Patients with Barrett's Esophagus

Although evidence proving the efficacy of screening to detect Barrett's esophagus is lacking, several retrospective studies illustrate a mortality benefit from surveil-

lance to detect and treat early cancer. These studies compared mortality from esophageal adenocarcinoma among patients who had previously undergone endoscopy with those who did not receive endoscopy and showed that mortality was significantly reduced among those who had previous endoscopy.¹³⁻¹⁶ However, the retrospective nature of these studies could not exclude bias due to lead or length time effects, nor could the studies exclude confounding by indication, ascertainment bias or other factors. In fact, it is likely that a part if not all of the effect of surveillance endoscopy on mortality is based on lead time bias. Lead-time bias occurs when a screening and surveillance program appears to prolong survival, but in reality only the duration with which the diagnosis is known is prolonged and the actual lifetime is not increased. For example let us assume that twin brothers develop cancer at the same time and die five years later. One of the brothers undergoes a screening test prior to the onset of symptoms and is diagnosed at an earlier, pre-symptomatic stage, while the other brother does not undergo screening and is diagnosed only after symptoms develop. The brother in whom screening was performed will have an apparent survival with cancer that is longer than the brother who did not undergo screening. Screening, however, did not prolong the lifespan of that brother; rather, screening merely allowed a diagnosis to be obtained at an earlier time and the duration with which the patient survives with cancer appears to be longer. Thus, lead-time bias is present when a patient undergoing screening and surveillance appears to have longer life when in actuality this gain is merely due to the added time between early diagnosis achieved through surveillance and the point at which symptoms would have prompted diagnosis had screening and surveillance not been conducted. We conducted a study in which the durability of the mortality benefit was examined and found that although 5-year survival appeared lengthened by surveillance this benefit disappeared with longer follow-up, indicating the presence of lead-time bias.¹⁷ Thus the mortality benefit from surveillance endoscopy has not been confirmed and remains to be proven through prospective clinical trials.

Another problem with our current management of Barrett's esophagus is that the incidence of cancer diagnosed through surveillance is lower than the prevalence of cancer found at screening. Screening will discover prevalent cancers while surveillance will identify incident cancers. A cohort of patients with Barrett's esophagus followed for a mean of 7.3 years reported that the prevalence of cancer diagnosed within the 1st year of the identification of Barrett's esophagus was 4.2% in contrast to the incidence of cancer, which was 2.1%.⁴ In essence, the people who are destined to develop esophageal adenocarcinoma already have it by the time we diagnose Barrett's esophagus. The only way a surveillance strategy will be

useful is if we alter our method of screening to detect Barrett's earlier than is currently practiced, prior to the development of cancer.

The Cost-effectiveness of Screening and Surveillance to Decrease Mortality from Esophageal Adenocarcinoma

Prior discussion notwithstanding, even if one assumes that surveillance decreases mortality by detecting cancer at a treatable stage there are economic barriers to implementation of surveillance. Using estimates from published retrospective studies, we compared screening with various strategies of surveillance to no screening or surveillance among patients at elevated risk of cancer, specifically White men over the age of 50 years with symptoms of gastroesophageal reflux disease. Through mathematical modeling using computer simulation we estimated that screening may be cost-effective compared to no screening in this population through the identification of patients with prevalent cancer as well as patients with dysplasia associated Barrett's esophagus that indicates a higher risk of cancer development.¹⁸ However, we also showed that continued surveillance among patients with Barrett's esophagus in the absence of dysplasia was unlikely to be feasible at costs considered reasonable by society. **Figure 1** illustrates the various costs and benefits associated with no screening or surveillance compared to screening with surveillance limited to patients with dysplasia and Barrett's esophagus, versus surveillance for patients without dysplasia at intervals of 2-5 years. The relatively modest incremental cost-effectiveness ratio (ICER) depicted by the slope of the line connecting the no screening or surveillance strategy with the screening with surveillance for dysplasia strategy indicate a cost-effectiveness less than \$50,000 per quality-adjusted life-year gained, which is the threshold U.S. society is willing to pay. In contrast, however, the steep line connecting the strategies in which surveillance is performed for patients without dysplasia indicate that this practice is extremely expensive with costs over \$380,000 per quality-adjusted life-year gained. An extensive sensitivity analysis was conducted and despite variation of input parameters within the entire range reported in the published literature, screening with surveillance limited to patients with Barrett's esophagus and dysplasia remained cost-effective in 99% of simulations. Conversely, continued surveillance for patient with Barrett's esophagus in the absence of dysplasia was never cost-effective at a threshold of \$50,000 per life year saved and only feasible at a threshold of \$100,000 in 7% of simulations. These results indicate that the conclusions of the analyses are robust and unlikely to change significantly unless new data significantly contradict current literature regarding the natural history of Barrett's

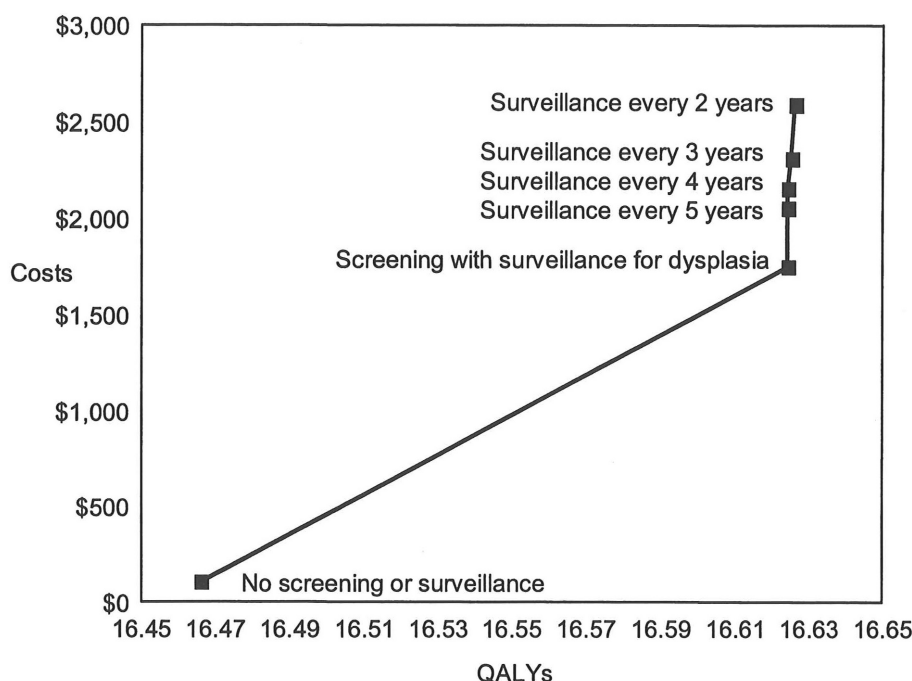


Fig. 1 Cost Effectiveness Analysis. The x-axis depicts benefit measured in units of quality adjusted life years (QALYs). The y-axis denotes the costs (U.S.\$) associated with various strategies including no screening or surveillance, screening with surveillance limited to patients with Barrett's esophagus and dysplasia, screening with surveillance for patients with Barrett's and no dysplasia at 5-, 4-, 3-, or 2-year intervals. The lines depict the incremental cost-effectiveness ratio (ICER) between non-dominated strategies. (Reproduced from "Screening and Surveillance for Barrett Esophagus in High-Risk Groups: A Cost-Utility Analysis." Inadomi, *et al.*, *Annals of Internal Medicine*, Feb 2003; 138 Fig. 2)

s esophagus or heighten the efficacy of surveillance to reduce mortality. Thus current guidelines recommend a strategy that is apparently beyond the budget that societal standards have established.

Biomarkers in Barrett's Esophagus

Implicit in the recommendation to screen patients with symptoms of gastroesophageal reflux disease is the use of heartburn as a biomarker to identify those with Barrett's esophagus. While heartburn is indeed a strong risk factor for the development of esophageal adenocarcinoma,¹⁹ the absence of heartburn does not necessarily exclude Barrett's. Fully 40% of patients diagnosed with esophageal adenocarcinoma do not report significant heartburn symptoms five years or more prior to the diagnosis of cancer.¹⁹ Indeed, while the prevalence of Barrett's esophagus among patients with heartburn is approximately 10%^{20,21} other studies have revealed the prevalence of Barrett's among patients without heartburn to be as high as 25%.^{22,23} It is clear that any strategy that relies upon the presence of heartburn to prompt screening will fail to identify a significant proportion of the patients with Barrett's esophagus.

The risk of cancer among patients with Barrett's

esophagus is lower than initially reported and despite the increase in cancer incidence, insufficient to allow any intervention including surveillance to achieve the threshold necessary to be economically feasible. Further risk stratification is attempted through the use of dysplasia as the marker to identify patients with Barrett's esophagus at highest risk for cancer development and utilize the grade of dysplasia to dictate the interval between surveillance endoscopies and to possibly indicate when interventions such as ablation therapy or endoscopic mucosal resection are indicated. The fallacies of this recommendation are the well-recognized deficiencies of dysplasia with regards to inter- and intra-observer variation, sampling error and the potentially evanescent nature of dysplasia. Studies have indicated that the correlation for the diagnosis of dysplasia between even expert pathologists is only fair.^{24,25} This problem is compounded when taken to the level of the community pathologist and only partially rectified by the recommendation to have all diagnoses of dysplasia reviewed by a second expert pathologist. The diagnosis of dysplasia cannot be considered a stable, linear process. Data from longitudinal studies illustrate that low-grade dysplasia can be seen at some time during follow-up in approximately two-thirds of patients with Barrett's esophagus;^{4,7} however, most pa-

tients do not progress to high-grade dysplasia or cancer and many regress to non-dysplastic metaplasia on subsequent surveillance examinations. While this may indicate sampling error since dysplasia may be focal and difficult to locate during endoscopy, an equally plausible explanation that has not been refuted is that dysplasia can regress as well as progress over time. Dysplasia may be the best biomarker currently available to predict likelihood of progression to cancer but it is seriously flawed and surveillance strategies that rely upon dysplasia to dictate clinical management will never be optimal.²⁵

One of the functions of decision analysis is to identify factors most likely to influence study conclusions.^{26,27} In the case of published studies of surveillance in Barrett's esophagus the method of detection of patients at high risk of cancer development was a significant factor and if methods were developed that improved beyond the capability of dysplasia the impact of surveillance could significantly improve. For the purposes of surveillance it would be important for a biomarker to not merely identify patients in whom cancer was already present but also accurately determine which patients were most likely to develop cancer.²⁸ We have examined this aspect of diagnosis in more detailed decision analysis using alternative methods of risk stratification, specifically asking whether flow cytometry could be a viable option for determining which patient with Barrett's esophagus should under surveillance. In a decision analysis study we compared traditional surveillance stratification by dysplasia with stratification by flow cytometry where only patients in whom abnormal flow is present would undergo surveillance endoscopy.²⁹ The results of this analysis indicate that using current estimates for the ability of flow cytometry to predict development of cancer, this technique to identify patients with Barrett's esophagus in whom to perform surveillance is inferior to the use of dysplasia as the biomarker. Improvements in the ability of flow cytometry or another biomarker to predict cancer development could potentially surpass dysplasia-mediated surveillance if the sensitivity and specificity exceeded 80-90% in the accuracy of predicting cancer development. Costs of the biomarker would also be important since if the test approached \$1000 the accuracy would need to substantially improve beyond 90% accuracy. This study demonstrated that while current technology is insufficient for alternative biomarkers to surpass dysplasia as the preferred method of stratification, the threshold for biomarker development has been set and will likely be attainable in the future.

Therapy for Barrett's Esophagus

Beyond diagnosis and stratification, the most pressing issue with regards to Barrett's management involves successful eradication of Barrett's metaplasia and dysplasia.

We and others have examined photodynamic therapy (PDT) for high-grade dysplasia associated with Barrett's esophagus.³⁰⁻³³ These analyses uniformly support the use of ablation as opposed to immediate esophagectomy or enhanced surveillance in this patient population. Despite the high cost and relatively high rate of complications (stricture and perforation) PDT performs favorably compared to alternatives, mainly due to its ability to potentially avert esophagectomy, which is associated with a decrement in quality of life. In fact, these analyses indicate that immediate esophagectomy for high-grade dysplasia is not only more expensive than surveillance but also expected to yield fewer quality adjusted life-years due to the negative impact on quality of life. The long-term effectiveness of PDT should be identified prior to widescale adoption of this strategy; additionally, complications such as strictures, perforations and the relatively high rate of recurrent intestinal metaplasia in the treated segment, especially recurrence beneath normal squamous epithelium, termed subsquamous intestinal metaplasia (SSIM), constitute significant barriers to this therapy. Based on the negative aspects of PDT it is not recommended for patients with low-grade or no dysplasia.

Radiofrequency ablation (RFA) holds the potential for ablation of metaplasia and dysplasia with reduced risks of complications seen with PDT. While data are hampered by short-term reporting, promise exists for this form of therapy for not only patients with dysplasia but also perhaps patients without dysplasia. Data with follow-up ranging from 12-14 months indicate that 80-90% of HGD or LGD may be ablated, while complete eradication of intestinal metaplasia may occur in 50-97% with follow-up out to 30 months.³⁴⁻³⁸ Data from these trials also indicate a rate of stricture formation or perforation far below that associated with PDT; moreover, post-therapy SSIM appears to be extremely rare, which also is an advantage for RFA. Formal economic analysis comparing RFA to PDT or surveillance strategies are forthcoming; however, it is likely that RFA will be a cost-effective alternative for patients with Barrett's esophagus and high-grade dysplasia since the costs and complication rate are lower than PDT and efficacy appears to be similar. Prior to adoption of RFA, however, long-term results must be obtained, specifically concerning the durability of ablation, whether cancer risk is truly reduced and whether surveillance may be discontinued after ablation is complete.

Endoscopic mucosal resection (EMR) also holds promise as an intervention that may reduce cancer incidence. Specialized techniques and tools have been developed to facilitate EMR, increasing the prevalence of this technique throughout the endoscopic community. At present EMR is best used to remove visible lesions including raised, ulcerated or depressed lesions. In this capacity and either alone or in conjunction with other ablative

techniques results appear quite favorable.^{11,12,39–42} Reports of extended resection of flat mucosa have been published; however, it is likely that such extensive therapy will require considerable expertise and not be routinely available in clinical practice.

Summary

Barrett's esophagus is the accepted precursor of esophageal adenocarcinoma. Despite the ability of Barrett's esophagus to be identified by endoscopy with biopsy it is unclear that screening for its presence and surveillance to detect cancer among patients diagnosed with this lesion is effective or economically feasible. Barriers to this strategy include the poor sensitivity of heartburn to identify all Barrett's patients, poor specificity of Barrett's to predict progression to cancer, and poor discrimination of dysplasia to further identify a sub-group of patients in whom the risk of cancer is sufficiently high to warrant intervention. Furthermore, the necessity of esophagectomy to treat cancer diminishes the health impact of surveillance based on the decrement in quality of life associated with surgery.

From perspectives of both efficacy and cost-effectiveness it is imperative that screening and surveillance strategies be built around interventions that decrease the risk of cancer as opposed to merely treating cancer at a stage that is hopefully curable. In short, it is always better to prevent than to treat cancer. Specifically, ablation of Barrett's esophagus among patients who have been identified to be at imminent risk of cancer would be an ideal goal. Risk stratification beyond the simple diagnosis of intestinal metaplasia is necessary to improve targeting of interventions that will incur morbidity, mortality and cost. Certainly histological assessment of dysplasia will be insufficient. Better biomarkers are needed, which will require improved understanding of the mechanism of the inciting events, proliferation and progression of intestinal metaplasia to dysplasia and cancer. Whether emerging techniques such as PDT, RFA or EMR will fulfill the therapeutic void remain to be seen and we will await results of long-term trials of these modalities. In the meantime it is difficult to support screening of patients with reflux symptoms to identify Barrett's esophagus. Moreover, our current recommendations to perform endoscopy with biopsy at surveillance intervals based on the presence of dysplasia are at most minimally effective and at least misleading in terms of the actual benefit accrued. Finally, surveillance in itself cannot improve survival without leading to interventions that alter the natural history of Barrett's esophagus and at present our interventions have little evidence to support their implementation.

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