

How Far to Go? Screening and Surveillance in Barrett's Esophagus

Based on a debate between David A. Lieberman, MD, and Richard E. Sampliner, MD

Debate Summary

There is no dispute that Barrett's esophagus (BE) is associated with an increased risk of esophageal adenocarcinoma. Detecting these cancers early can improve patient survival. But should screening be used to detect BE, or should a surveillance program monitor those already diagnosed with BE for neoplastic changes? Endoscopy and endoscopic biopsy are the only tools available for such screening and surveillance, and the cost effectiveness of either approach must be considered. Two possible solutions are discussed. First, screening could be limited to patients considered at high risk for BE and associated adenocarcinoma. With this approach, more precise risk stratification would be required. The second possible approach is to combine screening for high-risk patients and surveillance for those already diagnosed with BE. Additional outcomes data are needed to determine how often and for what length of time endoscopic surveillance should continue in a patient after several examinations are negative for adenocarcinoma.

annually, about half of which are adenocarcinomas with a 5-year survival rate of less than 5%. Another important demographic characteristic is that during the past 2 decades there has been a striking increase in the incidence of esophageal adenocarcinoma among white males.¹ The dismal survival rate associated with esophageal adenocarcinoma is probably a result of these cancers being detected too late in the disease process.

Evidence shows that 40% to 50% of patients with persistent GERD symptoms will develop esophageal injury, and of these, 10% to 15% will be found to have BE upon endoscopic examination.² Approximately 5% to 10% of BE patients are likely to have adenocarcinoma identified at the first endoscopic evaluation, and approximately 0.5% of the remaining 90% to 95% of BE patients will develop adenocarcinoma over time.²

Data suggest that some patients with GERD or GERD-related esophageal injury may develop adenocarcinoma directly, although the majority of adenocarcinoma cases are associated with BE. A recent study showed a strong association between GERD symptoms and esophageal adenocarcinoma with an odds ratio much higher than that between GERD symptoms and either gastric cardia cancer or squamous cell carcinoma of the esophagus (Table 1).³ In addition,

Dr. Lieberman:

Prevalence

To what extent should patients with gastroesophageal reflux disease (GERD) be screened for Barrett's esophagus (BE)? Approximately 12,000 cases of esophageal cancer are diagnosed in the United States

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the researchers found that the adenocarcinoma risk increased as the number of GERD symptoms in an individual patient increased.³

Screening Strategies

The goal of screening to detect BE and early esophageal adenocarcinoma should be to reduce mortality through the identification of cancers at an early, curable stage. Screening may also aim to identify those high-risk patients most likely to develop incidence cancers who would benefit from close surveillance. Various screening scenarios can be evaluated to determine how well they would accomplish these goals and what potential impact on mortality each scenario would have.

For example, of the 150 million adults in the United States, 40% have intermittent reflux symptoms, and approximately 20%—or a total of 30 million adults—are likely to have weekly GERD symptoms. Of these, about 20%, or 6 million people, require antireflux medication on a regular basis.⁴ We have previously determined that approximately 40%, or 2.4 million, of these patients are likely to have esophageal injury as a result of GERD. If patients with other symptoms such as dysphagia, bleeding, or weight loss are excluded, about 5%, or 300,000 patients, will have BE. And of these, 1%, or 3000 cases, of asymptomatic cancer would be expected. This indicates that 20

GERD patients would need to be screened to detect 1 case of BE and that 2000 screenings would be needed to identify 1 case of esophageal cancer. It would appear, therefore, that screening of all GERD patients is not practical.

However, because most patients who develop esophageal cancer are older than 40 years, have a longer duration of GERD symptoms (5 years or more), and are more likely to have symptomatic GERD recurrence without antireflux, the population of GERD patients requiring screening could be reduced to about 1 million. In this population, the incidence of BE is higher, about 10% or 100,000 cases, and the incidence of asymptomatic cancer would be approximately 3% or 3000 cases. Therefore, screening 10 of these higher-risk patients would result in 1 BE diagnosis, and 333 screenings would be needed to detect 1 case of esophageal cancer (**Table 1a**). This scenario is more reasonable but still requires numerous endoscopies to identify a single case of cancer.

Because the highest incidence of esophageal adenocarcinoma is among white males, the number of screenings can be further reduced by including white males and females and nonwhite patients with very severe symptoms. In this scenario, the patient population requiring screening would be approximately 500,000 with an estimated BE incidence of 15% or 75,000 patients and an estimated cancer incidence of 5% or 3750 patients. In this scenario, 6.7 screenings would be needed to detect 1 case of BE, and 136 screenings would be required to identify each case of cancer (**Table 1b**). This is a more feasible result and is similar to the statistics associated with colon-cancer screening, which requires 140 colonoscopy procedures to detect each case of cancer.⁵ Furthermore, in this revised GERD-screening population, if the risk of cancer among BE patients is 0.3%

Table 1. Odds Ratios Illustrate Association Between the Presence of GERD Symptoms and Esophageal Adenocarcinoma

Disease State	Odds Ratio
Esophageal-adenocarcinoma	7.7
Cancer-gastric cardia	2.0
Squamous cell cancer of esophagus	1.1

GERD = gastroesophageal reflux disease.

Source: Reference 3.

annually, then the 10-year cancer risk is 3%, resulting in 130 screenings needed to detect each case during a 10-year surveillance period.

Conclusion

It seems that screening all GERD patients is not practical, but if screening can be targeted to high-risk patients, it may be beneficial. However, before such screening is advocated, there should be a protocol for how to proceed with the BE patients who will be identified as a result. Most short-segment and long-segment BE patients do not go on to develop esophageal adenocarcinoma, and rational surveillance strategies will be needed to follow these patients to reduce cancer mortality while maintaining screening and follow-up programs that are both cost effective and practical.

Dr. Sampliner:

The latest data indicate an increasing incidence of esophageal adenocarcinoma, especially among white males, and that BE is the only predisposing factor for adenocarcinoma of which we are aware.¹ Also, early detection of these cancers would obviously offer an opportunity to prolong survival in these patients. Therefore, screening is an important issue.

Screening

The effectiveness of screening GERD patients to identify those with high-grade dysplasia associated with BE is a complex issue. Three criteria have to be met for this approach to be effective in terms of life-years saved. First, false-positive endoscopy results must be less than 10% in such a screening program. This condition may be difficult to meet because there is controversy within the pathology community concerning what constitutes a high-grade

dysplasia reading. Secondly, because the only effective treatment available for esophageal cancer is esophagectomy, postoperative health-related quality of life for patients identified through screening must be high enough to justify the procedure. And

Table 1a. Targeting High Risk Individuals May Support Use of Screening for BE

Population of GERD patients (reduced based on criteria*)	1,000,000
Incidence of BE in reduced population	100,000 cases (10%)
NNS to diagnose 1 BE	10
Incidence of esophageal cancer in reduced population	3000 cases (3%)
NNS to diagnose 1 esophageal cancer	333

*Based on a population of 1 million, reduced by the following criteria: Age > 40 years; symptomatic > 5 years; symptomatic relapse without medications. BE = Barrett's esophagus; NNS = number needed to screen.

Table 1b. Use of Additional Criteria to Reduce Screening Population: Argument for Screening for BE

Population of GERD patients (reduced based on criteria*)	500,000
Incidence of BE in reduced population	75,000 cases (15%)
NNS to diagnose 1 BE	6.7
Incidence of esophageal cancer in reduced population	3750 cases (5%)
NNS to diagnose 1 esophageal cancer	136

*Population is further reduced from 1 million in Table 1a to 500,000 by the following criteria: Age > 40 years, symptomatic > 5 years, symptom relapse; females, only with severe symptoms; nonwhites, only with severe symptoms. BE = Barrett's esophagus; NNS = number needed to screen.

thirdly, the prevalence of high-grade dysplasia and adenocarcinoma among BE patients has to be at least 10% to justify a screening program.⁶

One can argue that risk stratification is the key to developing a screening program. Screening male patients for BE may result in a significant number of cancer identifications. Although BE is more common among older patients, it is debatable whether the age threshold for screening should be 40 or 50 years. It has also been argued that long-standing reflux symptoms are associated with increased BE and cancer risk, and this may be a criterion for screening.⁷ Only 1 study has demonstrated that the severity of reflux symptoms is associated with increased BE.³ On the other hand, 2 other papers suggest that increased symptom severity is not a risk factor for BE.^{7,8}

Surveillance

Perhaps the best approach is to combine screening and surveillance programs. Screening should be used to detect the premalignant disease of BE, and BE patients should then undergo endoscopic surveillance to identify adenocarcinoma lesions as early as possible. Data from 3 retrospective studies show that surveillance of BE patients is beneficial in terms of survival. Outcomes of patients known to have

BE with a cancer detected during endoscopic surveillance showed 5-year survival rates ranging from 62% to 90%. In contrast, patients not under surveillance who were endoscopically diagnosed with BE and esophageal cancer simultaneously followed by resection of the cancerous lesions had 5-year survival rates of only 20% (Table 2).^{9,10} It is important to note that surgically treated patients represent a minority of all of those who present with BE and adenocarcinoma. Survival rates for those not having surgery would be expected to be less than 20%. The third retrospective study shows that a significant outcome difference between BE patients under surveillance (16 patients, 86% survival rate) and those not under surveillance (54 patients, 43% survival rate) can be observed in as little as 2 years' follow up.¹¹

Although these studies support an argument for surveillance, they also can be interpreted as an argument for BE screening because of the numbers of patients in the surveillance versus no-surveillance groups. Between 16 and 19 patients were identified with cancer while undergoing surveillance for BE; at least twice as many patients (between 35 and 58 individuals) had BE and adenocarcinoma diagnosed at the same time.⁹⁻¹¹

Additional data from the Tucson Veteran's Administration Medical Center show that 294 BE patients were identified using the rigorous criteria of an abnormal-appearing esophagus and intestinal metaplasia upon biopsy between 1983 and 1997. Prevalence cancers, defined as cancer diagnosed within 1 year of the BE diagnosis, amounted to 5% of the population being observed during the study period. The incidence of cancer detection with surveillance more than 1 year after the BE diagnosis was only 0.5% per year. This patient population was 98% male and 90% white and is

Table 2. Survival Rates: Endoscopic Surveillance Versus No Surveillance

	Surveillance		No Surveillance	
	n	% Survival	n	% Survival
Peters* ⁹	17	90	35	20
Streitz ¹⁰	19	62	58	20

*Excludes 4 HGD. P = 0.09.
Source: References 9,10.

considered at high risk for BE and associated cancers. Therefore, the lesson from these data appears to be that screening detects prevalence cancers with a much higher yield of cancer diagnoses than does surveillance. Approximately 10 years of surveillance would be needed before detecting the number of esophageal cancers found with BE screening.¹²

However, if we accept that the annual risk of cancer among BE patients is 0.5%, that the average age of BE detection is 60 years, and that the average remaining life expectancy for a 60 year old is 21 years, then the lifetime risk of cancer for a BE patient would be 10.5%.^{2,12} This leaves us with the question: if you had a 10.5% risk of developing esophageal adenocarcinoma, would you undergo surveillance?

REBUTTAL

Dr. Lieberman:

I think that the Tucson Veteran's Administration Medical Center data can be read a bit differently.¹⁰ These data support aggressive screening and not surveillance. Although the lifetime cancer risk is high at 10.5%, the largest yield in this study was the identification of the 5% of patients with prevalence cancers. It does no good to detect these cancers unless they are detected early, and the only way to accomplish early detection is with screening.

I also argue that the lifetime risk of incidence cancer, which in this study is 10.5%, is actually quite variable. We know this risk will be greater in white males and in patients who already have some form of dysplasia versus those who have no dysplasia upon repeated examinations. Therefore, I believe that if screening is performed to identify BE patients, it should be followed by a surveillance program that includes risk stratification and

targets specific high-risk groups. We also need to address the question of what to do after several surveillance examinations show no inflammation, dysplasia, or other signs of neoplastic formation. Studies are needed to determine at which point repeated surveillance becomes less effective.

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—David A. Lieberman, MD

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—Richard E. Sampliner, MD

Dr. Sampliner:

I agree that risk stratification is the name of the game, but we just do not have adequate data to support choosing specific screening criteria, including age thresholds and certain patient populations. Unfortunately, we do not yet have a validated biomarker that would potentially solve this problem for us. I believe a molecular biology approach will eventually help in terms of risk stratification among these patients. We may find those with a genetic predisposition for esophageal adenocarcinoma, or it may be that the pathophysiology of developing BE is completely different than that of

metaplastic to neoplastic lesion transformation. Meanwhile, it is important to recognize that even if the lifetime risk of esophageal adenocarcinoma among BE patients is closer to 5%, the remaining 90% to 95% of BE patients will die without cancer of the esophagus.

On the other hand, if the lifetime cancer risk in BE patients is 5%, that is similar to the lifetime risk of colon cancer among adults in the United States, and we screen for that. Therefore, I believe BE screening is worthwhile. But once BE is identified, there needs to be a surveillance strategy in place for that individual.

QUESTION-AND-ANSWER SESSION

Question: *We hear about using elevated cyclooxygenase-2 levels, oncogenes, or aneuploidy as markers for adenocarcinoma risk. Are you using any of these markers and if not, why not?*

Dr. Sampliner: We know that different markers, such as a p53 mutation, which increases in frequency as dysplasia progresses to adenocarcinoma, have been postulated. However, if you look at some of these data carefully, you see that histology produces the same results as using the markers. Also, no marker has ever been validated in a collaborative, multicenter study. I think it is not yet time to use these markers in clinical practice.

Question: *It seems that the issue with widespread screening for BE is cost. Everyone seems to want this service, but no one wants to pay for it. Could you comment on this?*

Dr. Lieberman: The economic issues do come into play, and we do not have much data regarding the

cost effectiveness of the screening approaches that have been suggested. However, cost is not the only issue. If we screen everyone with GERD for BE and then condemn those with BE to a lifetime of surveillance, we have to keep in mind that the majority of these patients will never develop cancer in their lifetime. Is the surveillance justified? I believe that if we embark on screening we must have strategies in place to determine what exactly needs to be done for those identified with BE.

Dr. Sampliner: This question serves as a challenge for us to better define the data and risks so we can present a rationale to society for screening and surveillance in BE. Also, as far as cost is concerned, would using an ultrathin endoscope without sedation on an outpatient basis to examine the esophagus make screening or surveillance more economically attractive?

Dr. Lieberman: It may, because as the endoscopic procedure becomes easier to perform, involves less time, and poses less risk to the patient, it becomes more economical. Therefore, the number needed to treat would be more attractive because cost effectiveness would be maintained.

Question: *How many of the prevalence cancers were symptomatic in your series?*

Dr. Sampliner: For the most part, these patients had warning symptoms. The vast majority presented with dysphagia, and the typical history was an older white male with reflux for a few decades. Many had difficulty swallowing and, unfortunately, had weight loss or chest pain. There was 1 patient without these symptoms who presented for a reflux study when endoscopy identified the adenocarcinoma. For

the most part, all of these patients had a warning symptom.

Question: *The key seems to be finding the time between BE diagnosis and the first cancer warning symptom. Can you speculate as to how many years this would be?*

Dr. Sampliner: That is one of the major problems with BE. We date the time of onset to when endoscopy and diagnosis occurs, but we really have no idea when BE started in a particular patient. We may have a history of when reflux symptoms began, but that is not necessarily when BE began. The classic textbook history for BE is that a patient had severe GERD that suddenly got better. It is at that point that BE developed. However, I have only seen 3 out of 300 such classic cases, so that is not a very sensitive way of recognizing BE onset.

Question: *What do you do with the patient in whom you have made the mistake of performing a biopsy of the gastroesophageal junction and find no change, while the patient has intestinal metaplasia? Do you put this patient under surveillance?*

Dr. Sampliner: I don't make that mistake. If someone has a normal squamocolumnar junction, I don't biopsy. The only significant difference may occur in the minority populations. If a minority patient has a family history of adenocarcinoma of the stomach, then one should consider evaluating that patient for *Helicobacter pylori* infection.

Question: *You recommend screening white males over the age of 40 years who have long-standing GERD symptoms. And women and nonwhites*

should be screened if they have severe symptoms. Is that correct?

Dr. Lieberman: That is correct. It makes sense to use this approach if our goal is to detect the early prevalent adenocarcinomas. If we can detect these at an early enough stage, we can have an impact on survival.

Dr. Sampliner: The challenge to that proposal is that 40% of patients

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surgically resected with adenocarcinoma had no history of reflux. Therefore, we really need to develop symptom information that is accurate as it relates to BE and cancer risk.

Question: *As far as surveillance, current guidelines suggest a surveillance interval of every 2 to 3 years in BE patients without evidence of dysplasia. Do you think recent data are sufficient to lengthen the surveillance interval to every 5 years?*

Dr. Sampliner: I don't know if we are ready for that yet. The recent surveys of endoscopic practice in the United States clearly indicate that the majority of endoscopists are evaluating BE patients more often than every 3 years even when there has been no sign of dysplasia upon the previous 2 endoscopy examinations. The key issue is that

if 2 endoscopy examinations and systematic biopsy results are negative for dysplasia, the patient is probably at lower risk, and the endoscopy and biopsy interval could be extended to at least 3 years and perhaps to 5 years.

In addition, approximately two thirds of the time we observe low-grade dysplasia, which is a transient lesion that appears to resolve spontaneously. If a patient shows low-grade dysplasia at endoscopy every 6 months for 4 years, you may want to question the rigorous surveillance approach and extend the surveillance intervals over a longer time to be more practical.

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